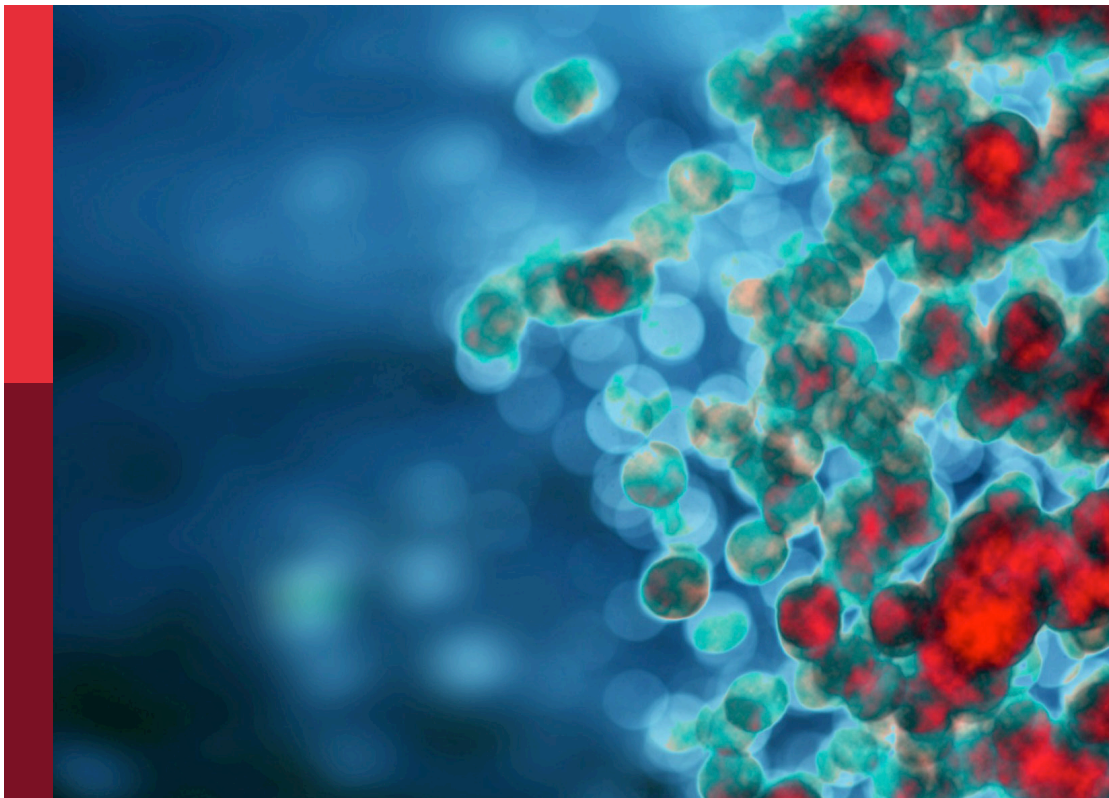
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# Case reports in autoimmune and autoinflammatory disorders

**Edited by**
Jemima Albayda, Mattia Bellan, Gian Marco Ghiggeri and Chris Wincup

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# Case reports in autoimmune and autoinflammatory disorders

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# Editorial: Case reports in autoimmune and autoinflammatory disorders

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Editorial on the Research Topic
Case reports in autoimmune and autoinflammatory disorders

Autoimmune and autoinflammatory disorders include a diverse group of multi-system clinical conditions that are characterized by either autoimmunity or exaggerated and persistent inflammatory responses as their basic mechanisms. In recent years, research investigating the basic science, immunology and translational medicine has played a crucial role in expanding our knowledge of the mechanisms involved in the pathogenesis of autoimmune diseases. Technologies for detecting proteins and small molecules, and the development of system analysis for large amounts of data (enhanced by advances in machine learning and artificial intelligence) have played a central role in identifying new auto-antibodies and mediators of inflammation while further contributing to the definition of the new borders of this evolving field. The availability of new drugs, particularly targeted monoclonal antibodies, immunotherapies and cell-based therapies, has also transformed the management of patients who for decades have experienced the effects of less targeted therapies, such as long-term steroids and anti-inflammatory agents. Given that many of these conditions are both rare and heterogeneous in terms of clinical manifestations and immunological drivers, many large clinical trials have sadly failed to achieve the primary endpoint. However, data from case reports, case series and open-label studies have seen many of these agents adopted for use in clinical practice, particularly in severe, refractory, or atypical cases.

Single case reports contain many elements that may help clinicians to resolve medical conditions in the setting of either challenging or difficult solutions, and represent a reasonable approach that may impact research through the generation of new data that may prompt further future investigation. Publishing case reports also involves an editorial effort associated with the risk that a new finding will not be directly linked to the disease pathogenesis but will represent an epiphenomenon that is useless to report. However, the

simple observation of well-reported cases may provide a solid basis for future discoveries and stimulate further discussion in the field (particularly in rare or atypical cases).

The Research Topicwas not limited to simple descriptions of single cases, but was also open to either systematic reviews of the literature or original research describing proteomics laboratory platforms that focus on exceptional, severe or rare conditions. This first volume of this Research Topic of Frontiers of Immunology was characterized by a wide variety of topics covered, the strong scientific basis of individual reports, and, in those cases describing new therapeutic approaches, the possibility that they may significantly impact clinical medicine.

We commend the reviewers for their efforts in evaluating the quality and interest of the manuscripts submitted for this special edition. Interest in this area was high with 150 submissions in total, nearly half of which were accepted for publication in this Research Topic; this is in line with the general acceptance of the journal and highlights the rigorous evaluation process that the reviewers employed for all submissions.

## Areas covered by volume I

Interestingly, three areas of medicine (Neurology, Dermatology and Rheumatology) accounted for 85% of the published papers, which is in line with the growing innovations that these areas are witnessing. Neurology was the most popular topic (39% of accepted papers), followed by Dermatology (24%) and Rheumatology (22%). Other important areas, such as Hemato-Oncology, Nephrology, Gastroenterology, and Ocular diseases, accounted for 15% of published cases.

When considering specific disorders, encephalitis was the main neurological topic in this Research Topic. This included anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis presenting with atypical features (e.g., psychosis, cerebellar symptoms) and its treatments such as the chimeric anti-CD20 monoclonal antibody-Rituximab) [ (1), Reda et al., Zhang et al., Xu et al.)], anti-Purkinje antibodies in PCA2 encephalitis (Li et al.), and one case of seronegative limbic encephalitis (Los et al.). The treatment of myasthenia gravis with Telitacicept (Zhang et al.) and of autoimmune necrotizing myopathy with the humanized anti-CD20 monoclonal antibody Ofatumumab (Chen et al.) highlights the role of targeting B cells in these diseases and may indicate this as an interesting area for new therapies. Furthermore, the role of TNFα inhibitors (TNF-αi) in neurological disorders was also discussed in one paper in this Research Topic (Kassabian et al.).

Several neurological cases with atypical clinical presentations that required novel laboratory approaches to reach a correct diagnosis were also submitted. Of note, one case involved a patient with Guillain-Barrè syndrome who presented with paralytic ileus. The diagnosis of Guillen-Barrè was reached based on autoimmune tests for anti-sulfatide antibodies, anti-GD1a antibodies, and anti-GT1a antibodies. Based on these results, the patient was treated and rapidly improved after plasma exchange and intravenous immunoglobulin treatment, thus avoiding significant bowel surgery (2). Neuropathic pain as the unique sign of nerve hyperexcitability occurring in the context of autoimmune targeting of the potassium channel complex was described in a young woman presenting with high serum levels of anti-contactin-associated protein-like 2 (Zhu et al.). This case highlights that complete resolution of this specific type of neuropathic pain can be brought about through the use of corticosteroids and immunoglobulin. This case also highlights how pain may be the first clinical sign of a severe pathology that is difficult to treat in advanced stages.

The major focus of the Dermatology collection of articles in this Research Topic was the use of innovative immunotherapies in cutaneous diseases. These included the use of Spesolimab and Secukinumab for psoriasis and Hallopeau acrodermatitis (Wen et al.), the use of Baricitinib with Dupilumab for severe alopecia associated with atopic dermatitis (Fang et al.), the role of Etanercept in necrotic epidermolysis (Jeong et al.), and the first case of perforating collagenosis treated with Baricitinib (Zheng et al.). Adverse events were also reported in a case of dermatomyositis induced by Imatinib (Silva et al.) an antineoplastic drug and tyrosine kinase inhibitor primarily used in the treatment of leukemia and stromal gastrointestinal cancer.

Rheumatology-focused case reports were predominantly descriptive of rare associations, such as VEXAS syndrome (Vacuoles, enzyme E1, X-linked, autoinflammatory, somatic) (Diral et al., Costa et al.), antiphospholipid syndrome (Chicharo et al.), and a case of lethal IL-1 deficiency supported by IL1-rec mutations (Urbaneja et al.). VEXAS syndrome is an acquired autoinflammatory disease that is characterized in the majority of cases by myelodysplastic disorders accompanied by cytopenia, macrocytic anemia, fever, skin vasculitis, and pleuropulmonary disorders. It is believed to be caused by somatic mutations in the UBA1 gene, which lead to the aberrant activation of the innate immune system and the production of proinflammatory cytokines. This Special Issue included descriptions of seven cases of VEXAS syndrome classified according to the 2022 WHO guidelines based on morphological, cytogenetic and molecular characteristics, which may help in proper treatment (Diral et al.). Another reported VEXAS case was a patient who presented atypically with sacroiliitis as an indolent symptom that responded to azacitidine (Costa et al.).

Several reports were submitted on antiphospholipid syndrome, including its association with COVID-19 infection (Li et al.). A case of complex tachycardia with atrioventricular block plus Wolf Parkinson White syndrome (WPW) transmitted to her fetus by a mother positive for anti-SSA antibodies supports the importance of a clear medical characterization before pregnancy in patients with a potential autoimmune condition (Chicharo et al.). Furthermore, a case of rheumatoid arthritis treated with Etanercept who developed aseptic meningitis was reported, indicating that this drug may cross the blood-brain barrier and exert toxicity. This highlights the challenges faced clinically with infections, which are a well-known risk of immunosuppressive therapy (Jeong et al.).

Additional cases included in this volume were the first description of DRESS syndrome following the use of sulfasalazine to treat COVID-

19 (Li et al.), and the successful treatment of Evans syndrome (hemolytic anemia with thrombocytopenia) with JAK inhibition (3). The potential occurrence of renal complications following immunotherapy with humanized monoclonal antibody against the programmed death cell protein (anti-PD1), which is now more frequently being used in the treatment of malignancy, was discussed in a paper reporting a case of IgA glomerulonephritis following pembrolizumab in a patient with non-small cell lung carcinoma (Chabannes et al.). Recognition of the adverse effects of anti-PD1 therapy is very important given the rapid increase in the use of these checkpoint inhibitors (Yang et al.) for different cancer types in which these antibodies are utilized (including melanoma and cancers of major organs such as the liver, lungs, colon, and others).

Autoimmune gastritis is a form of atrophic gastritis that may evolve to gastric neuroendocrine cancer and should be recognized and treated in the early stages. Diffuse homogeneous atrophy of the gastric body is a major endoscopic characteristic of advanced cases, although it is not always present at the onset of the disease. The endoscopic characteristics of two cases of early autoimmune gastritis were described and discussed in this Research Topic. The presence of anti-parietal cell antibodies confirmed the diagnosis in both cases, allowing for direct therapy for the autoimmune condition (Yu et al.).

The Research Topicalso contains two papers that can be considered atypical for a 'Case report collection'. One of these is a systematic review of fifty-three cases of pemphigus associated with end-stage renal failure, in addition to including eight relevant studies on the topic (Yang et al.). The efficacy of major therapies based on immunosuppression was widely discussed. The second paper was an original research study describing a proteomic laboratory platform that focused on patients with exceptionally severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and hypermobility spectrum disorders (Jahanbani et al.). The correct diagnosis of ME/CFS was made by profiling the Th2 cytokine levels, which highlighted a synergistic relationship between mast cells and eosinophils – a finding of interest for potential future biomarker investigations.

## Proposals for volume II

Following the success of Volume I, Volume II proposes to expand on the same topics and serve as a continuation of Volume I. Descriptions of single cases including those in the context of an accompanying review of the literature continue to be encouraged for submission. In addition, systematic reviews of literature on rare conditions are welcome. Original research will be considered if reporting and validating new laboratory assays for identifying biomarkers, such as auto-antibodies and cytokines that either facilitate the diagnosis or potentially anticipate clinical outcomes of autoimmune or auto-inflammatory conditions.

We welcome manuscripts focusing on, but not limited to, the following areas:

- Description of new links between autoimmunity and diseases of any kind
- Identification of new autoantibodies
- Identification of immune mechanisms involved in inflammation.
- Characterization of immune biomarkers of clinical worsening
- Factors predicting relapses and non-response to therapies
- New therapeutic targets and description of 'side effects' with an emphasis on immunotherapies

Therapies will have a special space in Volume II and, in consideration of the incredible evolution that we are witnessing in the area of 'immunotherapies', we hope that Volume II will attract the interest of clinicians involved in testing new human monoclonal antibodies that target specific immune cells (e.g., anti-CD20, anti-CD38 and others) along with cytokines, JAK inhibitors and anti-PD1/PD-1L in cancer. There is a vast area of autoimmune conditions that could potentially respond to newer monoclonal antibodies that is still to be investigated and now represents the new frontier.

Case-control studies of small to medium size also represent an important area in contrast to single cases, and we appreciate studies that present the positive effects of new treatments which could form the basis for important trials in the future. Descriptions of the adverse effects of new therapies are also welcome if they indicate a direct relationship, such as a rapid onset after the start of a therapy or a cessation of symptoms after withdrawal.

Volume I of this Research Topichas outlined that there is still much to learn in the identification and management of autoimmune and autoinflammatory diseases, while effectively demonstrating the value of well-written and highly innovative case reports in supplementing the existing literature.

## Author contributions

GG: Writing – original draft. CW: Writing – review & editing. AV: Writing – review & editing. SV: Writing – review & editing.

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# Case Report: Chronic inflammatory demyelinating polyradiculoneuropathy rather than hemophagocytic lymphohistiocytosis—the initial phenotype of PRF1 gene mutation

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Perforin is essentially involved in the granule-dependent killing activities of cytotoxic T lymphocytes and NK cells. Monoallelic PRF1 mutation increases the risk of autoimmune diseases, and biallelic PRF1 mutation causes familial hemophagocytic lymphohistiocytosis-2. Here, we report a case of a 12-year-old girl with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), followed by a rapidly progressive onset of hemophagocytic lymphohistiocytosis (HLH) 9 months later, alongside manifestations of demyelinating encephalopathy. Genetic sequencing revealed a heterozygous nonsense mutation in the PRF1 gene (c.984G>A; p.W328*) and a heterozygous missense mutation in the PRF1 gene (c.1349C>T; p.T450M). Eventually, she died because of no suitable allogeneic hematopoietic stem cell available in time. Our observations suggest that CIPD might represent the initial phenotype of biallelic PRF1 mutation and could serve as an early sign of subsequent HLH. A comprehensive understanding of this condition is paramount for timely diagnosis, treatment, and ultimately improved patient outcomes.

KEYWORDS

**familial hemophagocytic lymphohistiocytosis, chronic inflammatory demyelinating polyradiculoneuropathy, demyelination of the central nervous system, perforin, perforinopathy**

## Introduction

The pore-forming protein perforin (PRF1), belonging to the membrane attack complex/PRF (MACPF) protein family, is essentially involved in the granule-dependent killing activities of cytotoxic T lymphocytes (CTLs) and NK cells. Serving as a definite marker of the killing ability of immune cells, PRF1 participates in the establishment of immune homeostasis, elimination of pathogens, and tumor surveillance (1, 2). Biallelic mutations in the PRF1 gene account for up to 30% cases of familial hemophagocytic lymphohistiocytosis (FHL). Monoallelic and biallelic mutations of the PRF1 gene have also been verified to increase the risk of the development of autoimmune diseases, such as autoimmune lymphoproliferative syndrome, type 1 diabetes mellitus, and multiple sclerosis (MS). It has been shown that the frequency of missense/nonsense PRF1 variations is increased in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients, and patients with these variants are more likely to experience relapsing processes and axonal damage (3, 4). Previous studies have identified that three missense mutations of the PRF1 gene, c.272C>T, c.11G>A, and c.1153C>T (resulting in the p.Ala91Val, p.Arg4His, and p.Arg385Trp amino acid substitutions, respectively), and one nonsense mutation, c.1267C>T (leading to the premature stop codon p.Gln423Ter), increased the risk of developing CIDP by 4.47-fold (3). However, the relationship between PRF1 gene variants and CIDP is rarely studied and it is unknown whether patients with CIDP who carry biallelic variants in the PRF1 gene will develop FHL2.

## Case data

A 12-year-old girl initially noticed weakness in her left upper extremity without any inducement. This weakness progressed to affect her left lower extremity and right limb, eventually rendering her unable to walk unassisted. She also experienced atrophy in her left limb, numbness in both hands and lower extremities, and pain in both heels. Notably, she did not report double or blurred vision, blepharoptosis, facial weakness, dysarthria, or shortness of breath. Prior to the onset of her symptoms, she had no significant medical problems. Four months after onset, she was admitted to a local hospital because of her inability to stand. Electromyography demonstrated significantly decreased motor nerve conduction velocity. Head magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and spinal MRI results revealed no abnormalities. CSF analysis showed normal white blood cells (WBC) and increased protein levels (1,295.3 mg/L). She was diagnosed with CIDP and initiated treatment with intravenous methylprednisolone (20 mg/kg*3 days) and intravenous immunoglobulin (1 g/kg*2 days) pulse therapy, followed by maintenance steroid (2 mg/kg/day), which partially improved her symptoms. However, during the process of oral steroid reduction, CIDP symptoms worsened repeatedly, promoting an increase in oral steroid dosage by her parent. Approximately 9 months after symptom onset, the girl experienced recurrent fever; at the beginning, low fever was not paid attention to, and the peak temperature gradually increased, worsening limb weakness. She was sent to a local hospital again. Blood test results indicated pancytopenia, mild abnormal liver function, slight decrease in Fib, and significantly elevated C-reactive protein, but no specific pathogen was found. As anti-infective therapy was ineffective and her condition deteriorated, she was referred to our hospital.

Upon admission, her body temperature was up to 39.8°C, and there were two to three heat peaks every day; physical examination demonstrated a pale complexion and hepatosplenomegaly. Neurological examination revealed asymmetrically reduced muscle strength in her limbs, with a Medical Research Council (MRC) score of 3/5 in the left upper limb, 4/5 in the right upper limb, and 2/5 in both lower limbs. Additionally, she exhibited apparent limb atrophy, absent tendon reflexes, impaired perception of temperature, light touch, and pinprick in the limbs, with normal cognition and cranial nerves. Blood test results indicated pancytopenia, increased serum ferritin (>2,000 ng/mL), elevated triglyceride (2.7 mmol/L), and decreased fibrinogen (1.17 g/L). Further tests, including blood culture, EBV DNA, BCG, antinuclear antibody, and anti-ENA antibody showed negative results. The morphology results of medullary cell analysis revealed hemophagocyte. CSF analysis showed normal WBC counts, increased protein levels (1,532.6 mg/L), elevated myelin basic protein (MBP) levels (4.78 nmol/L), and a positive oligoclonal band (OB). Spinal cord MRI results showed abnormal signal in the cervical vertebra and the 3rd lumbar vertebra foramina, extending beyond the spinal canal. Cervical and lumbosacral plexus MRN results revealed extensive enlargement of the brachial plexus trunk and lumbosacral plexus nerve (Figures 1A-1). Fiber track results revealed markedly thickened nerve fibers (Figures 1A-2). Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) results also showed an increased 18F-FDG uptake in the thickening plexus nerve, but not elsewhere. Electromyography results exhibited significantly decreased motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) in the bilateral peroneal nerve, tibial nerve, and median nerve. It also revealed a vanished F-wave reflex in the left peroneal nerve and significantly prolonged F-wave latency in the left ulnar nerve (Table 1). Based on the patient's history, clinical manifestations, laboratory findings, and physical examination, a diagnosis of both CIDP and HLH was confirmed.

Regarding family history, one of her younger brothers died of HLH at the age of 3. Therefore, primary HLH was suspected, and exon sequencing revealed a heterozygous nonsense variation in the PRF1 gene (c.984G>A; p.W328*) and heterozygous missense variation in the PRF1 gene (c.1349C>T; p.T450M). The protein damage prediction results were analyzed by SIFT, PolyPhen-2, and MutationTaster. The c.1349C>T heterozygous missense variation is harmful and pathogenic, whereas c.984G>A heterozygous nonsense variation is suspected to be pathogenic. The abovementioned mutations might have caused the protein function to be affected. The mutation site c.1349C>T (p.T450M) had been reported in patients affected by FHL2 (https://www.ncbi.nlm.nih.gov/clinvar). While the pathogenicity of the variation c.984G>A has not been reported, nor has it been included in the dbSNP database. None of the abovementioned variations were polymorphic changes, which

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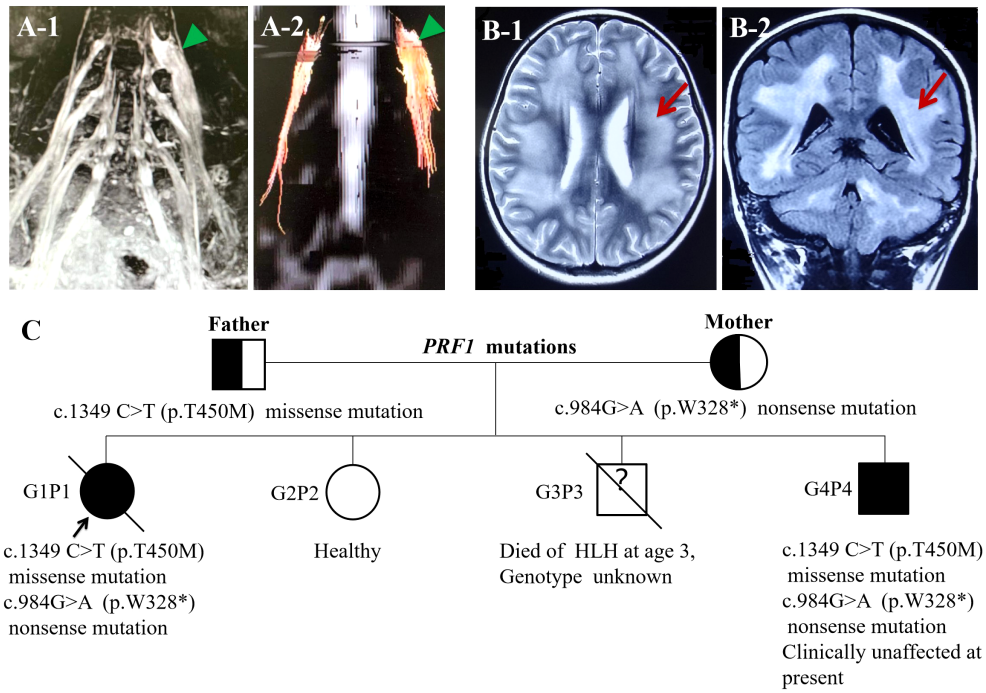



FIGURE 1
**(A-1)** Lumbosacral plexus MRN: lumbosacral plexus hypertrophy and hypersignal. **(A-2)** Fiber track showed markedly thickened nerve fibers. **(B)** Head MRI: **(B-1)** axial T2WI demonstrated the change of diffused, symmetrical long T2 signal in white matter of cerebral hemispheres. **(B-2)** Coronal FLAIR images revealed the change of generalized, symmetrical high signal in white matter of cerebral hemispheres and cerebellar hemispheres. **(C)** Identified complex heterozygous mutations in the PRF1 gene, c.1349 C>T (p.T450M) (paternal), and c.984>A (p.W328*) (maternal); G3P3 died of HLH at the age of 3 with an unknown genotype; G4P4 carried the same complex heterozygous mutations in the PRF1 gene and clinically unaffected.

have an extremely low frequency of occurrence in the population. The compound heterozygous variants found in the PRF1 gene of the patient were inherited from their parents. According to the American College of Medical Genetics (ACMG) guidelines, the above variants might be pathogenic variants that caused the onset of the disease. She was ultimately diagnosed with FHL2. Another 3.5-year-old brother of the patient carried the same complex heterozygous mutations in the PRF1 gene but was clinically unaffected at present (Figure 1C).

During hospitalization, she developed demyelinating encephalopathy before the commencement of the HLH-2004 therapeutic regimen, as evidenced by brain MRI, which revealed generalized, symmetrical demyelinating in white matter of the cerebrum and cerebellum hemisphere (Figures 1B-1, B-2), and EEG results indicated a slow wave, although subsequent HLH-2004 protocol provided some improvement. The lack of suitable allogeneic hematopoietic stem cells (HSCs) led to disease recurrence and severe lung infections, ultimately resulting in her passing.

## Discussion

FHL caused by the PRF1 gene is common; however, in this case, the patient experienced symptoms of CIPD for 9 months before the onset of HLH. No direct connections between these two diseases have been reported. It is well known that perforin is important for effector functions of cytotoxic T cells and natural killer (NK) cells. Abnormal or absent perforin function because of *PRF1* mutation could lead to impaired killing of target cells, uncontrolled T-cell activation, and high levels of inflammatory cytokines, in turn altering immune system activation and resulting in inflammation and risk of autoimmunity (5).

CIDP is an autoimmune-mediated demyelinating polyneuropathy with chronic progression or remission, resulting from a synergistic interaction of cellular and humoral immune responses. Pathological manifestations include multifocal demyelination of myeloid fibers, endoneuron edema, and inflammatory cell infiltration. Although the etiology and exact pathogenesis remain elusive, clonal expansion of cytotoxic T cells has been observed in the blood and peripheral nerves of patients with CIDP (6, 7). Monoallelic and biallelic pathogenic variations in the PRF1 gene have also been described in patients with CIDP (3, 8). HLH is a multisystem inflammatory disorder; biallelic PRF1 gene pathogenic mutations cause FHL-2, which is characterized by sustained overactivation and excessive proliferation of T lymphocytes and macrophages and increased cytokine levels, leading to infiltration and damage of organs including the bone marrow, liver, and spleen. Thus, we believe that both CIDP and HLH are the result of overactivation of T cells and a cytokine storm.

However, the isolated neurologic manifestations preceding HLH have long been regarded as initial manifestations of primary HLH. A list of child cases that were diagnosed with neurological diseases over the years, including CNS demyelination, MS, intracranial infection, or AIDP, which were later confirmed to

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TABLE 1 The results of electromyography.

| Coaxial single-core needle electrode | | | | | | | |
|---|---|---|---|---|---|---|---|
| Muscle | Voluntary activity | Motor unit potential during light contraction | | | | Motor unit potential during repeated contraction | |
| | | Duration (msec) | Change | Voltage (mV) | Polyphasic | Wave shape | Peak voltage |
| Left abductor pollicis brevis muscle | – | 11.9 | ↑ 38% | 1,781 | 11% | Simple phase | 1.6 |
| Left anterior tibialis muscle | – | 13.6 | ↑ 33% | 1,108 | – | Simple phase | 1.8 |
| Left quadriceps | – | 18.8 | | 373 | – | Simple phase | 1.4 |

| Motor nerve conduction | | | | | |
|---|---|---|---|---|---|
| Nerve | Latency (msec) | | Amplitude (mV) | | Conduction velocity (m/s) |
| | Proximal | Distal | Proximal | Distal | |
| Left common peroneal | No response | | | | |
| Right common peroneal | 13.0 | 4.2 | 0.3 | 0.6 | 26.1 |
| Left tibial | 14.3 | 4.2 | 1.5 | 3.2 | 29.7 |
| Right tibial | 12.7 | 3.7 | 1.6 | 3.4 | 33 |
| Left median | 8.7 | 2.8 | 3.2 | 3.4 | 27.1 |
| Left ulna | 7.6 | 2.6 | 4.3 | 5.0 | 44 |

| Sensory nerve conduction | | | |
|---|---|---|---|
| Nerve | Latency (msec) | Amplitude (μV) | Conduction velocity (m/s) |
| Left sural | 2.1 | 7.7 | 57.1 |
| Left ulna | 2.1 | 1.5 | 42.9 |
| Left median | 2.8 | 1.1 | 42.9 |

| F wave | | |
|---|---|---|
| Nerve | Latency (msec) | Occurrence rate |
| Right common peroneal | No response | |
| Left ulnar | 450 | 15% |

↑, elevated; -, no.

have biallelic PRF1 gene pathogenic variations, is summarized in Table 2 (9–22). In a total of 24 children (including this case), from the onset of neurological symptoms to the final genetic diagnosis, the shortest time was 1 month, the longest time up to 5 years, and one-third of the patients had a brain biopsy. All patients who did not undergo hematopoietic stem cell transplantation (HSCT) died. In fact, it turns out that HLH diagnosis and initiation of treatment have always been delayed. We propose that neuropathy should not be considered a common early-onset symptom of HLH, because the diagnostic criteria for HLH do not encompass the characteristics of autoimmune-mediated neuropathy (23). When the neuropathy, such as CIDP in this case, manifests before HLH, there is a high probability that the diagnosis will be limited to neuropathy, and immunotherapy may mask early signs and symptoms of systemic involvement which can result in a missed optimal treatment window when typical HLH eventually presents (9–22). Early diagnosis is essential for better therapeutic approaches, challenging the existing viewpoint and redefining the relationship between CIDP and HLH. The term "perforinopathy" has been proposed to describe the broad-spectrum manifestations resulting from perforin deficiency caused by abnormalities in the PRF1 gene (24). As in this case, in addition to CIDP, the patient also developed leukoencephalopathy before the commencement of the HLH-2004 therapeutic regimen, and subsequent to treatment with the HLH-2004 protocol, the leukoencephalopathy gradually alleviated. Based on this progression, we attribute both CIDP and leukoencephalopathy to an immune inflammatory damage triggered by the PRF1 gene mutation. HLH represents just one

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TABLE 2 PRF1 gene mutation loci with the nerve system as initial or isolated phenotype and characteristic analysis.

| No. | PRF1 gene mutation | Sex | Age at symptom onset | Time to diagnosis of FHL | Diagnostic method | Diagnosis of neurological disorders | Outcome |
|---|---|---|---|---|---|---|---|
| PRF1 gene mutation loci with CNS as first or isolated phenotype | | | | | | | |
| 1 (9) | c.1376C>T(p.P459L)<br>c.1376C>T(p.P459L) | M | 5 ms | 7 ms | Gene test | Severe and progressive encephalitis | Died |
| | c.1376C>T(p.P459L)<br>c.1376C>T(p.P459L) | F | 7 ms | 26 ms | Gene test | Aseptic meningitis | Died |
| 2 (10) | c.136G>U (p.Glu46stop)<br>c.272C>T (p. Ala91Val)<br>c.355A>U (p.Arg119Trp) | F | 3 ys 6 ms | 11 ms | Brain biopsy→ gene test | CNS vasculitis<br>ITP | HSCT |
| 3 (11) | c.508A>C(p.S170R)<br>c.727G>T(p. E243X) | F | 1 y 6 ms | Around 1–2 ms | Brain biopsy→ gene test | Septic emboli to the brain | HSCT |
| 4 (12) | c.1066C>T(p.R356W)<br>c.1349C>T(p.T450M) | M | 16 ys | 24 ms | Autopsy→ gene test | Demyelinating disorder | Died |
| 5 (13) | c.673C>T (p.R225W)<br>c.673C>T (p.R225W) | F | 12 ys 10 ms | Around 4 ms | Gene test | Brain lymphoma? | HSCT |
| 6 (14) | c.673C>T (p.R225W)<br>c.673C>T (p.R225W) | F | 1 y 10.5 ms | 38.5 ms | Gene test | Neurodegenerative disorder | Died |
| | c.673C>T (p.R225W)<br>c.673C>T (p.R225W) | F | 6 ys 3.5 ms | 1 y 3.5 ms | Gene test | Neurodegenerative disorder | Died |
| 7 (15) | c.394G>T (p.GLY132ARG)<br>c.394G>T (p.GLY132ARG) | M | 14 ys | 5 ys | Brain biopsy→ gene test | Unknown | HSCT |
| | c.148G>A(p.Val150MET)<br>c.673C>T (p.R225W) | F | Unknown (saw doctor at the age of 2.5 ys | Unknown | Brain biopsy→ gene test | Encephalitis | Condition deteriorated |
| 8 (16) | c.50delT(p.17fs)<br>c.1229G>C (p.R410P)) | F | 15 ms | Around 1–2 ms | Gene test | CNS demyelination? | HSCT |
| 9 (17) | c.452A>T (p.H151L)<br>c.666C>A (H222Q) | F | 5 ys | 60 ms | Brain biopsy→ gene test | Demyelinating CIS<br>CLIPPERS | HSCT |
| | c.443C>G (p.A148G)<br>c.666C>A (H222Q) | F | 6 ys | 24 ms | Brain biopsy→ gene test | ADEM<br>MDEM | Relapse occurred 9 months after HSCT |
| 10 (18) | c.634T>C(p.Y212H)<br>c.1083_1094Del (p.361_364del) | F | 1 y 5.5 ms | 12 ms | Gene test | CNS demyelination | Died |
| | c.1349C>T(p.T450M)<br>c.853_855del(p.285delK) | F | 4 ys 11 ms | 14 ms | Gene test | ADEM<br>MS | HSCT |
| | c.1349C>T(p.T450M)<br>c.1306G>T(p.D436Y) | F | 9 ys | 37 ms | Gene test | MS | HSCT |
| | c.65delC(p.22Rfs*2)<br>c.148G>A(p.V50M) | M | 1 y 8.5 ms | 2 ms | Gene test | CNS demyelination | HSCT |
| 11 (19) | c.4422G>A<br>c.4422G>A | M | 5 ys | 12 ms | Gene test | ADEM | HSCT |
| | c.4422G>A<br>c.4422G>A | M | 2 ys | 1 m | Gene test | Genetic leukodystrophy | HSCT |
| 12 (20) | c.1189_1190dupTG (p.H398Afs*23)<br>c.394G>A(p.G132R) | F | 2 ys 7 ms | 7 ms | Gene test | Mitochondrial encephalopathy? | HSCT |
| | | M | 4 ys 11 ms | 10 ms | Gene test | | Died |

*(Continued)*

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TABLE 2 Continued

| No. | PRF1 gene mutation | Sex | Age at symptom onset | Time to diagnosis of FHL | Diagnostic method | Diagnosis of neurological disorders | Outcome |
|---|---|---|---|---|---|---|---|
| | c.1189_1190dupTG (p.H398Afs*23) c.394G>A(p.G132R) | | | | | CNS infection; demyelinating disease; metabolic acidosis | |
| 13 (21) | c.1519G>T; (p.Glu507Ter) | M | 6 ys 5 ms | 11ms | Brain biopsy→ gene test | Tuberculous meningitis; CNS vasculitis; MS | Died |
| | c.1349C>T; (p.Thr450Met) | | | | | | |
| PRF1 gene mutation loci with PNS as first or isolated phenotype | | | | | | | |
| 14 (22) | c.694C>T (Arg232Cys) c.1191insTG (His398fsX32) | M | 6 ys | 1 m | Gene test | AIDP | Died |
| 15 | c.1349C>T (p.T450M) c.985G>A (p.W328X) | F | 11 ys 3 ms | 9 ms | Gene test | CIDP | Died |
| Other PRF1 gene mutation loci with CIDP as isolated phenotype | | | | | | | |
| 16 (3) | c.272C>T (p. Ala91Val) c.272C>T (p. Ala91Val) | Patients carrying PRF1 variations displayed increased frequency of relapsing forms and axonal damage compared with the other patients. In particular, the presence of PRF1 variations increases the risk of developing relapsing forms by fourfold and axonal damage by 5.3-fold. | | | | | |
| | c.272C>T (p. Ala91Val) c.11G>A (p.Arg4His) | | | | | | |
| | c.272C>T (p. Ala91Val) (Monoallelic mutation) | | | | | | |
| | c.1153C>T (p.Arg385Trp) (Monoallelic mutation) | | | | | | |
| | c.1267C>T (p.Gln423Ter) (Monoallelic mutation) | | | | | | |

ADEM, acute disseminated encephalomyelitis; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CIS, demyelinating clinically isolated syndrome; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; ITP, immune thrombocytopenic purpura; MDEM multiphasic ADEM; MS, multiple sclerosis; PNS, peripheral nervous system. →, followed by.

extreme on the spectrum of diseases caused by PRF deficiency. A comprehensive understanding of this concept is crucial for early diagnosis, early treatment, and improved patient prognosis.

Considering the potential association between the genetic etiology and inevitable development of primary HLH, the occurrence of CIDP may serve as an early warning sign. It has been reported that patients with CIDP carrying PRF1 variations exhibit a higher incidence of relapsing forms and increased likelihood of axonal damage compared with those without these variations. The presence of PRF1 gene variations elevates the risk of developing relapsing forms by fourfold and experiencing axonal damage by 5.3-fold. In contrast, no significant difference was detected in terms of gender distribution, disease duration, INCAT disability score, response to first- and second-line treatment, development of dysautonomia, and CNS involvement (3). In our case, the child also manifested axonal injury with a recurrent course. As such, promotion of genetic analysis is recommended for CIDP patients demonstrating recurrent forms and signs of axonal damage. This allows for a window of opportunity for preparation prior to allograft HSCT, including HLA typing and suitable donor searching, thereby avoiding irreversible consequences such as death.

For the patient's younger brother, who carries the same complex heterozygous PRF1 gene pathogenic mutations but shows no clinical signs of HLH or "perforinopathy", the molecular analysis was sufficient for an FHL2 diagnosis. He received allogeneic HSCT before the onset of "perforinopathy" and is currently in good health.

## Conclusion

This case highlights the potential for a neurological presentation of "perforinopathy" with CIDP as its initial manifestation. Awareness of this condition is crucial before the onset of HLH, because the disease is treatable. Certainly, for those patients with evidence of a genetic defect, allogeneic HSCT is strongly recommended, as it remains the only curative treatment for primary HLH to date.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by The Ethics Committee of Chinese PLA General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

L-YH: Data curation, Formal analysis, Investigation, Writing – original draft. LW: Data curation, Formal analysis, Investigation, Writing – original draft. Q-HW: Data curation, Formal analysis, Investigation, Writing – original draft. X-YS: Supervision, Validation, Writing – review & editing. YM: Supervision, Validation, Writing – review & editing. X-FY: Validation, Writing – review & editing. GY: Conceptualization, Supervision, Validation, Writing – review & editing. L-PZ: Conceptualization, Supervision, Validation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Anti-SRP immune-mediated necrotizing myopathy responsive to ofatumumab: a case report

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**Background:** Immune-mediated necrotizing myopathies (IMNM) is a rare disease that was first described in 2004. Due to the lack of large case series, there are no formal treatment recommendations for IMNM.

**Methods:** We presented a case of a 47-year-old woman who experienced progressive limb weakness, starting from the lower limbs and gradually affecting the upper limbs. She also reported experiencing dyspnea after engaging in daily activities. When she was admitted to the hospital, her upper limbs were almost unable to move and she could not stand even with support. Her Creatine kinase (CK) level significantly increased (> 3500 u/l). Electromyography showed myogenic damage, anti-Signal recognition particle (anti-SRP) and anti-Ro52 antibodies were highly positive. Pathological biopsy of the right biceps muscle showed necrotizing myopathy in the skeletal muscle. She was ultimately diagnosed with anti-SRP IMNN, and was given monotherapy with methylprednisolone and combination therapy with immunoglobulin, but her symptoms continued to worsen. The patient refused to bear the possible further liver dysfunction and blood system damage caused by Cyclophosphamide and Rituximab, and she chose to try to use Ofatumumab (OFA).

**Results:** After receiving three doses of OFA treatment without any adverse reactions, she reported that her muscle strength had basically recovered and she was able to walk independently. The B cells in the circulatory system have been depleted, and blood markers such as liver function have consistently remained within normal range. During the follow up, her activity tolerance continued to improve.

**Discussion:** We have presented a severe case of SRP-IMNM in which the patient showed poor response to conventional immunotherapy. However, rapid symptom relief was achieved with early sequential use of OFA treatment. This provides a new option for the treatment of SRP-IMNM, and more large-scale studies will be needed in the future to verify our results.

KEYWORDS

**anti-SRP, immune-mediated necrotizing myopathy, ofatumumab, OFA, case report**

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## Case report

A 47-year-old woman presented to the gastroenterology outpatient clinic with elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measuring 211IU/L and 280IU/L respectively. She only presented a slight fatigue, and the laboratory examination showed a high positive Hepatitis A Virus-IgG (HAV-IgG) antibodies and antinuclear antibody (ANA) greater than 1:1000. She has no underlying medical conditions and she had received regular annual physical examination on March 2023. The result of chest CT showed no abnormalities at that time. Therefore, she was diagnosed with AIH despite the lack of liver biopsy evidence. She received the treatment of entecavir 10mg q.d and prednisone 4mg q.d for two months, but her liver function and physical endurance did not show evident improvement. After infected with coronavirus-19 (COVID-19), and her condition rapidly deteriorated, as she began experiencing difficulties in lifting her neck, walking, holding objects with both hands, and even developed dyspnea during moderate activities. When she was admitted, the muscle power of Grade 2 (MMT8 score) proximal, Grade 3 distal muscle strength of the limbs, and Grade 2 the head raising and neck flexion muscle strength without significant muscle atrophy or fasciculation. Tendon reflexes were absent, Babinski's sign, sensory and autonomic abnormalities were negative.

The laboratory examination revealed a significant increase in levels of creatinine kinase (CK) and myocardial markers (Table 1). Electromyography (EMG) showed typical features of myopathic impairments (Supplementary Material). Myositis-specific autoantibodies including anti-SRP and anti-Ro52 antibody were high positive (+++). Biopsy of the right biceps brachii muscle showed necrotizing myopathy with minimal local inflammation (Figure 1). Echocardiography (ECHO) showed a small amount of pericardial effusion, and electrocardiogram showed abnormal ST-T segment changes. Further examinations did not reveal the presence of an underlying tumor, and the patient denied having any other diseases. She was diagnosed with SRP- IMNM according to the new European Neuromuscular Centre criteria (1).

The patient was initially treated with methylprednisolone for 5 days (1 g/day), but her muscle weakness became progressively worsened (Grade 1 the head raising and neck flexion muscle strength, Grade 1 proximal and Grade 2 distal muscle strength of the limbs), with dysphagia and more severe dyspnea. She underwent high-resolution chest CT immediately, which revealed mild interstitial changes in her lungs. Then, she received intravenous IVIG (0.4mg/kg/d) for 5 days, but her condition was not attenuated. Sequential immunotherapy with a second round of IVIG, rituximab (RTX), cyclophosphamide and OFA was recommended. However, the patient and her guardians chose OFA but refused other recommendations because they worried about the potential side effects especially the impairment of liver function.

On the second day after the completion of IVIG, she received the first dose of OFA (20 mg) *via* subcutaneous injection. On the second day of first OFA therapy, her muscle strength of limbs and dyspnea were markedly improved (the head raising and neck flexion muscle strength recovered to Grade 2, and distal muscle strength of the limbs recovered to Grade 3), and the absolute B cell counts decreased from 314 to 29 (cell/ul). The patient received the second and third needle of OFA once a month, and the dose for these two injections was 20mg each. Her activity tolerance continued to improve, and B cell remained at a relatively low level during the use of OFA (Figure 2). The changes of her clinical symptoms during the treatment are shown in Table 2. Myocardial markers, ECG and ECHO returned to normal, but the EMG at two follow-up visits showed that nerve conduction velocities in the extremities were normal but without any improvement in the typical myopathy features (Supplementary Material).

TABLE 1 Auxiliary examinations in this patient.

| Items | *value* | Reference range |
|---|---|---|
| CK (u/l) | 5437 | 20-140 |
| LDH (u/l) | 958 u/l | 120-250 |
| Creatinine (ng/ml) | 22 | 48-79 |
| Hemoglobin (ng/ml) | 401.4 | 115-150 |
| Myoglobin (ng/ml) | 824.80 | <58.0 |
| CK-MB (ng/ml) | >300.00 | <2.88 |
| Troponin-T (ng/ml) | 2369.0 | 0-14 |
| NT-pro-BNP (g/l) | 220.0 | 0-153 |
| ALT (umol/L) | 211 | <40.0 |
| AST (umol/L) | 280 | <35.0 |
| Bilirubin (umol/L) | 9.0 | 5.0-28.0 |
| CER (mg/L) | 252 | 210-530 |
| ANA | 1:1000 | negative |
| C3 (ng/l) | 0.7150 | 0.758-1.520 |
| C4 (ng/l) | 0.1100 | 0.145-0.360 |
| Ferritin (ng/l) | 401.1 | 15-200 |
| High precision HBV load (IU/ml) | negative | negative |
| D-dimer (mg/u) | 0.74 | <0.55 |
| Fibrinogen (g/l) | 1.75 | 2.0-4.0 |
| Tumor markers | negative | negative |
| IgG4 | negative | negative |
| IgG/A/M | negative | negative |
| gamma-globulin | negative | negative |
| Other autoimmune antibodies | negative | negative |

CK, Creatine kinase; LDH, lactic dehydrogenase; CK-MB, Creatine kinase isoenzyme; NT-pro-BNP, N-terminal fragment brain natriuretic peptides; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CER, Ceruloplasmin; ANA, Antinuclear antibody. C3, Complement C3; C4, Complement C4; IgG/A/M, Immunoglobulin G/A/M.

## Discussion

The present case was initially diagnosed as AIH. Although both ALT and AST levels can be derived from liver and muscle, ALT is

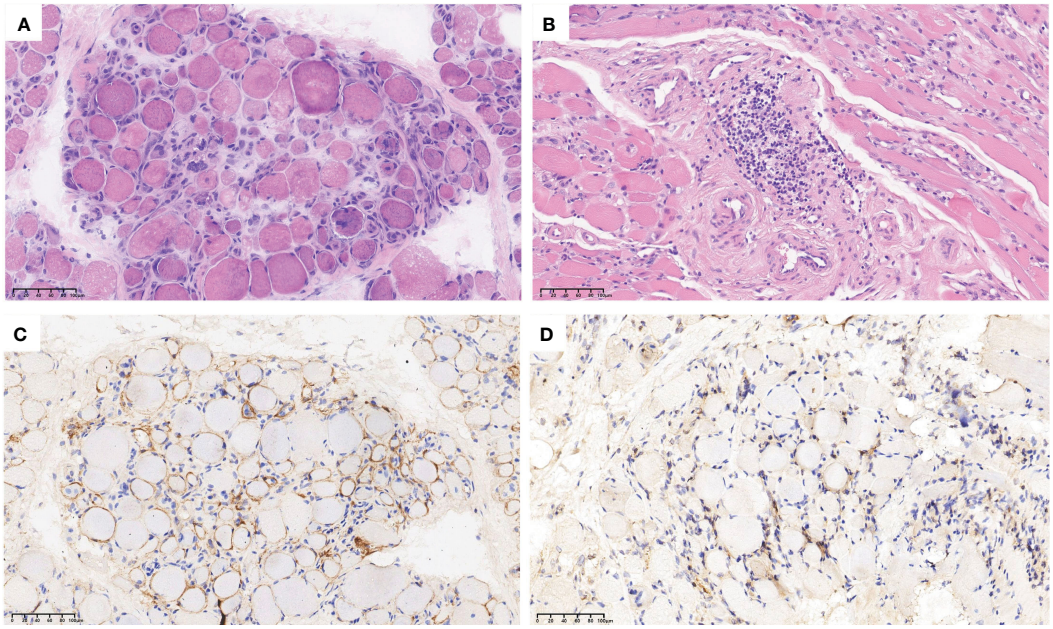



FIGURE 1
Histopathological and immunohistochemical analysis (H&E) revealed a significant presence of degenerated, necrotic, and regenerating muscle fibers with heterogeneous sizes **(A)**; Around the perimysium of small blood vessels, there were clusters and infiltration of lymphocytes **(B)**; C5b-9 showed strong positivity on the muscle fiber membrane **(C)**; MHC-I was also expressed on the muscle fiber membrane **(D)**.

mainly derived from the liver, while AST is primarily derived from the heart and muscle (2). In this patient, the significantly higher AST compared to ALT, without any cardiac involvement, raised concerns about muscle damage. In addition, a recent study found that some IMNM patients may remain asymptomatic for a long time, with only abnormalities in liver enzymes (3). Therefore, abnormal liver function may be a subclinical manifestation in IMNM; CK and EMG examinations are helpful for the diagnosis.

Our patient experienced a significant worsening of clinical symptoms following the COVID-19 infection. Several case reports have been published regarding IMNM associated with COVID-19 infections (4–6). These reports highlighted the potential connection between infections and the exacerbation of IMNM symptoms. COVID-19 may cause IMNM either by infecting muscle fibers directly or by activating the complement system by virus-antibody complexes and viral toxin deposition (7). Interestingly, the patient's symptoms showed significant improvement after OFA treatment, although there were no significant changes observed in the EMG results. It is possible that the already necrotic muscle cells were too severe to be salvaged or that the follow-up time was not sufficient to observe changes in the EMG. However, the decrease in spontaneous potential does suggest a controlled progression of the acute phase.

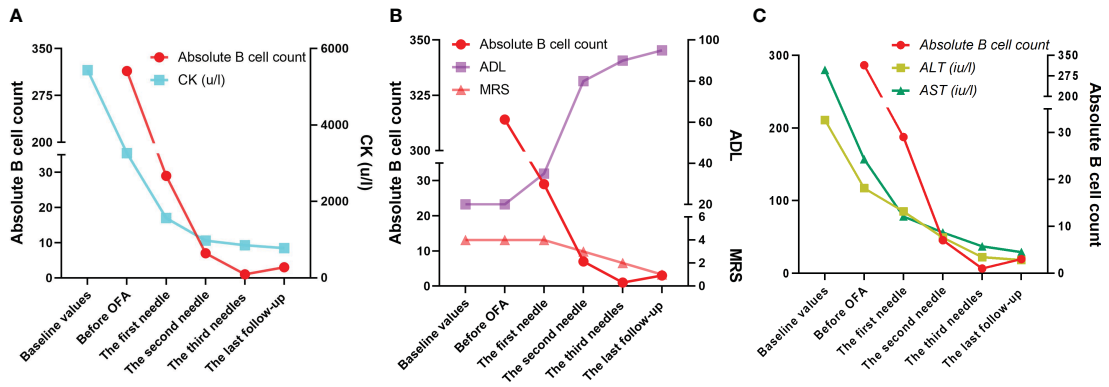



FIGURE 2
During treatment with OFA, the patient's CK level declined in line with his absolute B-cell count **(A)**. The MRS scores increased with the decrease of absolute B cell count, but the ADL scores increased significantly, indicating that her ability of daily living was significantly improved **(B)**. ALT and AST levels decreased as the patient's absolute B-cell count decreased, and both normalized by the second dose of OFA **(C)**. OFA, Ofatumumab; CK, Creatine Kinase; MRS, Modified Rankin Scale; ADL, Activity of Daily Living Scale; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

TABLE 2 Changes in clinical symptoms during the medical treatment.

| | | Onset time of treatment | Progressive disease progression | The first injection OFA | The second day OFA | The second injection OFA | The third injection OFA | The last follow-up |
|---|---|---|---|---|---|---|---|---|
| | Time | On April 15, 2023 | On April 20, 2023 | On April 25, 2023 | On April 26, 2023 | On May 25, 2023 | On June 22, 2023 | On August 25, 2023 |
| | Medication | Methylprednisolone | IVIG, Prednisone | OFA, Prednisone | OFA, Prednisone | OFA, Prednisone | OFA | OFA |
| Muscle strength (MMT8) | Proximal left upper limb | 2 | 1 | 1 | 1 | 3 | 3 | 3 |
| | Distal left upper limb | 3 | 2 | 2 | 3 | 4 | 4+ | 4+ |
| | Proximal right upper limb | 2 | 1 | 1 | 1 | 2+ | 3 | 3 |
| | Distal right upper limb | 3 | 2 | 1 | 3 | 4 | 4+ | 4+ |
| | Proximal left lower limb | 2 | 1 | 1 | 1 | 3 | 4 | 4 |
| | Distal left lower limb | 3 | 2 | 2 | 3 | 4 | 4 | 4 |
| | Proximal right lower limb | 2 | 1 | 1 | 1 | 2+ | 3+ | 4 |
| | Distal right lower limb | 3 | 2 | 1 | 3 | 4 | 4 | 4 |
| | Head raising muscle | 2 | 1 | 1 | 2 | 4 | 5 | 5 |
| | Neck flexion muscle | 2 | 1 | 1 | 2 | 4 | 5 | 5 |
| Other symptoms | Dyspnea (yes/no) | yes | yes | yes | no | no | no | no |
| | Dysphagia (yes/no) | no | yes | yes | yes | no | no | no |

MMT8, manual muscle test; OFA, Ofatumumab.





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Anti-B cell therapy is currently being explored as a potential treatment for IMNM (8). However, when second-line therapies including anti-B cell therapy should be initiated, is still in the exploratory stage. In a study involving 18 IMNM patients treated with RTX, it was observed that more than half of these patients experienced either no or only partial clinical remission. The authors suggested that this outcome may be attributed to the delayed administration of RTX (1). A recent case reported the efficacy of OFA in treating refractory SRP-IMNM (9). Unlike RTX, OFA is a human IgG1 monoclonal antibody against which prevents the risk of antidrug-antibodies production. A previous study has found that the patient who had severe adverse reactions to the infusion of RTX can still be safely and effectively treated with OFA (10). OFA also has the ability to increase B cell binding affinity and enhance complement-dependent cytotoxicity (11). Other studies have also demonstrated the significant therapeutic effects of OFA for conditions resistant to RTX, such as nephrotic syndrome and other systemic autoimmune diseases (12, 13).

We presented a case of severe IMNM in which early administration of OFA was initiated. This patient experienced difficulties with swallowing and breathing as the disease progressed. Despite receiving high-dose methylprednisolone and IVIG treatment, there was no improvement. However, these symptoms rapidly improved following OFA treatment. The rapid clinical improvement observed following OFA treatment and the close correlation between circulating B cell counts and clinical presentation suggest a significant role for OFA in the treatment of SRP-IMNN. In addition, this patient did not report any adverse effects and she has a continued improvement in liver function during the administration of OFA, suggesting the safety and well tolerated of OFA.

Our case is different from the previous case (9). Our patient was treated with OFA the day after the end of IVIG treatment, whereas that case started OFA 10 days after the end of conventional immunotherapy. Our patient seems to have faster clinical remission than that patient. Previous studies have also shown that delayed use of RTX may not be conducive to the improvement of clinical symptoms in patients with IMNM (1). Actually, our study explores the potential of "triple therapy," incorporating OFA, and proposes that earlier initiation of OFA treatment may offer greater benefits to patients with severe SRP-IMNM. From the mechanism of drug action, IVIG has unique advantages for pre-existing autoimmune antibodies in the circulatory system. IVIG has a broad-spectrum effect against normal human proteins and some special antibodies, allowing it to rapidly neutralize autoimmune antibodies. However, there was no significant effect on pathogenic B cells (12). OFA plays a role mainly through the combination of two unique epitopes on CD20-expressing B cells, inducing the lysis and elimination of pathogenic B cells and reducing the re-production of autoimmune antibodies (13). Therefore, IVIG and OFA may have a synergistic effect in the treatment of IMNM, and earlier sequential use of OFA may provide greater benefit to the severe SRP-IMNM patients.

Although significant efficacy has been observed, we still need further follow-up to clarify the role of OFA in long-term prognosis and recurrence of SRP-IMNN patients.

## Conclusion

Early or asymptomatic anti-SRP-IMNN should be differentiated from liver disease. For severe anti-SRP-INMN patients with a poor response to conventional immunotherapy, early sequential OFA therapy may be an effective, safe, and convenient choice.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Ethics Committee of West China Hospital, Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

SC: Data curation, Investigation, Writing – original draft, Writing – review & editing. JY: Investigation, Resources, Supervision, Writing – review & editing. DH: Data curation, Resources, Supervision, Writing – original draft. JF: Data curation, Writing – review & editing. XL: Data curation, Writing – review & editing. BZ: Data curation, Resources, Writing – review & editing. XC: Resources, Supervision, Writing – review & editing. HS: Data curation, Resources, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1301109/full#supplementary-material

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# Case report: Excessive daytime sleepiness as a presenting manifestation of autoimmune glial fibrillary acidic protein astrocytopathy

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Autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) is a recently discovered autoimmune inflammatory disease of the central nervous system. It presents with a variety of clinical symptoms, including fever, seizures, psychiatric symptoms, limber weakness, and sensory symptoms. However, the symptoms of sleep disorders have not been sufficiently addressed. Here, we report a case of GFAP-A in which the patient complained of excessive daytime sleepiness and an excessive need for sleep. Our patient was a 58-year-old male who experienced excessive daytime sleepiness for 50 days following SARS-CoV-2 infection. He was diagnosed with coronavirus disease 2019 on June 1st. On the 7th of June, he experienced excessive daytime sleepiness, nausea, reduced food intake, lower limb weakness, and dysuria. Subsequently, his sleepiness significantly deteriorated on July 21st. Five months prior, the patient underwent laparoscopic partial right nephrectomy for clear-cell renal cell carcinoma. Brain MRI revealed abnormal hyperintense lesions in the pontine brain and around the mesencephalic aqueduct on T2 and T2-fluid attenuated inversion recovery (T2-FLAIR) sequences However, these lesions did not exhibit any pathological enhancement. Spinal cord MRI revealed lesions in the C6–C7 and T2–T3 segments on the T2 sequence. His Epworth Sleepiness Scale (ESS) score was 16 (reference range, <10), and 24-hour polysomnography supported the diagnosis of rapid-eye-movement sleep disorder and severe sleep apnea-hypopnea syndrome. Glial fibrillary acidic protein IgG antibodies were detected in the cerebrospinal fluid (1:32, cell-based assay) but not in the serum. The level of hypocretin in the cerebrospinal fluid was 29.92 pg/mL (reference range ≥110 pg/mL), suggesting narcolepsy type 1. After treatment with corticosteroids for approximately 1 month, the patient showed considerable clinical and radiological improvement, as well as an increase in hypocretin levels. Although repeated polysomnography and multiple sleep latency tests suggested narcolepsy, his ESS score decreased to 8. Our findings broaden the range of clinical manifestations associated with

GFAP-A, thereby enhancing diagnostic and therapeutic strategies for this disease. Additionally, our results indicate a potential common autoimmune mechanism involving GFAP-A and orexin system dysregulation, warranting further investigation.

KEYWORDS

case report, autoimmune glial fibrillary acidic protein astrocytopathy, glial fibrillary acidic protein, narcolepsy, sleep apnea-hypopnea syndrome

## 1 Introduction

Autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A) is a corticosteroid-responsive novel autoimmune inflammatory central nervous system disease defined by Fang (1) et al. in 2016; it usually presents as meningitis, encephalitis, myelitis, optic neuritis, or a combination of the above. The characteristic MRI features of GFAP-A are linear radially enhancing lesions perpendicular to the lateral ventricles, meningeal enhancement, and early brainstem and spinal cord involvement (2). Additionally, a small proportion of patients develop reversible lesions in the splenium of the corpus callosum (3, 4). The detection of glial fibrillary acidic protein (GFAP)- IgG in the cerebrospinal fluid (CSF) by both tissue- and cell-based testing serves as a biomarker for GFAP-A (5).

Most GFAP-A patients present with inflammatory CSF with elevated levels of CSF proteins and lymphocyte-predominant pleocytosis, which may last for months. Additionally, patients may show transiently increased CSF adenosine deaminase levels during the first month after disease onset (6, 7). Furthermore, these patients may have a history of infections, tumors, or other autoimmune illnesses such as thyroid dysfunction or type 1 diabetes. GFAP-A patients may also experience headache, fever, seizures, psychiatric symptoms, limb weakness, sensory symptoms, abnormal autonomic nervous function, or blurred vision (1, 6, 8, 9). In 2021, Gao et al. (10) reported a patient presenting with area postrema syndrome with intractable nausea and vomiting as the predominant symptoms. The MRI revealed abnormal hyperintensities on the T2 sequence in the dorsal medulla oblongata and right pontine arm.

Here, we report the case of a patient with excessive daytime sleepiness associated with GFAP-A, which has rarely been reported as a predominant symptom, to improve physicians' understanding of GFAP-A.

**Abbreviations:** AHI, apnea-hypopnea index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale score; GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; GFAP, glial fibrillary acidic protein; HLA, human leukocyte antigen; MSLT, Multiple Sleep Latency Test; NT1, narcolepsy type 1; PSG, polysomnography; RBD, rapid-eye-movement sleep behavior disorder; SAHA, sleep apnea-hypopnea syndrome.

## 2 Case description

A 58-year-old male patient experienced excessive daytime sleepiness for 50 days after being infected with SARS-CoV-2. On June 1st, the patient presented with fever, reaching a maximum temperature of 38.5°C, and a cough, and was diagnosed with SARS-CoV-2 infection. Following treatment, his symptoms resolved. On June 7th, the patient exhibited excessive daytime sleepiness, slept for 12–13 hours daily, and experienced sensations of nausea, reduced food intake, weakness in the lower limbs, and dysuria. After the onset of sleepiness, the patient did not experience fever recurrence, and there was no significant weight loss. On July 21st, the patient's symptoms markedly worsened. During this time, the patient slept for 20 h per day, even during meals and conversations. He fell asleep in seconds, showing no response to external stimuli and talking in his sleep, and awakened spontaneously after approximately 20 min, reporting nightmares during his recent sleep. The patient had undergone laparoscopic partial right nephrectomy for renal clear-cell carcinoma 5 months prior (Figure 1). However, he had not been diagnosed with any other illnesses and did not regularly use any drugs, toxins, or psychotropic substances. The patient did not report any previous subjective sleep complaints, noted that he slept for 6–7 hours daily before the onset of the disease, and did not exhibit cataplexy, nocturnal shouting, sleep paralysis, or hypnagogic hallucinations. The patient was 169 cm tall, weighed 70 kg, and had a body mass index of 24.5 kg/m$^2$. A neurological examination upon admission revealed somnolence and weakness in both lower limbs (Medical Research Council Scale score of 4 +). The Epworth Sleepiness Scale (ESS) is the most commonly used self-reported questionnaire used by clinicians and researchers to measure daytime sleepiness. A score of ≥10 is indicative of abnormal sleepiness, with higher scores indicating greater severity of sleepiness (10). The patient attained a score of 16 on the ESS scale. Blood analysis showed that his tumor marker carbohydrate antigen 724 level was 22.90 U/mL (reference range <10 U/mL), while his thyroid function and levels of antineutrophil cytoplasmic antibodies, antinuclear antibodies, anti-dsDNA antibodies, anti-Jo-

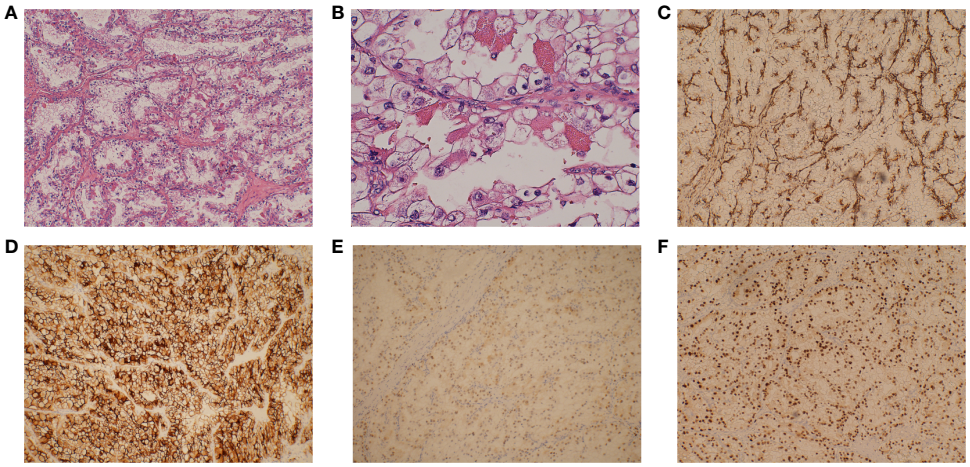



FIGURE 1
Pathological examination of this renal mass indicates the presence of clear cell renal cell carcinoma. **(A)** The tumor is arranged in vesicular or nested clusters, with numerous interstitial capillaries, a clear cytoplasm (original magnification ×100), and **(B)** conspicuous and eosinophilic nucleoli (original magnification ×400). **(C)** Tumor cells that are positive for vimentin (original magnification ×100). **(D)** Tumor cells that are positive for CD10 (original magnification ×100). **(E)** Tumor cells that are positive for PAX2 (original magnification ×100). **(F)** Tumor cells that are positive for PAX8 (original magnification ×100).

1 antibodies, anti-Sm antibodies, anti-PM-Scl antibodies, and anti-Ro52 antibodies were normal.

Brain MRI revealed abnormal hyperintense lesions in the pontine brain and around the mesencephalic aqueduct T2 and T2-fluid attenuated inversion recovery (T2-FLAIR) sequences; however, these lesions did not show pathological enhancement. Spinal cord MRI revealed lesions in the C6–C7 and T2–T3 segments on the T2 sequence (Figures 2A, C). Moreover, the electroencephalogram was normal, ruling out epilepsy. PET-CT of the whole body also showed no evidence of abnormal cancerous hypermetabolism. Furthermore, the normal electroneurography and electromyography results of the limbs also ruled out Lambert-Eaton syndrome, as well as weakness due to myogenic disease or peripheral nerve damage.

The Multiple Sleep Latency Test (MSLT) is an objective measure for quantifying the level of daytime sleepiness by having the patient take a series of naps during the day. It requires the patient to take five 20-minute naps, two hours apart, during which the patient must remain awake. The first nap is usually scheduled 3 hours after the patient has awakened from the previous night's polysomnography (PSG). Additionally, if a patient falls asleep and enters REM sleep within 15 min of sleep onset, it is recorded as a sleep-onset rapid eye movement period (SOREMP) (11). In this case, the patient's sleepiness was too severe to perform MSLT; therefore, the patient underwent 24-hour PSG, which showed a total sleep time of 539.5 minutes (Figure 3A), sleep latency of 8.5 minutes, rapid-eye-movement sleep without atonia, and dream enactment behavior.

The apnea-hypopnea index (AHI) is a measure of sleep apnea severity. The AHI assesses how often apnea (stopping breathing) and hypopnea (restricted and shallow breathing) events occur per hour during the night's sleep. Typically, an AHI of less than five occurrences per hour is considered normal. In this case, the patient's AHI was 75.6/h (obstructive AHI, 51.3/h; central AHI, 16.9/h; mixed AHI, 7.4/h), indicating Cheyne-Stokes respiration. Further examinations, including a CSF analysis on July 27, 50 days after the onset of symptoms, revealed an intracranial pressure of 115 mm$H_2O$ (reference range 80–180 mm $H_2O$), a protein level of 1.44 g/L (0.15–0.45 g/L), and a leukocyte count of 140×10^6/L (reference range <8×10^6 cells/L), composed of 96% lymphocytes and 4% monocytes. Additionally, his glucose level was 1.98 mmol/L (reference range 2.3–4.1 mmol/L) and his IgG level was 151.93 mg/L (reference range <34 mg/L). The CSF analysis revealed the presence of oligoclonal bands in the CSF. Additionally, glial fibrillary acidic protein (GFAP) IgG antibodies were found to be positive in the CSF (1:32, cell-based assay) but not in the serum (Figure 4), whereas AQP4 antibodies and MOG antibodies were negative in both the CSF and serum. The level of hypocretin in the CSF was 29.92 pg/mL (reference range >200 pg/mL), and his detected human leukocyte antigen (HLA) allele was *HLA DQB1*06:02/02:01*. The patient was diagnosed with GFAP-A, narcolepsy type 1 (NT1), rapid eye movement sleep behavior disorder (RBD), and severe sleep apnea-hypopnea syndrome (SAHS), which included obstructive, central, and mixed apnea or hypopnea events, with central apnea manifesting as Cheyne-Stokes respiration (12).

The patient's treatment included antiviral treatment and high-dose intravenous methylprednisolone at 1,000 mg/day for 3 days, followed by 500 mg/day for 3 days, 250 mg/day for 3 days, and 60 mg/day for 3 days, which was then switched to 60 mg/day orally. From the third day of steroid therapy, the patient's sleepiness significantly reduced, and his sleep duration gradually decreased to daily levels. In the follow-up after one month of treatment, the patient's sleepiness, weakness in both lower limbs, and dysuria resolved, and his ESS score dropped to 8. Follow-up CSF examination revealed decreased leukocyte (23×10^6/L), protein (0.96 g/L), and IgG levels (61.94 mg/L). The level of hypocretin in the CSF had increased to 87.81 pg/mL. Repeated PSG revealed a total sleep time of 393 min (Figure 3B), with a decrease in AHI to 26.4 times/h, and only obstructive respiratory events were observed. Despite these improvements, RBD persisted. The MSLT indicated a

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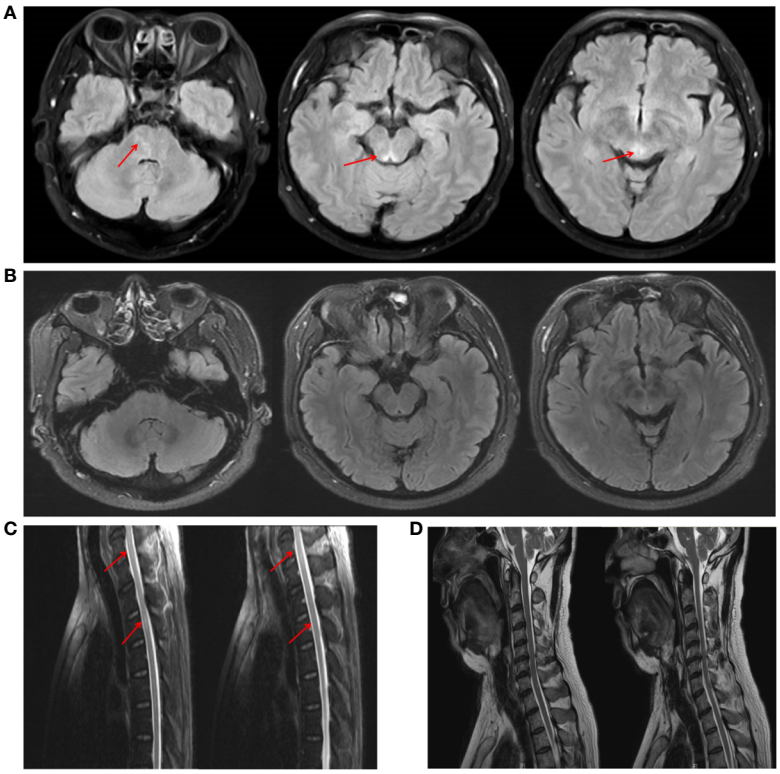



FIGURE 2
MRI imaging of the patient before and after treatment. **(A)** Brain MRI showed abnormal signals around the mesencephalic aqueduct and the pontine brain on the T2-FLAIR sequence. **(C)** Spinal cord MRI revealed spinal cord lesions in the C6–C7 and T2–T3 segments on the T2 sequence. **(B, D)** After treatment, the patient's intracranial lesions had almost disappeared.

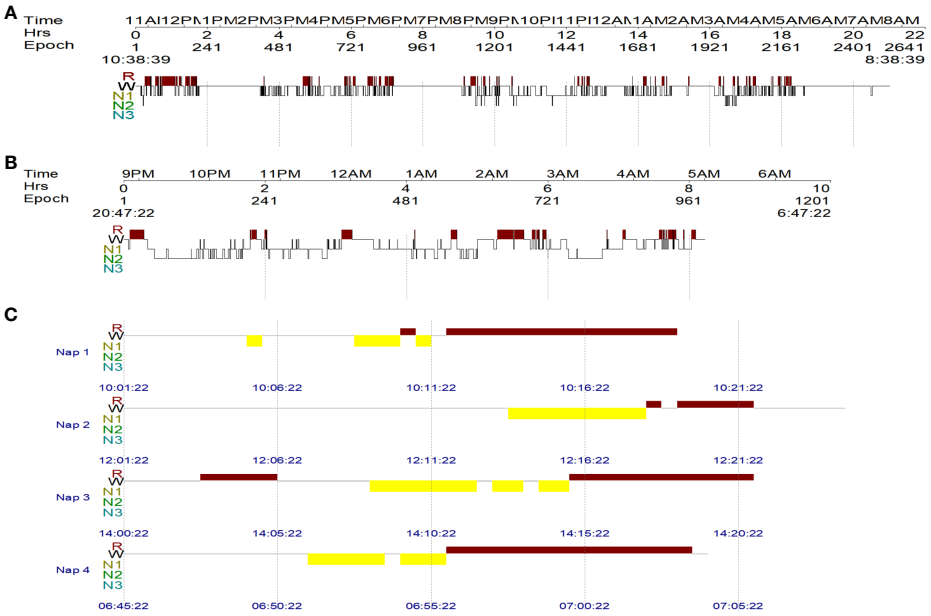



FIGURE 3
The patient's sleep architecture before and after treatment. W = wakefulness; R = rapid eye movement (REM) sleep; N1, N2, and N3 = non-REM N1, N2, and N3 sleep stages. **(A)** The 24-hour PSG result of the patient before treatment, showing a total sleep time of 539.5 min. **(B)** Overnight PSG revealed a total sleep time of 393 min after treatment. **(C)** MSLT followed the overnight PSG and revealed 4 consecutive sleep-onset rapid eye movement periods.

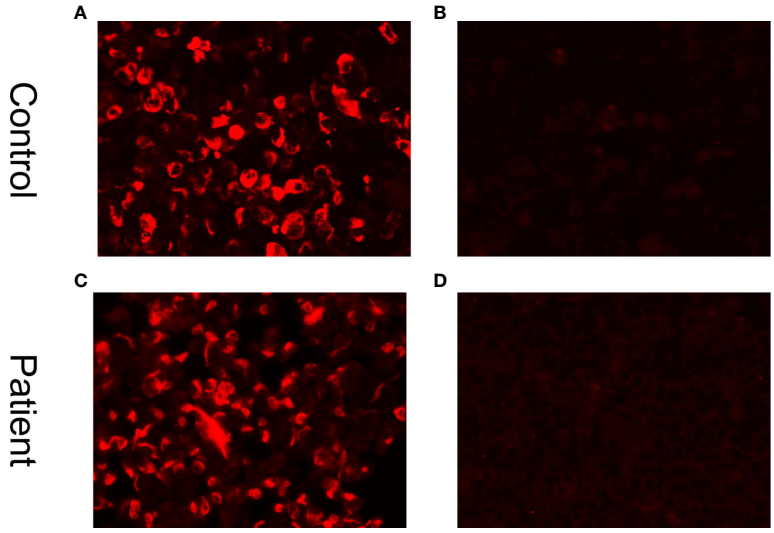



FIGURE 4
Cell-based indirect immunofluorescence assays demonstrate positivity for GFAP IgG antibodies. **(A)** Positive control with human GFAP IgG. **(B)** Negative control in a healthy individual. **(C)** Positive result in the CSF (titer at 1:32). **(D)** Negative result in serum.

mean sleep latency of 6.3 min (normal >8 min) and the occurrence of four consecutive SOREMPs (Figure 3C). On repeat head MRI, the patient's intracranial lesions had almost disappeared (Figure 2B). After 2 months of treatment, a follow-up examination showed that the patient's spinal cord lesions had disappeared (Figure 2D).

## 3 Discussion

GFAP-A is a rare autoimmune inflammatory disease of the central nervous system, and its prevalence remains undefined. Among patients suspected of neurological autoimmune disease, Fang et al. (1) reported a GFAP-A prevalence of 0.134% (134 per 100,000) whereas Iorio et al. (13) reported a prevalence of 4.87% (22/451). In the population-based comparative research undertaken in Olmsted County, USA, the prevalence of GFAP-A was calculated to be 0.0006%(0.6/100,000) (14). In terms of patient characteristics, individuals with GFAP-A tend to have acute or subacute disease onset and can develop the disease at any age (median 44–50 years), with no significant difference in incidence between men and women (5, 8).

The etiology of GFAP-A remains unknown. Notably, 30–40% of GFAP-A patients have a history of infection, especially viral infections, before disease onset (8). Additionally, GFAP-A may be associated with neoplastic conditions. Fang et al. (1) reported that 38% of patients present with neoplasms, in contrast to the 34% (35/102) documented in the study of Flanagan et al. (5). Transitioning to specific neoplasm types, ovarian teratoma emerges as the most common, while other types are both rare and diverse. Remarkably, Flanagan et al. (5) previously reported a GFAP-A patient with combined renal cell carcinoma, which is consistent with our case.

GFAP is a type III intermediate filament protein expressed in mature astrocytes. It is an important component of the cytoskeleton and plays an essential role in the formation of the blood–brain barrier and myelination (15). The diagnosis of GFAP-A relies on the detection of GFAP antibodies in the CSF, currently considered a biomarker for this condition. However, the pathogenesis of GFAP-A remains elusive, with potential involvement of aberrant activation of the tumor necrosis factor pathway or GFAP peptide-specific $CD8^+$ T lymphocytes, leading to astrocyte damage (16–18). Regardless, most patients with GFAP-A show inflammatory changes in the CSF, including increased white blood cell counts, elevated protein levels, and the presence of CSF-exclusive oligoclonal bands (8).

GFAP is predominantly expressed in the subpial and white matter, whereas in the gray matter, it is most abundant in the cerebral cortex and spinal cord, followed by the brainstem, hypothalamus, thalamus, hippocampus, amygdala, and basal ganglia (19). Moreover, the distribution of GFAP-A lesions on MRI is identical to that of histologically GFAP-enriched areas, often with linear radially enhanced lesions perpendicular to the lateral ventricles, meningeal enhancement, or early involvement of the brainstem and spinal cord (20).

There are some comparable clinical characteristics between our patient and previous reports. In this report, the middle-aged male patient had a SARS-CoV-2 infection prior to the onset of the disease and a history of neoplasia. Imaging studies revealed encephalitis and myelitis, and laboratory tests indicated inflammatory changes and oligoclonal bands in the CSF. However, excessive daytime sleepiness in patients with GFAP-A is an infrequent symptom. This contrasts with the findings reported by Fang et al. (1), who documented a case with GFAP-A who presented with subacute onset lethargy and T2 hyperintensities in the periventricular white matter. However, further details were not provided.

Excessive daytime sleepiness can stem from a range of factors, including sleep deprivation, sleep disorders such as OSA, restless legs syndrome, circadian rhythm disorders, and central hypersomnolence. Medical and psychiatric conditions such as depression, as well as

medication-induced effects, may also be responsible (21). In this case, the patient had no previous medical conditions, medication history, or reported sleep disorders. Meanwhile, he experienced an acute worsening of excessive daytime sleepiness. As a result, we concluded that the patient's excessive daytime sleepiness was due to severe SAHS and NT1, secondary to GFAP-A. The patient did not experience fluctuating drowsiness during the hormone tapering. Therefore, it is believed that the improvement in somnolence was due to the immunotherapeutic effect of methylprednisolone on GFAP-A rather than to the wakefulness-promoting effect of methylprednisolone.

Hypocretin is secreted by hypocretin-producing neurons in the hypothalamus, and its decline can present with narcolepsy-like symptoms, such as excessive daytime sleepiness, catalepsy, and rapid eye movement sleep behavior disorder (22, 23). Notably, our report marks the first documentation of decreased hypocretin in a patient with GFAP-A. However, the mechanism underlying the decrease in hypocretin in patients with GFAP-A is not well understood. Feneberg et al. (24) discovered that only patients with narcolepsy who experienced decreased hypocretin levels displayed increased GFAP levels in the CSF. Thus, it is believed that heightened GFAP is linked to gliosis of hypocretin-producing neurons and predicts more severe cellular damage. Additionally, it has been hypothesized that a decrease in hypocretin levels may be related to immunological factors secondary to the destruction of hypocretin neurons by GFAP peptide-specific $CD8^+$ T lymphocytes. In the case of anti-Ma2-associated diencephalitis with NT1, immunohistochemical staining of brain sections confirmed that the $CD8^+$ T cell-mediated autoimmune response induced by the anti-MA2 antibody caused the destruction of hypocretin-producing neurons (25), and a similar pathophysiological mechanism may be involved in our case. Notably, previous instances of various autoimmune antibodies, including anti-Ma antibodies (25–30), anti-Hu antibodies (31), AQP4 antibodies (32, 33) and anti-NMDA receptor antibodies (34) have been associated with decreased hypocretin, indicating a common yet unidentified antigen that attacked by multiple autoimmune antibodies in hypocretin-producing neurons. *HLA DQB1*06:02*, the main genetic factor responsible for susceptibility to NT1 (35), may also play a role in the development of an autoimmune response, ultimately resulting in the onset of secondary NT1 in the patient.

The substantial improvement in excessive daytime sleepiness and elevation of hypocretin levels observed in patients following hormone therapy implies that autoimmune neuronal damage has the potential for reversal at an early stage. Notably, our patient also presented with central respiratory events, including those that may have been associated with abnormal brainstem lesions, specifically in the pons. These lesions correspond to the functional brain network underlying the pathophysiology of central sleep apnea (36). Additionally, the concurrent disappearance of both central respiratory events and lesions supports this correlation. This suggests the importance of conducting screening and initiating treatment for central respiratory events in patients with GFAP-A who exhibit brainstem lesions.

GFAP-A is responsive to corticosteroid therapy but typically exhibits a relapsing-remitting course. Thus, in severe cases, additional treatments such as immunosuppressants may be necessary. While the patient in this case showed a positive response to corticosteroids, the persistence of NT1 warrants additional follow-up to monitor any potential regression in the patient's condition.

## 4 Conclusion

In conclusion, we present the inaugural case of GFAP-A characterized by excessive daytime sleepiness as the primary manifestation, accompanied by a decrease in hypocretin and SAHA. The precise mechanism of this presentation remains elusive, but it is speculated to be associated with autoimmunity mediated by GFAP peptide-specific CD8+ T lymphocytes, with steroid treatment proving to be effective. This unique case highlights the diverse clinical spectrum of GFAP-A and the need for further research to unravel its intricate pathophysiological mechanisms.

## Data availability statement

The datasets presented in this article are not readily available because this is a case report. Requests should be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MT: Writing – original draft. SH: Writing – original draft. WG: Writing – review & editing. JZ: Writing – review & editing. ZH: Writing – review & editing. WL: Writing – review & editing. QS: Writing – review & editing. ZW: Writing – review & editing.

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## Conflict of interest

The authors declare that this research was conducted in the absence of commercial or financial relationships that could be construed as potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1302514/full#supplementary-material

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# Case report: Approaches to treatment-refractory and super-refractory glutamic acid decarboxylase antibody-spectrum disorders

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**Background:** Glutamic acid decarboxylase antibody-spectrum disorders (GAD-SDs) include a group of autoimmune neurological diseases associated with neuronal excitability, most noticeably stiff person syndrome. Immune modulators are the mainstay of treatment, but a significant number of patients remain refractory.

**Methods:** We present our single-center experience of eight cases of GAD-SD, two of which were refractory to immune modulatory treatments.

**Results:** Of the two cases that were refractory to immunomodulation, one showed significant improvement with bilateral globus pallidus interna deep brain stimulation (GPi DBS) placement, and the other showed significant improvement with autologous hematopoietic stem cell transplant (aHSCT).

**Discussion:** To our knowledge, this is the first instance of GPi DBS placement being noted to improve GAD-SD movements.

KEYWORDS

**stem cells, rituximab, stiff person syndrome, GAD-65, deep brain stimulation**

## Introduction

Glutamic acid decarboxylase (GAD) plays a vital role in the synthesis of the inhibitory gamma-aminobutyric acid (GABA) neurotransmitters, which influence the brain's ability to control movement, coordination, and cognition. High serum titers of autoantibodies against GAD have been associated with an array of neurological diseases (1, 2). GAD antibody-spectrum disorders (GAD-SDs) include a group of autoimmune neurological

diseases associated with neuronal excitability, most noticeably stiff person syndrome (50%), cerebellar ataxia (43%), epilepsy (29%), and limbic encephalitis (16%) (1). Diagnostic criteria for simple partial seizure (SPS) include the following: "1) muscular rigidity in the limbs and axial (trunk) muscles, prominent in the abdominal and thoracolumbar paraspinals; 2) continuous co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically; 3) episodic spasms precipitated by unexpected noises, tactile stimuli, or emotional upset; 4) absence of any other neurologic disease that could explain stiffness and rigidity; and 5) positive anti–glutamic acid decarboxylase (GAD)65 (or amphiphysin) antibodies assessed by immunocytochemistry, Western blot, or radioimmunoassay" (3). Plasma exchange (PLEX) and intravenous immunoglobulins (IVIG) are the mainstays of disease-modifying treatment (3, 4). However, a significant number of patients are refractory to both. Below, we describe our single-center experience with refractory GAD-SD, which was observed in five of our eight patients. Two cases were deemed "super refractory", as they did not respond to rituximab but did have partial success to bilateral globus pallidus interna deep brain stimulator placement and autologous hematopoietic stem cell transfer. Patients were asked to submit a statement from their perspective but declined to do so.

## Case presentations

Our clinic is a university-based tertiary referral center in southern California serving a population of 3 million people. Between 2018 and 2022, we identified nine individuals who were diagnosed with GAD-SD through a consensus between our neuroimmunology and movement disorder specialists based on examination findings and serum positivity and after undergoing imaging and serum studies to rule out mimics as consistent with standard-of-care guidelines (Table 1). Six of the seven living patients consented to the publication of their cases, and the case of one patient who declined is not discussed here. Seven of the eight patients were female, with a median age of onset of 44 ( ± 16) years and a range of 18–71. SPS was the most common presentation (75%), followed by cerebellar ataxia (25%). There was one case with epilepsy + SPS. Two of our six SPS cases had electromyography (EMG) findings consistent with diagnostic criteria (5), two had normal findings, and two others did not undergo testing. Pre-existing autoimmune disorders were seen in two cases, and underlying malignancy was suspected in two others. However, the patient with a suspected intestinal source (case 8) died from sepsis secondary to aspiration pneumonia before the diagnostic workup had been completed, and the patient with an ovarian mass had a biopsy confirmation of cystic adenoma. Five cases were refractory to IVIG and PLEX treatment, two of which had at least moderate response to rituximab. One patient who was refractory to PLEX died from sepsis secondary to chronic leukopenia in the setting of PLEX (case 6). The two cases refractory to rituximab (super-refractory cases) have been followed up for 5 years since symptom onset and roughly 2 years since receiving their "super-refractory" treatments. One had significant improvement with bilateral globus pallidus interna deep brain stimulation (GPi DBS) placement with some fluctuations, and the one that underwent autologous hematopoietic stem cell transplant (aHSCT) had total resolution of painful spasms but still had moderate impairments in function due to spasticity and dystonia. These two cases (cases 1 and 4) are described in detail in the next section.

### Case 1

Our first patient is a 23-year-old Asian woman who initially presented with abdominal pain, nausea, and diarrhea at age 16. A biopsy of an ovarian mass confirmed a cystadenoma. At 1.5 years after her tumor resection, the patient returned with an insidiously progressive decline in speech and writing, blepharospasm, suicidal ideation, and mood lability. Upon initial examination by a movement disorder specialist, she was noted to have dystonic movements affecting bilaterally extensor spinal musculature, knee flexors, orbicularis oculi, and lateral neck muscles.

Brain MRI was normal. Electroencephalography (EEG) was of limited value due to motion artifacts from the patient's movements but did not identify any epileptiform abnormalities. EMG of selected muscles showed continuous firing of normally configured and recruited motor unit potentials, consistent with diagnostic criteria for SPS (3). Her serum GAD-65 ab titer returned positive at 2.67 nmol/L (reference range ≤0.02 nmol/L) with the additional finding of a singular allele for spinocerebellar ataxia type 2. Lumbar puncture revealed an opening pressure of 12 cm $H_2O$, with a profile of 0 red blood cells (RBC)/$mm^3$, 0 white blood cells (WBC)/$mm^3$, glucose 59 mg/dL, and protein 19 mg/dL. Further extensive autoimmune/infectious cytology studies of cerebrospinal fluid (CSF) were also negative. It is important to recall that CSF samples of GAD-65 antibody titer are not considered accurate, as serum and serum measurements are the preferred standard (6). She was empirically treated with methylprednisolone and rituximab for suspected autoimmune encephalitis but showed no improvement. The patient's symptoms were refractory to benzodiazepines, muscle relaxants, botulinum toxin, and trihexyphenidyl.

Eight months later, her serum GAD-65 ab remained at 72 IU/mL (reference range <5 IU/mL), and she was started on rituximab q6 months. Within 2 months, serum GAD-65 ab levels were undetectable (decreasing from 53 IU/mL to 6 IU/mL to <5 IU/mL), with some improvement in her hyperkinetic movements, but her symptoms returned. A repeat transvaginal ultrasound confirmed no new evidence of malignancy.

Six months afterward, she was admitted to the intensive care unit (ICU) for status dystonicus at an outside facility and had bilateral GPi DBS placement. Brain MRI at that time noted interval development of mild diffuse non-specific atrophy throughout the bilateral cerebral hemispheres and minimal atrophy of the midbrain. She had significant improvement in her large amplitude movements and could ambulate independently with a front-wheel walker and required minimal to moderate assistance for activities of daily living (ADLs).

Four months after discharge, she returned for acute-onset status dystonicus in the setting of DBS battery failure. She presented with

TABLE 1 Summary of cases.

| Case no. | Age of symptom onset | Sex | Pre-existing conditions | Presenting symptoms | Diagnostic confirmation | EMG consistent with SPS? | Treatments | Complications | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 18 | F | Bx confirmed cystic adenoma ovarian mass | SPS, emotional lability | Serum GAD 2.67 nmol/L | Yes | IVIG ->PLEX ->Rituximab | Refractory status dystonicus s/p DBS placement | Significant improvement s/p DBS placement |
| 2 | 34 | M | History of alcohol abuse, Anxiety | SPS, hyperekplexia | Serum GAD 0.08 nmol/L | No | IVIG ->Rituximab ->IVIG | No | Moderate improvement in stiffness, mild improvement in hyperekplexia |
| 3 | 37 | F | | SPS | Serum GAD 0.28 nmol/L | Did not have EMG | IVIG ->Rituximab | No | Stable with IVIG, awaiting further observation on rituximab |
| 4 | 41 | F | Epilepsy during pregnancy, Hashimoto's thyroiditis | SPS, hyperekplexia, epilepsy | Serum GAD 136 nmol/L, gliadin 102 CU (<20.0 CU) | No | IVIG ->PLEX ->Rituximab | Refractory spasms treated with HSCT | Moderate improvement of spasms s/p HSCT |
| 5 | 49 | F | | Cerebellar ataxia 1 month s/p flu-like illness | Serum GAD >250 IU/mL Antigliadin 23 U, (<20 U) Antithyroid abs 46.7 IU/mL (≤20 IU/mL) | N/A | PLEX ->Rituximab | no | Significant improvement |
| 6 | 52 | F | | SPS | Serum GAD 591 nmol/L | Yes | IVIG ->PLEX | Leukopenia secondary to chronic immunosuppression | Minimal improvement before passing from leukopenia |
| 7 | 53 | F | RA since age 15. Primary immunodeficiency since age 49, anti-TPO, VGKC abs | SPS, OCD | Serum GAD 4.72 nmol/L | Did not have EMG | IVIG | No | Significant improvement |
| 8 | 71 | F | | Cerebellar ataxia | Serum GAD 443 nmol/L CSF GAD 1 nmol/L | N/A | IVIG ->PLEX | G-tube placement for severe dysphagia | Minimal improvement before passing from sepsis |

Reference ranges are provided in parentheses. Reference ranges for GAD-65 ab in serum and CSF are ≤0.02 nmol/L and <5 IU/mL, respectively.
Anti-TPO, thyroid peroxidase antibodies; Bx, biopsy; DBS, deep brain stimulation; GAD, glutamic acid decarboxylase; HSCT, hematopoietic stem cell transplant; IVIG, intravenous immunoglobulins; OCD, obsessive-compulsive disorder; PLEX, plasma exchange; RA, rheumatoid arthritis; s/p, "status post" (i.e., after the procedure); SPS, stiff person syndrome; VGKC abs, voltage-gated potassium channel antibodies; EMG, electromyography; CSF, cerebrospinal fluid. NA, not applicable.



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rhabdomyolysis with a CK of up to 18,000 U/L (reference range 30–223 U/L). Her status dystonicus remained refractory to aggressive medical management. Her symptoms rapidly improved after battery replacement with a return to baseline within 2 days. Three months later, roughly 18 months from symptom onset, she had age-appropriate intact cognition, could speak in one- to two-word phrases, and could stand up from a chair. She underwent reprogramming of her DBS and had marked improvement in her speech, now able to speak one to two full sentences, and was able to walk 20 feet with assistance (see Video 1). She remains at this level of functioning, now 3 years after symptom onset. A summary of the patient's treatment course is provided in Table 2. The patient's DBS settings are presented in Figure 1.

## Case 4

Our second patient is a 47-year-old Hispanic woman with a history of Hashimoto thyroiditis, pernicious anemia, celiac disease, and epilepsy with focal and focal to bilateral tonic–clonic seizures. A description of her case from a hematological perspective has been previously published (7). Prior to her SPS diagnosis, the patient was followed up in the epilepsy clinic after having three probable nocturnal seizures starting in the 25th week of her pregnancy in 2014. Extensive workup for an underlying etiology for her new-onset epilepsy with MRIs, EEGs, serum studies, and paraneoplastic screening was unrevealing. She remained seizure-free on levetiracetam 1,000 mg twice daily, and this was reduced to 500 mg twice daily in 2018 due to irritability. She underwent an epilepsy monitoring unit admission in 2022, which did not capture any seizures but noted that her episodes of body spasms and jerks did not have epileptiform correlates.

In 2017, SPS symptoms began with back spasms leading to multiple ground-level falls for which she sought multiple opinions and was suspected to have a functional movement disorder after EMG was within normal limits. She presented to our clinic in 2019 with stiff lumbar paraspinal muscles, left medial thigh and calf spasticity, left foot inversion, and spastic gait. Her serum GAD-65 ab was 136 nmol/L. She was diagnosed with SPS, which was refractory to IVIG and PLEX. Her condition continued to worsen despite rituximab infusions. By 2022, she underwent aHSCT with ATG/cyclophosphamide conditioning regimen and cyclophosphamide + G-CSF and aHSC collection. Her course was complicated by neutropenic fever; however, she stabilized and was discharged on day 14 of aHSCT.

By day 27 post-autologous transplant, she had complete resolution of her spasms. At 2 months of follow-up, she remained spasm-free. On the physical examination, she had residual generalized weakness and hyperreflexia. Her ambulation continued to be difficult, and repeat anti-GAD measured 40.2 nmol/L. Her condition remains stable.

# Discussion

The objective of this case series is to review potentially effective treatments for refractory and super-refractory GAD-SDs. However, there are some important differences between our cohort and prior reports that may limit the generalizability of our findings. In our cohort of patients, we saw a female:male predominance of 8:1, which is higher than most reports of roughly 6:1. Additionally, our rates of pre-existing autoimmune disorders or underlying malignancy were on the lower side of prior reports. Diagnoses were confirmed for all our patients by the presence of GAD autoantibodies, but only two of our six SPS cases had EMG confirmation. We acknowledge that, as per the description notice provided by Mayo Laboratories, "GAD65 antibody values less than 2.00 nmol/L have a lower positive predictive value for neurological autoimmunity than values of 20.0 nmol/L and higher", and this was seen in two of our cases (cases 2 and 3) (8). However, this is often

TABLE 2 Summary of case 1.

| Case 1 | April–May 2018 | August–December 2018 | January–April 2019 | | | February 2021 | |
|---|---|---|---|---|---|---|---|
| Serum GAD-65 ab value | 2.67 nmol/L 5/2018 | <5 IU/mL 8/28/2018 | 72 IU/mL 1/30/2019 | 53 IU/mL 2/8/2019 | 6 IU/mL 4/8/2019 | | 0.47 nmol/L 2/17/2021 |
| Treatments | Rituxan 1,000 mg 4/23/2018 | 4 doses IVIG 12/2018 | Rituxan 500 mg 2/5/2019 6 doses IVIG 1/2019 | Rituxan 1,000 mg 2/25/2019 | Rituxan 1,000 mg 3/11/2019 | DBS placed 12/16/2019 | DBS battery dies, 2/25/2021 |
| Exam findings | Blepharospasm Dysarthria | Craniofacial dystonia Stiff gait | | Infrequent craniofacial movement Normal gait | Decreased frequency of hyperkinetic movements Dystonia persists | Refractory status dystonicus resolves s/p DBS | Status dystonicus resolves with battery replacement |

Disease and treatment course.
DBS, deep brain stimulation; GAD-65 ab, glutamic acid decarboxylase-65 antibody; GPi, globus pallidus interna; IVIG, intravenous immunoglobulin; s/p, status post.

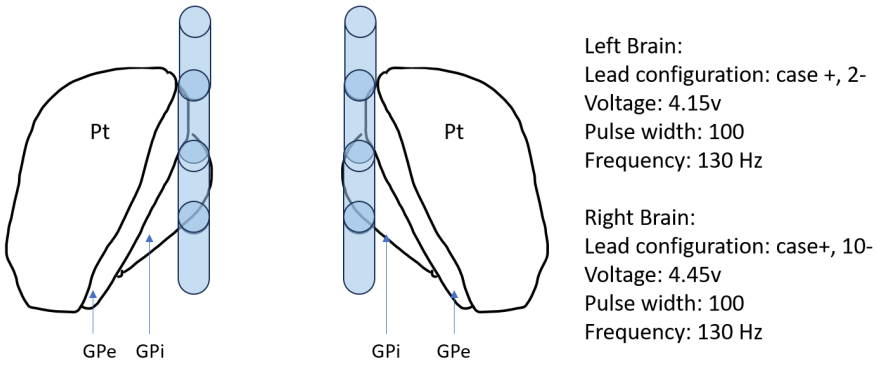



FIGURE 1
Depiction of case 1 deep brain stimulation settings. Axial depiction of Case 1 Deep Brain stimulation bilateral globus pallidus internus placement with settings. GPe, Globus pallidus externus; GPi, Globus pallidus internus; Pt, putamen; v, voltage; µs, microseconds; Hz, hertz.

the case in patients with diabetes mellitus, thyroid disorders, or pernicious anemia (8), which neither patient had, and highlights the importance of why the diagnosis of GAD-SD is not based solely on serum antibody titers but on the combination of titers with clinical findings (3).

There was no correlation between the quantitative antibody titer and the severity of the initial presentation, consistent with previous reports and current understandings (6, 7). Seronegativity may be seen in up to 20% of cases (9), and CSF antibody testing should be considered if clinical suspicion remains high. Overall, immunomodulatory therapies were effective. Five of our cases were refractory to either IVIG or PLEX, and only two were refractory to rituximab. Unfortunately, none of the patients, regardless of their treatment, had a full return to baseline. Two patients died from sepsis but for different reasons. Case 6 developed chronic leukopenia while on PLEX, but it cannot be determined if this was a consequence of repeated PLEX therapy or due to an underlying leukemia.

Alternative fourth-line treatments were employed for two super-refractory patients. For one patient, HSCT was effective and has been previously described (4, 9–14). In our first patient, GPi DBS was placed specifically for her refractory status dystonicus in accordance with the standard-of-care treatment for refractory status dystonicus and not as an experimental approach to treating her stiff person syndrome. GPi DBS for medically refractory dystonia has been approved by the Food and Drug Administration in the United States since 2003, and two multicenter studies demonstrated clinical benefit in generalized dystonia since 2006 (15, 16). Example images of GPi DBS placement for dystonia may be found here (17). For a review of its indications and uses, see (17–20). A 2021 systematic review of medically refractory dystonia of 35 studies (n = 319) found that GPi DBS placement was consistently safe and effective and noted that primary dystonias achieved better motor symptom and disability score improvement than secondary dystonias (21). To our knowledge, this is the first reported example of GPi DBS use in GAD-SD, which suggests that it may be an effective alternative treatment for super-refractory SPS patients. Further investigation of the safety and efficacy of bilateral GPi DBS placement as a treatment for super-refractory SPS through open-label and randomized controlled clinical trials is needed to validate this possible intervention.

## Conclusion

Immunomodulatory therapies are an effective means of treatment for the majority of patients with GAD-SDs. In super-refractory cases, GPi DBS (in the context of refractory status dystonicus) and aHSCT were observed to be effective treatments. Further exploration is needed to understand their efficacy across a wider patient population of super-refractory GAD-SDs.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

RR: Conceptualization, Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing. SB: Data curation, Investigation, Writing – original draft. DN: Data curation, Investigation, Writing – original draft. ES: Data curation, Investigation, Writing – original draft. MS: Conceptualization, Data curation, Supervision, Writing – review & editing. SA: Conceptualization, Data curation, Supervision, Writing – review & editing. DS: Conceptualization, Supervision, Writing – review & editing.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1297340/full#supplementary-material

SUPPLEMENTARY VIDEO 1

Video of case 1 with deep brain stimulation (DBS) off *vs.* on. The patient presented to clinic for adjustment of her DBS settings. Note the difference in attempted ambulation when the DBS is turned off *vs.* on with the following settings. Left brain: lead configuration, c+2-; current, 4.00 mA; pulse width, 60 μs; frequency, 130 Hz. Right brain: lead configuration, c+10-; current, 4.05 mA; pulse width, 60 μs; frequency, 130 Hz.

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# Case report: Cytopenias in VEXAS syndrome - a WHO 2022 based approach in a single-center cohort

Elisa Diral[1]*, Corrado Campochiaro[2,3], Alessandro Tomelleri[2,3], Gregorio M. Bergonzi[1,3], Umberto Pizzano[1,3], Maurilio Ponzoni[3,4], Lucia Bongiovanni[3,4], Paola Ronchi[5], Cristina Tresoldi[5], Silvia Rigamonti[5], Federico Scarfò[3,4], Gloria M. Latino[3], Emma Rinaldi[3], Massimo Bernardi[1], Lorenzo Dagna[2,3] and Fabio Ciceri[1,3]

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VEXAS syndrome is an acquired autoinflammatory disease characterized in most cases by cytopenias and macrocytic anemia. Dyshematopoiesis is a frequent finding in chronic inflammatory conditions and therefore, cytopenias are not easily classified in VEXAS patients. Here we report a series of 7 patients affected by VEXAS associated cytopenias, treated at our center. The use of NGS, together with morphological assays, integrated with the WHO 2022 criteria, allowed to identify three subsets of VEXAS associated cytopenias: ICUS (idiopathic cytopenia of uncertain significance), CCUS (clonal cytopenia of uncertain significance) at high risk of clonal evolution, and MDS. This approach could help to better understand the nature of VEXAS associated cytopenias and to guide the use of specific targeted treatments in order to achieve long lasting responses.

KEYWORDS

**myelodysplastic neoplasms (MDS), VEXAS syndrome, next generating sequencing, azacytidine, ruxolitinib, vacuoles**

## Introduction

VEXAS (Vacuoles, enzyme E1, X-linked, autoinflammatory, somatic) syndrome is an autoinflammatory disease (1) caused by a somatic mutation in the UBA1 gene that leads to aberrant activation of the innate immune system and production of proinflammatory cytokines.

VEXAS syndrome is usually diagnosed in adult men with a median age between 65 and 75 years (2), and manifests with fever, skin vasculitis, pleuropulmonary disorders,

polychondritis and ocular inflammation (3). Hematological involvement is very common and vacuolization of hematopoietic precursors is considered one of the hallmarks of the disease (4); indeed, the finding of at least two vacuoles in more than 10 per cent of neutrophil precursors is associated with high sensitivity and specificity for VEXAS syndrome diagnosis (5). Cytopenias are also frequent, with macrocytic anemia (1, 6) being the most common finding. In addition, patients with VEXAS syndrome present with myelodysplastic syndrome (MDS) in about 40% of cases (3). Studies have hypothesized that chronic inflammation leads to accelerated ageing of hematopoietic stem cells, favouring the onset of driver mutations usually belonging to the DTA triad (DNMT3A, TET2, ASXL1) (7). VEXAS associated MDS tend to show a low risk profile according to the Revised International Prognostic Scoring System (IPSS-R) (6, 8), even if evolution to acute myeloid leukemia has been reported (9). However, in VEXAS syndrome, cytopenias are not easy to classify, due to the frequent dyshematopoiesis found in bone marrow samples (typical of chronic inflammatory conditions) and to the presence of clonal hematopoiesis of indeterminate potential mutations (10). Typical marrow findings in VEXAS-associated MDS include hypercellular bone marrow, with cytoplasmic vacuolization and dysplasia in more than 10 per cent of erythroid and myeloid precursors; less frequently, vacuoles can be seen in plasma cells and megakaryocytes. Also, a variable degree of reticulin fibrosis, karyotype abnormalities, ring sideroblasts and acquired somatic mutations can be found. On the other hand, cytopenias without criteria for MDS also show cytoplasmic vacuolization of marrow precursors and bone marrow hypercellularity, with a minimal degree of dysplasia without blast excess and normal karyotype (6, 11). With regard to persistent and not otherwise explained cytopenias, the latest WHO classification of 2022 (12) has introduced two novel entities: clonal cytopenias of uncertain significance (CCUS), defined by the presence of clonal mutations with cytopenias in the absence of dysplasia (13), and idiopathic cytopenias of uncertain significance (ICUS), defined by cytopenias in the absence of clonal myeloid mutations (14). Actually, a precise classification of cytopenias in VEXAS syndrome is not available, due to the rarity of the disease and to the limited knowledge about pathogenic mechanisms (11). For this purpose, the new WHO 2022 classification could help in classifying VEXAS associated cytopenias, considering morphological, cytogenetic and molecular characteristics. This might help clinicians to better define the risk of clonal evolution of cytopenias and to choose proper treatments.

## Methods

In this study, we retrospectively analyzed bone marrow samples from 7 patients diagnosed with VEXAS syndrome at our centre between 2021 and 2022. Aspirates and trephine biopsies were performed at diagnosis and repeated during follow up in case of changes in blood counts. Morphological, cytogenetic, and molecular testing by next generation sequencing (NGS) were exploited. MDS, CCUS and ICUS were defined according to WHO 2022 criteria (12). All samples were collegially reviewed by a team composed by hematologists, morphologists and pathologists. Therapeutic decisions were performed by a multidisciplinary team of hematologists and rheumatologists.

## Results

The main features of the included patients are summarized in Table 1. All patients were men older than 60 years at diagnosis and presented with autoinflammatory symptoms and cytopenias. Two patients (28.5%) were diagnosed with low/intermediate risk MDS according to IPSS-R, without cytogenetic abnormalities or additional somatic mutations. Three patients (43%), who did not fulfil criteria for MDS and did not harbor somatic mutations or cytogenetic abnormalities, were diagnosed with ICUS. Two patients (28.5%), who did not fulfill criteria for MDS but with somatic mutations consistent with clonal hematopoiesis, were diagnosed with CCUS. All patients showed vacuolization of hematopoietic precursors, and all samples displayed a physiological karyotype.

None of the three patients with ICUS had significant changes in blood counts during a median follow up of 11 months. At diagnosis, patient-3 (PT3) marrow evaluation showed mild hypoplasia with mild dyshematopoiesis; the patient underwent several lines of therapy and eventually achieved good clinical control with ruxolitinib. A second marrow evaluation performed before ruxolitinib initiation was still compatible with ICUS. PT6 had bone marrow hyperplasia without additional myeloid mutations. The patient achieved initial good disease control with low dose glucocorticoids and tocilizumab. However, about six months after diagnosis he had an aggressive inflammatory relapse with pulmonary, renal, and central nervous system involvement. The patient was refractory to high dose glucocorticoids and eventually died. A NGS assay ruled out clonal evolution at the time of death. PT7, currently lost to follow-up, was transfusion dependent due to macrocytic anemia; given his age and multiple co-morbidities, he was only treated with low-dose glucocorticoids.

Two patients were classified as CCUS. At diagnosis, PT2 had marrow hyperplasia with mild dyshematopoiesis and hemophagocytosis without criteria for MDS; the karyotype was normal and NGS testing showed an oncogenic mutation in DNMT3A. One year later, a bone marrow re-evaluation was performed due to a drop in hemoglobin levels despite controlled systemic inflammation, and it showed evolution to MDS with low blasts (MDS-LB) with no changes in karyotype and molecular mutational pattern. Hence, erythropoietin-stimulating agents (ESA) were added to the ongoing therapy with cyclosporine and low-dose glucocorticoids. PT1 had oncogenic mutations in DNMT3A and ZRSR2 at diagnosis and was treated with cyclosporine and low dose glucocorticoids. A marrow re-assessment performed six months after diagnosis for clinical worsening showed stable histological characteristics, with the appearance in NGS of a new oncogenic mutation in ASXL1. He was eventually switched to ruxolitinib.

The two patients who presented with MDS at VEXAS diagnosis had worsening cytopenias during disease course leading to an increased risk according to IPSS-R but without any signs of clonal evolution. PT4 initially presented with MDS-LB, normal karyotype and no myeloid additional mutations. He was initially treated with

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TABLE 1 Classification of cytopenias in VEXAS syndrome.

| | Timing of bone marrow evaluation | Classification WHO 2022 | IPSS-R | NGS (VAF %) ┼ | Karyotype | Clinical manifestations at diagnosis | Treatment |
|---|---|---|---|---|---|---|---|
| **PT1** | Diagnosis | CCUS | | ZRSR2 (3.79%)<br>DNMT3A (38%) | 46, XY [23] | Cytopenia<br>Orbital pseudotumor | GC + CSA |
| | Follow up | CCUS | | ZRSR2 (3.47%)<br>DNMT3A (37%)<br>ASXL1 (2.12%) | 46, XY [20] | | GC + Ruxo |
| **PT2** | Diagnosis | CCUS | | DNMT3A (39%) | 46, XY [19] | Cytopenia<br>Ear chondritis,<br>orbital pseudotumor | GC + CSA |
| | Follow up | MDS-LB | Low | DNMT3A (40%) | 46, XY [21] | | GC + CSA + EPO |
| **PT3** | Diagnosis<br>Follow up | ICUS<br>ICUS | | Negative<br>Negative | 46, XY [28]<br>46, XY [20] | Cytopenia<br>Lung inflammation,<br>cutaneous vasculitis | GC + tocilizumab *<br>GC + Ruxo |
| **PT4** | Diagnosis | MDS-LB | Low | Negative | 46, XY [24] | Cytopenia<br>Ear and nose<br>chondritis<br>lung inflammation | GC + Ruxo * |
| | Follow up | MDS-LB | Intermediate | Negative | 46, XY [20] | | 5-aza + Ruxo + GC |
| **PT5** | Diagnosis | MDS-LB | Very low | Negative | 46, XY [18] | Cytopenia<br>Ear chondritis,<br>cutaneous vasculitis,<br>lung inflammation | GC |
| | Follow up | MDS-LB | Low | Negative | 46, XY [28] | | GC + canakinumab<br>+<br>CSA + EPO |
| **PT6**<br>§ | Diagnosis | ICUS | | Negative | 46, XY [22] | Cytopenia<br>Ear chondritis,<br>arthritis<br>cutaneous vasculitis. | GC + tocilizumab |
| **PT7** | Diagnosis | ICUS | | Negative | 46, XY [20] | Cytopenia<br>Ear chondritis | GC |

ICUS, idiopathic cytopenia of undetermined significance; CCUS, clonal cytopenia of undetermined significance; MDS, myelodysplastic neoplasia; MDS-LB, myelodysplastic neoplasia with low blasts. GC, glucocorticoids; CSA, Cyclosporine A; Ruxo, ruxolitinib; EPO, erythropoietin; 5-aza, 5-azacytidine. ┼ Only oncogenic and potentially oncogenic variants are reported; § a second NGS testing performed during follow up on peripheral blood was negative. *Pretreated patients – here we indicate the last line of therapy before switching to novel therapies.

various combined therapies, including ESA, glucocorticoids, cyclosporine and canakinumab. One year after diagnosis, ruxolitinib treatment was started due to relapsing inflammatory events, increased transfusion requirement and progressive bone marrow failure. A good response in systemic inflammation was obtained, along with platelet count increase; however, due to persistent transfusion dependent anemia, 5-azacytidine was added. PT5 presented at diagnosis with MDS-LB and was initially treated with low-dose glucocorticoids monotherapy. Two years after diagnosis, he showed inflammatory signs and worsening anemia; a new bone marrow evaluation excluded clonal evolution, so a treatment with canakinumab, cyclosporine, low dose steroids and ESA was initiated with good clinical response.

## Discussion

Our case series of bone marrow features in VEXAS-associated cytopenias shows high heterogeneity, as already reported in other works (11). Cytoplasmic vacuoles in myeloid and erythroid precursors, marrow hyper- or hypocellularity, varying degrees of dysplasia and hemophagocytosis are among these features. Given that a various grade of dyshematopoiesis is frequent in autoinflammatory disorders, it is not always easy to classify cytopenias in VEXAS syndrome (10). The use of molecular analysis by NGS, together with morphological assays, integrated with the WHO 2022 criteria, could help in this setting, by identifying mutations associated with clonal hematopoiesis and therefore patients at risk of clonal evolution. Moreover, the correct diagnosis of VEXAS associated cytopenias allows the use of specific targeted treatments, which might overcome the need for chronic moderate-to-high dose glucocorticoids and the lack of a prolonged response to conventional or biologic disease-modifying agents (15). Hematologic treatments are now used in VEXAS patients, such as ESA and 5-azacitidine; the latter has been successfully explored in a phase II trial in patients with VEXAS syndrome for the control of both inflammatory signs and cytopenias (16). For this reason, cooperation between hematologists, hematopathologists and rheumatologists is fundamental for both diagnosis and treatment optimization (15).

Specifically, our experience classifies VEXAS associated cytopenias into three groups:

1) NGS-negative cytopenias (ICUS according to the WHO 2022 classification – Figures 1A, B), probably related to the inflammatory status ("VEXAS-associated cytopenia");
2) "VEXAS-associated CCUS", that is cytopenia associated with somatic mutations in myeloid genes but without morphologic criteria for MDS diagnosis, at high risk of clonal evolution (Figures 1C, D);
3) "VEXAS-associated MDS" (Figures 1E, F), that is cytopenia with marrow morphologic criteria for myelodysplastic neoplasia, with or without mutations in myeloid genes. In our case series, patients with VEXAS-associated MDS showed low risk of leukemic evolution but high risk of progressive bone marrow failure.

The prognostic value of cytopenias in VEXAS needs to be further investigated; however, the first case of evolution into acute leukemia has been recently described in a patient affected by VEXAS and MDS (9). Moreover, Ferrada and colleagues identified transfusion dependency among predictors of mortality in VEXAS syndrome (17). Our study has several limitations (i.e., small sample size, retrospective nature) and further studies are warranted to better characterize myeloid alterations in VEXAS patients and their relationship with the UBA1 clone. For example, incorporation of UBA1 to standard NGS diagnostic panels could help to determine the true prevalence of UBA1 mutations in patients with cytopenias.

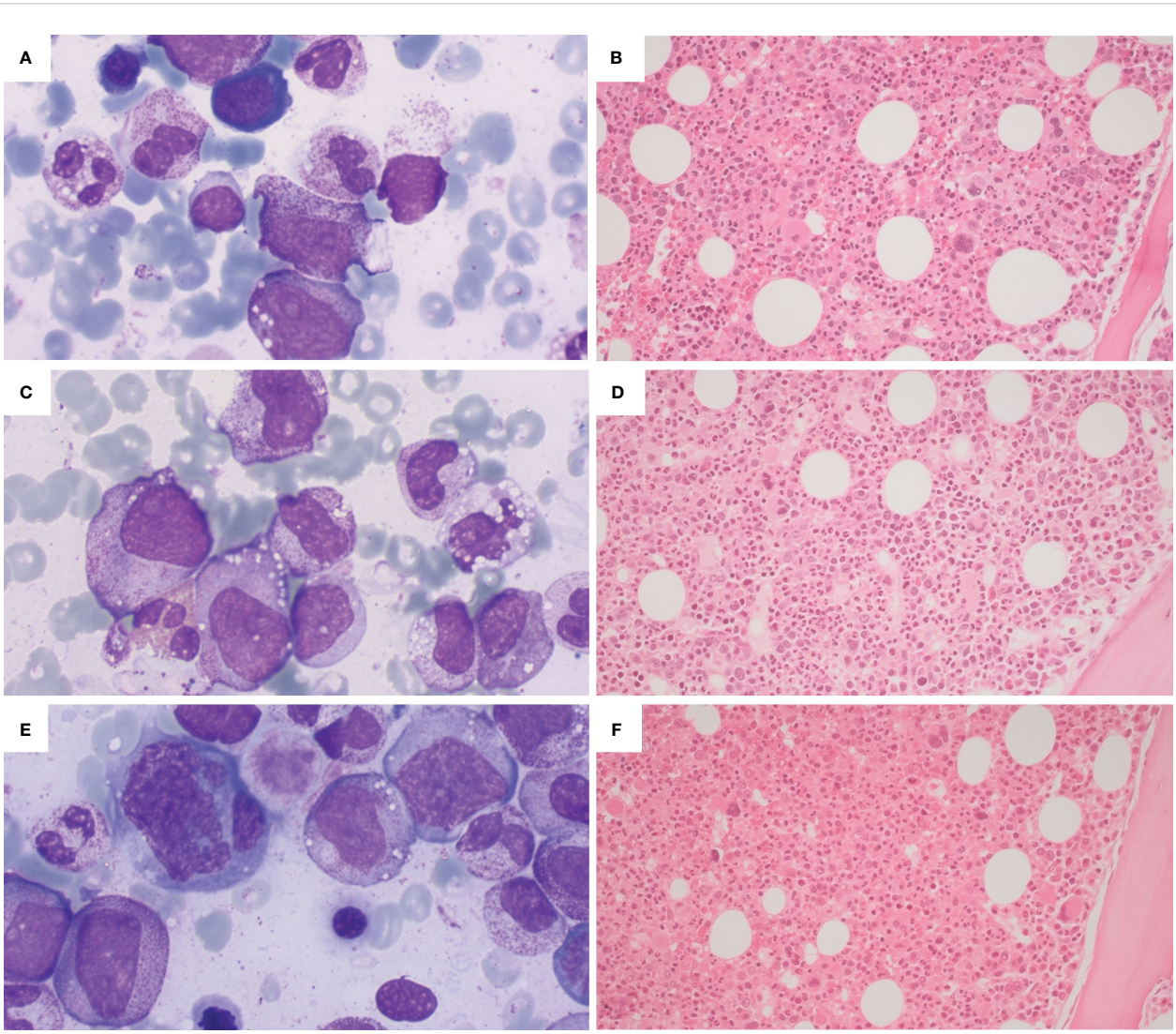



FIGURE 1
Illustrative bone marrow findings from VEXAS patients with cytopenias. **(A, B)** Cytological and histologic findings from a patient with ICUS (idiopathic cytopenia of undertermined significance): hypercellular bone marrow with maturating haemopoietic series, without dysplasia (**A** - Wright-Giemsa stain, 100x; **B** - H&E, 20x). **(C, D)** Cytological and histologic findings from a patient with CCUS (clonal cytopenia of undertermined significance), showing a hypercellulated bone marrow without morphological criteria for MDS (myelodysplastic neoplasia); presence of haemophagocytosis (**C** - Wright-Giemsa stain, 100x; **D** - H&E, 20x). **(E, F)** Cytological and histological findings from a patient with VEXAS and concomitant MDS, showing a markedly hypercellular bone marrow with trilinear dysplasia (**E** - Wright-Giemsa stain, 100x; H&E, 20x).

## Conclusion

In our case series, we classified cytopenias in VEXAS syndrome according to the WHO 2022 classification. This approach could allow the implementation of personalized medicine in VEXAS syndrome, depending on the nature of the associated cytopenia and therefore improve patient outcomes. However, prospective studies are envisaged to deeply investigate the pathogenesis of the disease and effective treatments.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

ED: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. CC: Conceptualization, Methodology, Supervision, Writing – review & editing. AT: Conceptualization, Writing – review & editing. GB: Data curation, Writing – original draft. UP: Writing – original draft. MP: Resources, Writing – original draft, Writing – review & editing. LB: Resources, Writing – original draft, Writing – review & editing. PR: Resources, Writing – original draft, Writing – review & editing. CT: Resources, Writing – original draft, Writing – review & editing. SR: Resources, Writing – original draft, Writing – review & editing. FS: Resources, Writing – review & editing. GL: Writing – review & editing. ER: Writing – review & editing. MB: Writing – review & editing. LD: Writing – review & editing. FC: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Etanercept treatment for pediatric toxic epidermal necrolysis induced by deflazacort: a case report and literature review

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Toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous disorder commonly caused by drugs. TEN is often treated with corticosteroids, intravenous immunoglobulin (IVIG), or cyclosporine; however, the efficacy of these treatments is controversial. Etanercept (a TNF-α antagonist) was proven to decrease skin-healing time in a randomized clinical trial. Herein, we report the case of a 44-month-old boy who developed TEN due to deflazacort as the probable culprit drug and was successfully treated with etanercept. The patient presented to the emergency department complaining of erythematous maculopapular rashes and vesicles all over the face and body, with vesicles on the hands, feet, and trunk. Symptoms started 4 days before presentation, with edema of the upper lip, which progressed to erythematous macules over the body. He was started on deflazacort for nephrotic syndrome 21 days before the visit. Approximately 20% of the body surface area (BSA) was covered by vesicular lesions. Under the diagnosis of Steven Johnson syndrome/TEN, deflazacort was discontinued, and intravenous dexamethasone (1.5 mg/kg/day), a 5-day course of IVIG (0.4 mg/kg/day), and cyclosporine (3 mg/kg/day) were administered. The lesions seemed to be stationary for 3 days, but on the 6$^{th}$ day of hospitalization, when IVIG was discontinued, the vesicular lesions progressed to approximately 60% of the BSA. Etanercept 0.8 mg/kg was administered subcutaneously. Lesions stopped progressing, and bullous lesions started epithelialization. However, on the 15th day, around 30% of the BSA was still involved; thus, a second dose of etanercept was administered. No acute or sub-acute complications were observed. In conclusion, the use of etanercept in children with TEN that is not controlled with conventional therapy is both effective and safe.

KEYWORDS

**toxic epidermal necrolysis, Steven Johnson syndrome, etanercept, deflazacort, severe cutaneous adverse reaction, pediatric**

**Abbreviations:** TEN, toxic epidermal necrolysis; BSA, body surface area; NSAID, nonsteroidal anti-inflammatory drug; ALDEN, algorithm of drug causality for epidermal necrolysis; IVIG, intravenous immunoglobulin.

# 1 Introduction

Toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous disorder often induced by drugs (1). Patients with TEN exhibit over 30% body surface area (BSA) for epidermal detachment, while those with Steven Johnson syndrome (SJS) have less than 10% BSA for skin detachment. Approximately 10%–30% of skin detachments are classified as overlapping SJS-TEN. Flu-like symptoms, such as fever, malaise, poor oral intake, sore throat, and headache, precede the onset of mucocutaneous symptoms, which are atypical targetoid maculopapules that form blisters (2).

TEN is mostly caused by drugs, such as sulfonamide or beta-lactam antibiotics, anti-seizure medications (phenytoin, lamotrigine, and carbamazepine), allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) (3, 4). Other causes include *Mycoplasma pneumoniae*, dengue virus, cytomegalovirus, and the use of contrast agents (2). The probability of the culprit drug is assessed through algorithm of drug causality for epidermal necrolysis (ALDEN), which is based on six parameters: 1) the time interval between the start of the drug and the onset of the reaction (index day), 2) the likelihood that the drug was present on the index day, 3) the presence of a history of adverse effects with the same drug, 4) whether the drug was discontinued as the disease progressed, 5) whether the drug has been documented in previous studies (3, 4), and 6) consideration of alternative possibilities (5).

TEN treatment involves systemic steroids, intravenous immunoglobulin (IVIG), or cyclosporine; however, the efficacy of these treatments is controversial (6). Recent studies showed elevated TNF-α levels in patients with SJS-TEN (7), and etanercept, a TNF-α antagonist, reduced skin-healing time in a randomized clinical trial (8). Herein, we report a case of a 44-month-old boy who developed TEN due to deflazacort as the probable culprit drug and was successfully treated with etanercept.

# 2 Case description

A 44-month-old boy presented to the emergency department with a fever of up to 38.4°C, sore throat, and erythematous maculopapular rashes and vesicles all over the face and body, with vesicles on the hands, feet, and trunk. The rashes and vesicles made the patient complain of severe pain and itching sensation. Symptoms began 4 days prior to presentation, with edema of the upper lip and vesicles in both hands. He was diagnosed with nephrotic syndrome and was taking deflazacort for nephrotic syndrome 21 days prior to the visit. Other complaints included diarrhea and dysuria. Physical examination showed that his eyes were also involved, with swelling of the eyelids, conjunctival injection, and yellowish mucous discharge. Erythematous maculopapular rashes appeared on the cheeks, neck, trunk, arms, penis, and fluid vesicles on both hands and feet. The patient also had a crust on his lips.

Laboratory tests showed a white blood cell count of 12,260 cells/$mm^3$ (eosinophil count of 800 cells/$mm^3$), hemoglobin level of 15.4 g/dL, and platelet count of 375,000 cells/$mm^3$. Serum biochemistry showed blood urea nitrogen (BUN) level of 10 IU/L, creatinine level of 0.48 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) level of 12/27 IU/L, C-reactive protein level of 1.83 mg/dL, and procalcitonin level of 0.206 ng/mL. Blood and urine cultures were negative for *Mycoplasma pneumoniae*, herpes simplex virus, varicella-zoster virus, and human herpes virus antigen.

Under the diagnosis of SJS/TEN involving 20% of BSA with severity-of-illness score for TEN (SCORTEN) (6) of 1 (tachycardia, heart rate 162), deflazacort was discontinued, and dexamethasone (1.5 mg/kg/day), a 5-day course of IVIG (0.4 mg/kg/day), and cyclosporine 3 mg/kg/day were initiated. The lesions appeared to be stationary for 3 days; however, when IVIG was discontinued on the 6th day of hospitalization, the vesicular lesions progressed to approximately 60% of BSA (Figures 1A–C). Etanercept (0.8 mg/kg) was administered subcutaneously (Figure 2). After administration, the lesion did not progress, and the bullous lesion also began to epithelialize. However, when re-evaluated on day 15, approximately 30% of the BSA was still involved (Figures 1D–F); therefore, a second dose of 0.8 mg/kg of etanercept was administered. Since then, the patient's condition improved without any complications (Figure 1G–I).

# 3 Discussion

TEN is a severe, potentially fatal mucocutaneous disorder (1). Despite the life-threatening nature of TEN, there are currently no standard treatment guidelines for TEN. The mainstay of treatment for TEN involves discontinuation of the culprit drug and provision of supportive care. The efficacy of commonly used systemic therapies, such as systemic steroid therapy, IVIG, and cyclosporine, has not been proven in large randomized trials and has yielded controversial results in smaller studies (6).

Deflazacort, a derivative of prednisolone oxazoline, is commonly used to treat nephrotic syndrome and is associated with low rates of steroid-induced osteoporosis and growth retardation (9). Although steroids are not commonly associated with the risk of SJS/TEN, in our case, deflazacort was the "probable" causative drug according to the ALDEN criteria. While notoriety of deflazacort is not "high risk", the delay from initial drug intake to index day was "suggestive", drug was present in the patient at index day, patient had not been exposed to this drug in the past and he had not been introduced to another culprit drug prior to the event (3–5). There have been some prior reports of SJS/TEN caused by deflazacort in literature (9–11). Steroids are classified into four classes based on their cross-reactivity. Deflazacort and corticosteroids are both in class A for cross-reactivity. Therefore, we used dexamethasone, which is in class C (12). Dexamethasone has been used in several cases to treat steroid-induced TEN (11, 13, 14).

While the complete pathogenesis of TEN remains elusive, TEN is understood as a T cell-mediated disease with CD8+ cells causing keratinocyte death with the contribution of granulysin, soluble Fas ligand, and TNF-α (2, 8). Systemic treatments, such as steroids, IVIG, and cyclosporine, inhibit these cytokines; however, their efficacy remains unclear (6, 15, 16). Etanercept is a monoclonal antibody that functions as a TNF-α antagonist by fusing to the extracellular binding domain of the human TNF receptor 2 (7, 17). In preclinical studies, etanercept showed significant immunosuppressive effects by reducing granulysin and TNF-α secretion in blister cells of patients




FIGURE 1
Toxic epidermal necrolysis. **(A–C).** HD#7: Prior to the first etanercept injection, the patient had maculopapular rashes and vesicles throughout the body. **(D–F).** HD#11: After the first dose of etanercept, epithelization began, but some vesicles and bullae remained. **(G–I)**. HD#18: After the second dose of etanercept, the patient's skin was mostly epithelialized. HD, hospital day.

with CTL-mediated severe cutaneous adverse reactions. In a randomized controlled trial comparing etanercept with steroids, etanercept was more effective than systemic corticosteroids in promoting reepithelialization in patients with TEN (8).

However, the use of etanercept in the pediatric population is limited (Table 1). In the previously mentioned randomized controlled study (8), the study population was mostly adults with a mean age of 56 years. Six pediatric patients were included in the study, only one of whom was treated with etanercept. Few case reports have described the use of etanercept in pediatric patients with TEN. The predominant causative drug is sulfamethoxazole-trimethoprim, a sulfonamide antibiotic. Treatment protocols varied, with some cases managed solely with etanercept while others concurrently treated with conventional systemic treatments, such as corticosteroids, IVIG, and cyclosporine. In most cases, the etanercept dosage was chosen using a small value of either 0.8 mg/kg/dose or 50 mg. The dosing interval varied from daily to once every 3 days. Physicians are prudent when using etanercept in pediatric patients with TEN due to its off-label application (24).

In this case, the patient experienced an increase in skin detachment despite conventional systemic treatment. After the administration of etanercept on the 7th day of hospitalization, skin healing commenced, leading to a reduction in the degree of detachment. The patient recovered without complications and was discharged.

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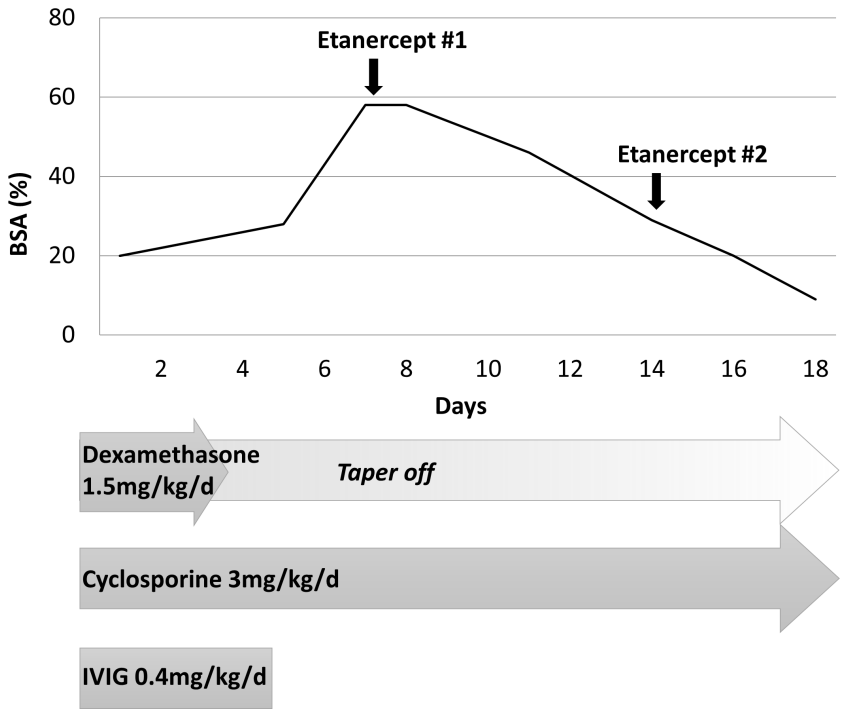



FIGURE 2
Skin detachment extent according to time. Extent of skin detachment due to toxic epidermal necrolysis during admission. Etanercept (0.8 mg/kg) was injected on hospital day #7 and hospital day #14. BSA, body surface area; HD, hospital day.

TABLE 1 Pediatric cases of SJS/TEN treated with etanercept in the literature.

| | Age | Sex | Culprit drug | BSA | Onset date (before admission) | Dose of etanercept | Date of administration | Other treatments | Inpatient days | 6 months follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| This study | 44 months | M | Deflazacort | 60% | 4 days before | 0.8 mg/kg/dose | HD 6, 15 | IV dexamethasone 1.5 mg/kg for 4 days<br>IVIG 0.4 mg/kg/day for 5 days<br>Cyclosporine 3 mg/kg/day | 19 | Postinflammatory hyperpigmentation, improving |
| 1 (18) | 2 years | M | Ibuprofen or acetaminophen | (–)* | (–)* | 0.4 mg/kg/dose | HD 6, 8 | Prednisone 1 mg/kg for 10 days<br>IVIG 1 g/kg/d for 4 days | 52 | Persistent skin dyspigmentation |
| 2 (19) | 11 years | F | SMX/TMP | 25% | (–)* | 25 mg (0.75 mg/kg/dose) | HD 4, 5 | IV methylprednisolone 30 mg/kg for 4 days<br>Cyclosporine 5 mg/kg/day for 3 days | (–)* | (–)* |
| 3 (20) | 17 years | M | Carbamazepine | 45% | (–)* | 50 mg (0.8 mg/kg/dose) | HD 1 | IV dexamethasone 1 mg/kg for 3 days<br>Cyclosporine 3 mg/kg for 7 days<br>1.5 mg/kg for 7 days | 14 | No sequelae |
| 4 (21) | 4 years | M | SMX/TMP | 12% | 4 days before | 0.8 mg/kg/dose or 50 mg | HD 1 | none | 17 | Postinflammatory hyperpigmentation, mild atrophic scarring, dry eye disease |

*(Continued)*

TABLE 1 Continued

| | Age | Sex | Culprit drug | BSA | Onset date (before admission) | Dose of etanercept | Date of administration | Other treatments | Inpatient days | 6 months follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 (21) | 7 years | F | acetaminophen or influenza vaccine | 50% | 4 days before | 0.8 mg/kg/dose or 50 mg | HD 1, 3 | none | 13 | Postinflammatory hyperpigmentation, mild atrophic scarring, dry eye disease, trichiasis |
| 6 (21) | 18 years | F | SMX/TMP | 0%** | 1 day before | 0.8 mg/kg/dose or 50 mg | HD 1 | none | 4 | (–)* |
| 7 (21) | 7 years | F | amoxicillin-clavulanate or mefenamic acid | 10% | 1 day before | 0.8 mg/kg/dose or 50 mg | HD 1, 2 | none | 10 | Postinflammatory hyperpigmentation, mild atrophic scarring, trichiasis, excessive tearing |
| 8 (22) | 13 years | M | SMX/TMP | (–)* | 2 days before | 50 mg | HD 2, 5 | IV methylprednisolone 5 mg/kg on HD#2, 2.5 mg/kg q8h for 5 days<br>IVIG 1 g/kg/day for 4 days | 13 | No sequelae |
| 9 (23) | 11 years | M | Unidentified | (–)* | (–)* | 25mg | HD 1 | Prednisone, IVIG | 12 | (–)* |

BSA, body surface area; HD, hospital day; IVIG, intravenous immunoglobulin; SMP/TMP, sulfamethoxazole-trimethoprim.
*Not mentioned. **0% of denudation but 30% of targetoid rash.

This study has limitations in that we have diagnosed TEN due to deflazacort as the probable culprit drug and did not perform skin biopsy to pathologically confirm TEN and *in vivo* or *in vitro* test to confirm the culprit drug. Furthermore, the use of etanercept was not initiated from the onset but rather after other treatments, making it challenging to attribute the observed effects solely to etanercept. Nevertheless, the noticeable improvement in skin lesions following etanercept administration suggests a potentially positive effect of etanercept.

As cases involving the administration of etanercept in pediatric patients are relatively scarce, this study is significant in that etanercept was safely used in children with TEN and led to improvement. Considering the limited number of pediatric patients, this study underscores the importance of further research, including randomized clinical trials, to assess the efficacy and safety of etanercept in the pediatric population.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by the Seoul National University Hospital Institutional Review Board. (No. 2210-077-1368) Written informed consent to participate in this study was provided by the patient's parents. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MJ: Writing – original draft, Investigation. YC: Investigation, Methodology, Writing – review & editing. YA: Investigation, Writing – review & editing. KL: Writing – review & editing. JP: Writing – review & editing, Conceptualization, Supervision, Writing – original draft. DS: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Concurrence of dermatomyositis and psoriasis: a case report and literature review

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Dermatomyositis (DM) is a type of inflammatory myopathy with unknown causes. It is characterized by distinct skin lesions, weakness in the muscles close to the body, and the potential to affect multiple organs. Additionally, it may be associated with the presence of malignancies. The development of DM is influenced by genetic susceptibility, autoimmune response, and various external factors like cancer, drugs, and infectious agents. Psoriasis is a chronic, recurring, inflammatory, and systemic condition. Scaly erythema or plaque is the typical skin manifestation. The etiology of psoriasis involves genetic, immune, environmental and other factors. It is uncommon for a patient to have both of these diseases simultaneously, although individuals with DM may occasionally exhibit symptoms similar to those of psoriasis. Our patient was diagnosed with psoriasis in his 50s because of scalp squamous plaques, but he did not receive standard treatment. Ten years later, he developed symptoms of muscle pain and limb weakness. He was diagnosed with psoriasis complicated with dermatomyositis in our department and received corresponding treatment. Moreover, we reviewed the relevant literature to evaluate similarities and differences in clinical manifestation and treatment to other cases.

KEYWORDS

psoriasis, dermatomyositis, pathogenesis, corticosteroid, case report

## 1 Introduction

Dermatomyositis (DM), an idiopathic inflammatory condition involving muscles and skin, is characterized by varying degrees of skin, muscle, and visceral organ involvement. The laboratory assay findings of DM patients revealed an elevation in muscle enzyme levels, while the electromyogram indicated damage to the muscles. Approximately 1 to 6 out of every 100,000 adults in the United States are believed to suffer from DM (1). DM has a considerable genetic component, and some human leukocyte antigen (HLA) alleles are related to DM (2). For example, HLA-B*08:01 has a significant association with adult-onset DM, and HLA-DRB1*03:01 is associated with juvenile-onset DM (3). Additionally, the interferon (IFN) pathway has been demonstrated to play a role in DM (4), and cutaneous activity in adult DM is connected with a type I IFN gene signature (4).

Psoriasis is an immune-mediated chronic, recurrent, inflammatory, and systemic disease. Common clinical signs include localized or widely distributed scaly erythema or plaques. Psoriasis is caused by a combination of genetic, immune, and environmental factors (5). Genetic factors are the main risk factors for psoriasis development (6). HLA-C*06:02 is associated with the earlier-onset age of psoriasis (7). HLA-B27 may contribute to the susceptibility of psoriatic arthritis(PsA) (8), And the T helper (Th)17/interleukin (IL)-23 pathway is considered to be the primary pathway in psoriasis (9). Even HLA alleles play an important role in both diseases, there seems to be no report indicating that these two diseases share similar HLA haplotypes.

From a clinical perspective, psoriasis can occur alongside autoimmune conditions like autoimmune bullous diseases, vitiligo, alopecia, and thyroiditis (10), the concurrence of DM and psoriasis. Herein, we reported a case of psoriasis combined with DM, and a literature review was performed to speculate on the possible pathogenesis and treatment.

## 2 Case description

In 2021, a 63-year-old Chinese male presented with a four-month history of infiltrative erythema on his face, neck, and upper chest, accompanied by muscle soreness and weakness in his limbs. Additionally, he had a 10-year history of psoriasis that only had topical therapies, and the symptoms were often recurrent. The physical examination revealed facial and periorbital edematous violaceous erythema (Figure 1A), erythema on the neck and upper chest (Figure 1B), Gottron's papules (Figure 1C), Gottron's sign (Figure 1D), scaly plaques on his scalp (Figure 1E) and back (Figure 1F). There was no arthralgia or nail involvement. Both the upper and lower limbs exhibited a grade 4 muscle strength accompanied by muscle tenderness.

Laboratory assay results revealed increased levels of lactate dehydrogenase (LDH) [417 U/L, normal range (NR) 120–246], aspartate aminotransferase (AST) (55 U/L, NR 15–46) and creatine kinase (CK) (229 U/L, NR 55–170). Biomarkers for lung cancer such as cytokeratin-19 fragment (CYFRA21-1) (27.1 ng/ml, NR 0–16.3) and neuron-specific enolase (NSE) (3.89 ng/ml, NR 0–3.3) were increased. However, his myositis-specific antibodies (MSAs) and autoantibody profiles were negative. Myogenic injuries to the right deltoid muscle and the biceps brachii muscle were seen on the electromyogram (EMG). A CT scan revealed chronic inflammation in the middle lobe on the right side and upper lobe on the left side of the lung, without any additional irregularities. Inflammation was detected in the lateral muscle groups of both shins through muscle MRI, along with the presence of effusion. A skin biopsy from the facial lesion revealed liquefaction of basal cells, edema of the superficial dermis, infiltration of lymphocytes around small vessels with nuclear dust (Figure 1G). Another skin biopsy from a scaly erythema lesion on his shoulder showed hyperkeratosis, parakeratosis, neutrophil accumulation, disappearance or thinning of the granular layer, mild thickening of the spinous layer, infiltration of lymphocytes and histiocytes around small vessels in the superficial dermis and deposition of mucinous substances in the interstitium (Figure 1H). The patient was diagnosed with dermatomyositis according to the Bohan and Peter's criteria (11) and received treatment consisting of 24 mg/day methylprednisolone (MPSL), 400 mg/day hydroxychloroquine (HCQ), and 15 mg/week methotrexate(MTX). One month later, there was a notable relief in symptoms, with CK, LDH, and AST levels falling within the normal range. Additionally, the dosages of MTX and HCQ were reduced to 10 mg per week and 200 mg per day respectively. Subsequently, the

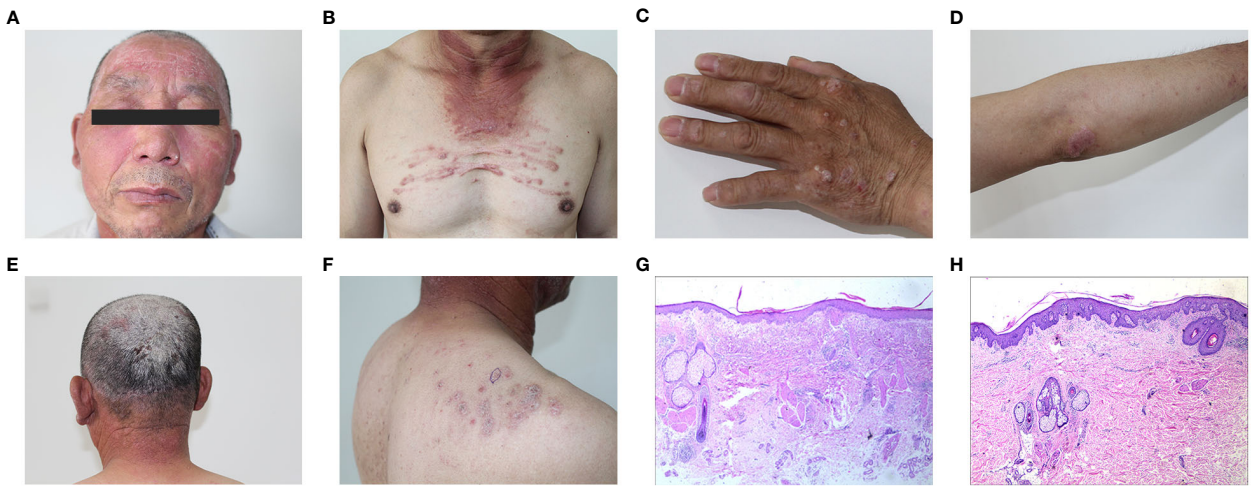



FIGURE 1
**(A)** Edematous violaceous erythema on the face and periorbital tissues. **(B)** Erythema on the neck and upper chest. **(C)** Left hand displaying Gottron's papules. **(D)** The upper limb displays Gottron's sign. **(E)** Scaly plaques on the scalp. **(F)** Scaly plaques on the back. **(G)** Histology from the facial lesion revealed liquefaction of basal cells, edema of the superficial dermis, infiltration of lymphocytes around small vessels with nuclear dust. **(H)** Skin biopsy from a scaly erythema lesion on the shoulder showed hyperkeratosis, parakeratosis, neutrophil accumulation, disappearance or thinning of the granular layer, mild thickening of the spinous layer, infiltration of lymphocytes and histiocytes around small vessels in the superficial dermis and deposition of mucinous substances in the interstitium.

doses of the three medications were gradually tapered, and now he receives 8 mg/day MPSL, 200 mg/day HCQ, and 5 mg/week MTX for treatment without any signs of recurrence. During the follow-up period, no clinical or radiological evidence of malignancy was observed in our patient.

## 3 Discussion

Autoimmune diseases like systemic lupus erythematosus (SLE), systemic sclerosis, and rheumatoid arthritis may coexist with psoriasis (10). Cases of psoriasis concurrent with dermatomyositis are also occasionally seen in daily clinical practice. As far as we know, there have been limited instances documented in the literature (Table 1) (12–23). In these cases, five were male and ten were female, of which six patients were under thirty years old, and they were all diagnosed with juvenile dermatomyositis. Six cases developed psoriasis prior to dermatomyositis, and dermatomyositis preceded in other cases. Among these cases, one had diabetes, hypertension, and anti-glomerular basement membrane disease, another had a hepatic tumor, a third had Hashimoto's thyroiditis and Sjögren syndrome, and a fourth had interstitial lung disease.

Regarding the possible triggers, three cases might be associated with medications, including adalimumab, secukinumab, and withdrawal of prednisolone. One case might be linked to a hepatic tumor. As for our case, he had no medication history or underlying disease. He was a farmer who had been exposed to prolonged sunlight without any protection in this summer. We suspected that sunlight exposure might be the possible trigger.

Mechanistically, both DM and psoriasis are autoimmune diseases. Previous evidence has shown that these two diseases share some signaling pathways and cytokines (24, 25). For example, IFN can induce apoptosis and cause vascular damage directly (25), while TNF-α may also play a direct role in causing muscle inflammation in DM patients (25). In psoriasis, IFN can activate myeloid dendritic cells to secrete IL-12 and IL-23, and induce the activation and

TABLE 1 A summary of reported cases of DM coexistence with psoriasis.

| | Age | Sex | Previous Situation | Interval Period | DM Subset | Psoriasis Subset | MSAs | Possible Trigger | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| Pavlović MD et al. (12) | 63 | F | DM | 4y | DM | psoriasis | N/A | N/A | MPSL, AZA |
| Gran JT et al. (13) | 50s | M | psoriasis | N/A | DM | erythrodermic psoriasis | – | hepatic tumor | MPSL |
| Machado NP et al. (14) | 51 | M | DM | 4y | DM | psoriasis | – | N/A | MPSL, CTX |
| Kim NN et al. (15) | 18 | F | JDM | 9y | JDM | psoriasis | N/A | N/A | MTX |
| | 8 | F | psoriasis | 10m | JDM | psoriasis | N/A | N/A | MPSL, MTX, MMF |
| | 4 | F | JDM | 2y | JDM | psoriasis | N/A | N/A | TCS |
| Dicaro D et al. (16) | 37 | F | psoriasis | 7y | CADM | psoriasis | – | adalimumab | MTX |
| Akiyama M et al. (17) | 52 | F | DM | 8y | DM | psoriasis | anti-TIF-1 Ab | withdrawal of PSL | PSL, MTX |
| Montoya CL et al. (18) | 20 | M | CADM | 5y | AJDM | erythrodermic psoriasis | – | N/A | ustekinumab |
| Inkeles MS et al. (19) | 45 | F | psoriasis | 4y | CADM | psoriasis | N/A | N/A | CsA |
| Kato Y et al. (20) | 30 | F | DM | 5y | DM | psoriasis | – | N/A | PSL |
| Xing Y et al. (21) | 21 | M | JDM | 6y | JDM | Psoriasis | – | N/A | PSL, CsA, MTX |
| Schreiber C et al. (22) | 45 | F | PsA | N/A | DM | PsA | anti-Jo Ab | N/A | PED, MTX |
| Perna DL et al. (23) | 20s | F | N/A | N/A | JDM | psoriasis | N/A | secukinumab | MTX |
| Present Case | 63 | M | psoriasis | 10y | DM | psoriasis | – | sunlight exposure | HCQ, MPSL, MTX |

F, female; M, male; DM, dermatomyositis; JDM, juvenile dermatomyositis; CADM, clinically amyopathic dermatomyositis; PsA, psoriatic arthritis; y, years; m, months; AJDM, amyopathic juvenile dermatomyositis; MSA, myositis-specific antibody; anti-TIF-1, anti-transcription intermediary factor 1 antibody; anti-Jo, Anti-Jo antibody; MPSL, methylprednisolone; AZA, azathioprine; CTX, cyclophosphamide; MTX, methotrexate; MMF, mycophenolate mofetil; TCS, topical corticosteroid; PSL, prednisolone; CsA, cyclosporin; PED, prednisone; HCQ, hydroxychloroquine.

proliferation of Th1, Th17, and Th22 cells, resulting in the secretion of cytokines such as TNF-α, IL-17, and IL-22. These cytokines further stimulate keratinocytes, which produce related cytokines and chemokines to form inflammatory circuits and promote the characteristic changes in psoriasis (5). However, although psoriasis and dermatomyositis share some signaling pathways and cytokines, the mechanisms of their co-occurrence are still unclear. Based on previous studies, we speculate that there seems to be a complex, interacting, and self-sustaining inflammatory circuit among these cytokines in psoriasis (5). However, drugs such as adalimumab and secukinumab can disrupt the balance of the inflammatory circuit, leading to the accumulation or dominance of certain cytokines within inflammatory circuit and ultimately resulting in the appearance of clinical symptoms of DM, even though this condition is relatively rare (16, 23). As mentioned above, sunlight exposure may be a possible trigger for our patient. On one hand, ultraviolet (UV) radiation in sunlight is a proposed trigger for DM (26). On the other hand, UV radiation could suppress the IL-23/IL-17 axis, resulting in the inhibition of the production of IL-17 (27). This immune response results in a reduction of IL-17-mediated inflammation in skin lesions, which is similar to the effect of IL-17 inhibitors, and can also disrupt the inflammatory circuit. Accordingly, we think that UV radiation present in sunlight might play a significant role in the pathogenesis of the co-existence of dermatomyositis and psoriasis. However, further investigation is needed to confirm this point.

As for the treatment, 9 patients received corticosteroid treatment, 8 patients received MTX, other treatments included cyclosporin (CsA), cyclophosphamide (CTX), azathioprine (AZA), mycophenolate mofetil (MMF), HCQ, ustekinumab and topical corticosteroid (TCS). While two diseases share some inflammatory pathways and some therapy options could apply simultaneously, it could also be seen that treatment of one disease may exacerbate another one. For instance, UV phototherapy is safe and effective for psoriasis (28), but it is also a trigger for DM and even exacerbates the symptoms of DM (26). TNF-α inhibitors such as adalimumab, IL-17 inhibitors such as secukinumab, are effective for psoriasis, and are frequently used worldwide. However, there are studies reporting dermatomyositis or psoriasis occurring or exacerbating after receiving these two therapies (16, 23). And while TNF-α inhibitors may be a potential therapy for DM, the worsening of the disease can also be seen during treatment (29). Further observation is necessary when using TNF-α inhibitors to treat either both diseases simultaneously or only DM. Furthermore, corticosteroids are considered the preferred first-line therapy for DM-associated myopathy (30), but their use in psoriasis is not advised unless the situation is highly critical and the symptoms cannot be controlled by other therapies. Thus, when treating dermatomyositis accompanied by psoriasis, corticosteroids need to be used carefully. Clinically, immunosuppressive agents such as MTX are commonly given with corticosteroids to reduce the doses and side effects of corticosteroids (30). It seems to be most commonly combined with corticosteroid in treating dermatomyositis accompanied by psoriasis. Intravenous immunoglobulin (IVIG) was not mentioned in the treatment of the co-existence of dermatomyositis and psoriasis. On one hand, although IVIG shows efficacy in treating dermatomyositis (31), the evidence for the treatment of psoriasis is limited and may even lead to the aggravation of psoriasis (32). On the other hand, economic burden is a common reason for patients not to receive IVIG treatment. Additional drugs such as CsA (19), CTX (14) and ustekinumab (18) have shown efficacy in treating the concurrent presence of dermatomyositis and psoriasis. But these treatments are case reports, lacking high-quality evidence, and should only be for reference. Currently, the management of the simultaneous occurrence of dermatomyositis and psoriasis is still in the preliminary stage of investigation.

Limitations associated with this case report warrant mention. For example, the muscle biopsy and examination of the specific HLA alleles were not performed as consent was not obtained. Moreover, there is a lack of results for nail-fold capillary capillaroscopy, which is characteristic in dermatomyositis and could reflect the ongoing disease activity (33).

While dermatomyositis coexistence with psoriasis has been reported in various instances globally, this case stands out as the initial one to have achieved successful treatment through the combination of corticosteroids, methotrexate, and hydroxychloroquine. Herein, we report this case to provide some experience for clinical practice.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

DC: Conceptualization, Writing – original draft. WY: Methodology, Writing – original draft, Writing – review & editing. JN: Investigation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Refractory Evans syndrome in two patients with spondyloenchondrodysplasia with immune dysregulation treated successfully with JAK1/JAK2 inhibition

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Biallelic mutations in the *ACP5* gene cause spondyloenchondrodysplasia with immune dysregulation (SPENCDI). SPENCDI is characterized by the phenotypic triad of skeletal dysplasia, innate and adaptive immune dysfunction, and variable neurologic findings ranging from asymptomatic brain calcifications to severe developmental delay with spasticity. Immune dysregulation in SPENCDI is often refractory to standard immunosuppressive treatments. Here, we present the cases of two patients with SPENCDI and recalcitrant autoimmune cytopenias who demonstrated a favorable clinical response to targeted JAK inhibition over a period of more than 3 years. One of the patients exhibited steadily rising IgG levels and a bone marrow biopsy revealed smoldering multiple myeloma. A review of the literature uncovered that approximately half of the SPENCDI patients reported to date exhibited increased IgG levels. Screening for multiple myeloma in SPENCDI patients with rising IgG levels should therefore be considered.

KEYWORDS

**spondyloenchondrodysplasia, ACP5, tartrate-resistant acid phosphatase, autoimmunity, interferonopathy, JAK inhibitor, myeloma**

## Introduction

SPENCDI (OMIM 607944) is a rare immuno-osseous dysplasia, with an increasing number of affected individuals reported in the literature (1–9). Clinically, the syndrome exhibits a broad phenotypic variability, but most patients present with skeletal and immune manifestations. Adaptative immune dysregulation and autoinflammation comprise the prevailing immune phenotype (1–4, 6–8) although immunodeficiency has also been reported (5, 9). In addition, SPENCDI can manifest with neurologic symptoms (1, 2, 4, 6, 8). Immune dyscrasias, most commonly manifesting as cytopenias and SLE-like symptoms (10–12), are often recalcitrant and refractory to conventional immunomodulatory therapies (1, 2, 6, 10, 13). SPENCDI is an autosomal recessive disease secondary to biallelic pathogenic variants in the *ACP5* gene. *ACP5* encodes for tartrate-resistant acid phosphatase (TRAP). In patients with SPENCDI, *ACP5* mutations lead to abolished TRAP activity in the serum and increased phosphorylation of osteopontin (OPN). OPN has emerged as a possible unifying mediator, as it is expressed in osteoclasts and in cells of the immune system (Figure 1). Increased OPN phosphorylation has been linked to increased osteoclast activity, which is believed to contribute to the observed bone and cartilage defects in this disease (6). In antigen presenting cells of the immune system, increased OPN phosphorylation has been associated with increased interferon (IFN)-α release (6). Increased levels of IFN-α may contribute to both, cell autonomous largely autoinflammatory manifestations propagated by innate immune cells as well as non-cell-autonomous systemic autoimmunity in which deregulatory inflammatory signals adversely affect adaptive immune responses.

The constellation of clinical symptoms and biomarkers, i.e. increased type I interferon (IFN) levels and upregulated expression of interferon stimulated genes (ISGs) suggest that SPENCDI is a type I interferonopathy (1, 2, 6, 14, 15). Janus kinase (JAK) inhibitors, also known as jakinibs, are immunomodulators that inhibit the activity of one or more of the JAK enzyme family. The JAK inhibitors ruxolitinib and baricitinib inhibit JAK1 and JAK2 activity downstream of the type I interferon receptor. JAK inhibitors have shown therapeutic benefits in patients with type I interferonopathy, such as SAVI (stimulator of IFN genes–associated vasculopathy with onset in infancy), CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), and Aicardi Goutières syndrome (AGS), as well as patients with undefined interferonopathies (16–18). Two of the patients with higher initial IFN signatures and undefined interferonopathies improved significantly, suggesting that genotype was not necessary to tailor treatment decisions (6). We therefore reasoned that our two patients with SPENCDI may also benefit from targeted JAK inhibition. Here, we report the favorable clinical and biological response of two patients with SPENCDI and recalcitrant cytopenias to ruxolinitb therapy.

## Results

## Patient 1

is a 19-year-old male who initially presented at 3-years of age with short stature, hypothyroidism (Hashimoto's disease), and Evans syndrome, manifesting with autoimmune hemolytic

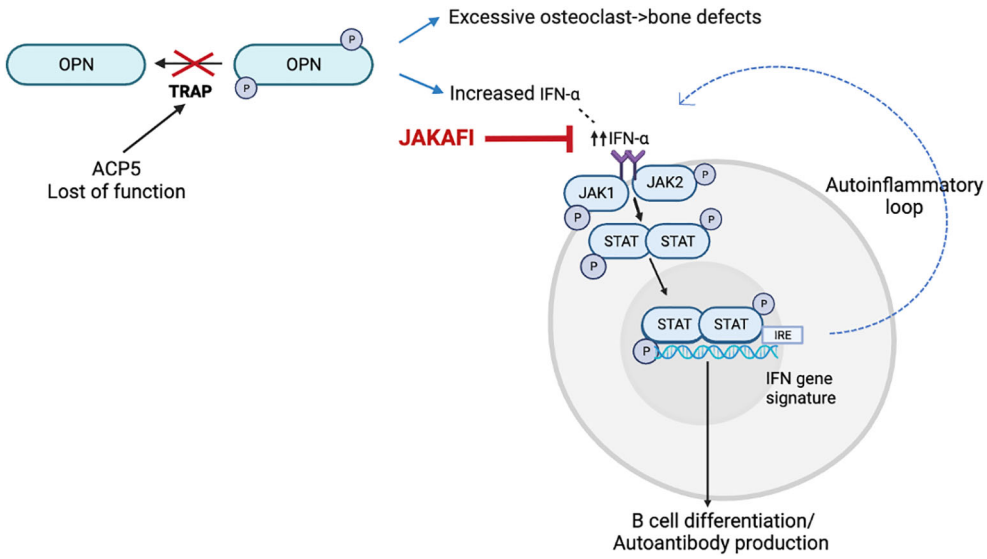



FIGURE 1
Model for the disease mechanism in SPENCDI, adapted from (6). *ACP5* encodes for tartrate-resistant acid phosphatase (TRAP). Lack of TRAP phosphatase activity results in hyperphosphorylation of OPN. Increased OPN phosphorylation has been linked to increased osteoclast activity, which is believed to contribute to the observed bone and cartilage defects in this disease (6). In antigen presenting cells of the immune system, increased OPN phosphorylation has been associated with increased interferon (IFN)-α release (6). This figure was created using BioRender.com.

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TABLE 1 Clinical features, laboratory parameters and treatments rendered prior to ruxolitinib therapy for patients #1 and #2.

| | Patient #1 | Patient #2 |
|---|---|---|
| **Ethnicity** | Hispanic | Hispanic |
| Age of onset | 3 yo | 4 yo |
| Short stature | Yes | Yes |
| Developmental delay | No | Yes |
| Infections | No | Yes (pneumonia) |
| Hepatosplenomegaly | Yes | Yes |
| Autoimmunity | Yes | Yes |
| Thyroid dysfunction | Yes | Yes |
| Autoantibodies (ANA, DNA, myeloperoxidase, and thyroglobulin antibody) | Positive ANA | Positive thyroglobulin antibody |
| Cytopenia | Evans syndrome: ITP, AIHA, neutropenia | Evans syndrome: ITP, AIHA, neutropenia |
| Laboratory parameters at time of presentation | | |
| CD4 T cells (/uL) (NR: 300-2,000) | 216 | 236 |
| CD8 T cells (/uL) (NR: 300-1,800) | 223 | 954 |
| CD19 Cells (/uL) (200-1,600) | 247 | <20 (s/p Rituximab) |
| CD56CD16 cells (/uL) (92-1,200) | 73 | 40 |
| IgG (mg/dL) (NR: 440-1,470) | 3,460 | 761 (on IVIG) |
| IgA (mg/dL) (NR: 31 – 180) | 169 | <8 |
| IgM (mg/dL) (NR: 25-190) | 87.2 | 272 |
| Titer to Diphtheria (NR: positive) | Positive | Positive |
| Titer to Tetanus (NR: positive) | Positive | Positive |
| Titers to Pneumovax | 21/23 | |
| ESR (mm/h) (NR: 0-10) | 78 | |
| CRP (mg/dL) (NR<0.50) | 1.2 | 1 |
| Bone marrow biopsy | Normal cellularity | Hypercellularity |
| Xray | Metaphyseal dysplasia and platyspondyly | Metaphyseal dysplasia and platyspondyly |
| Brain MRI | Calcification of the bilateral globus pallidus | Symmetrical bilateral basal ganglia calcifications, bilateral cerebral subcortical calcifications, and symmetrical bilateral cerebellar calcifications |
| Cytokine testing (Luminex) | | |
| IFNa2 (pg/mL) | 136.8 | 224.69 |
| IL-1Ralpha (pg/mL) | 17008398.6 | 521.06 |
| IL-6 (pg/mL) | 3421.89 | 9.38 |
| IL-18 (pg/mL) | NA | 490.84 |
| TNF-alpha (pg/mL) | 1052.83 | 25.93 |
| Therapy prior to ruxolitinib treatment | Prolonged therapy with steroids, sirolimus, rituximab, IVIG, bortezomib, MMF | Prolonged therapy with steroids, rituximab, IVIG, MMF |

anemia (AIHA), thrombocytopenia and neutropenia (Table 1). He had been glucocorticoid-dependent since diagnosis. Although his AIHA had initially been responsive to prednisone, the subsequent discovery of multiple vertebral compression fractures (Figure 2A) led to discontinuation of glucocorticoids due to concerns for bone metabolism side effects. These therapeutic considerations preceded the diagnosis of SPENCDI with osseous dysplasia as a possible alternative explanation for the vertebral abnormalities. Various other combinations of immunosuppressive therapies including immunoglobulins (IVIG), rituximab, sirolimus, bortezomib and mycophenolate mofetil (MMF) failed to improve his cytopenias or caused severe side effects, such as transaminitis (sirolimus) and anaphylaxis (bortezomib), ultimately necessitating their discontinuation. Further details on presentation and treatment are listed in the Supplementary Materials. After a brief period of clinical stability on MMF, the patient's AIHA eventually recurred, requiring prolonged courses of oral steroids, and prompting referral to immunology for evaluation of an underlying immune dysregulation syndrome.

Trio whole-exome-sequencing (WES) revealed biallelic compound heterozygous pathogenic variants in the *ACP5* gene (c.325G>A, p.Gly109Arg/c.526C>T, p.Arg176*) establishing the diagnosis of spondyloenchondrodysplasia with immune dysregulation (SPENCDI). Both parents were identified as heterozygous asymptomatic carriers of one of the variants (Figures 2B, C; Supplementary Materials; Supplementary Table 1). Based on the favorable therapeutic response of other patients with type I interferonopathies to JAK inhibitors (3, 4, 12, 19–21), and the shared pathophysiologic hallmarks of SPENCDI with other type I

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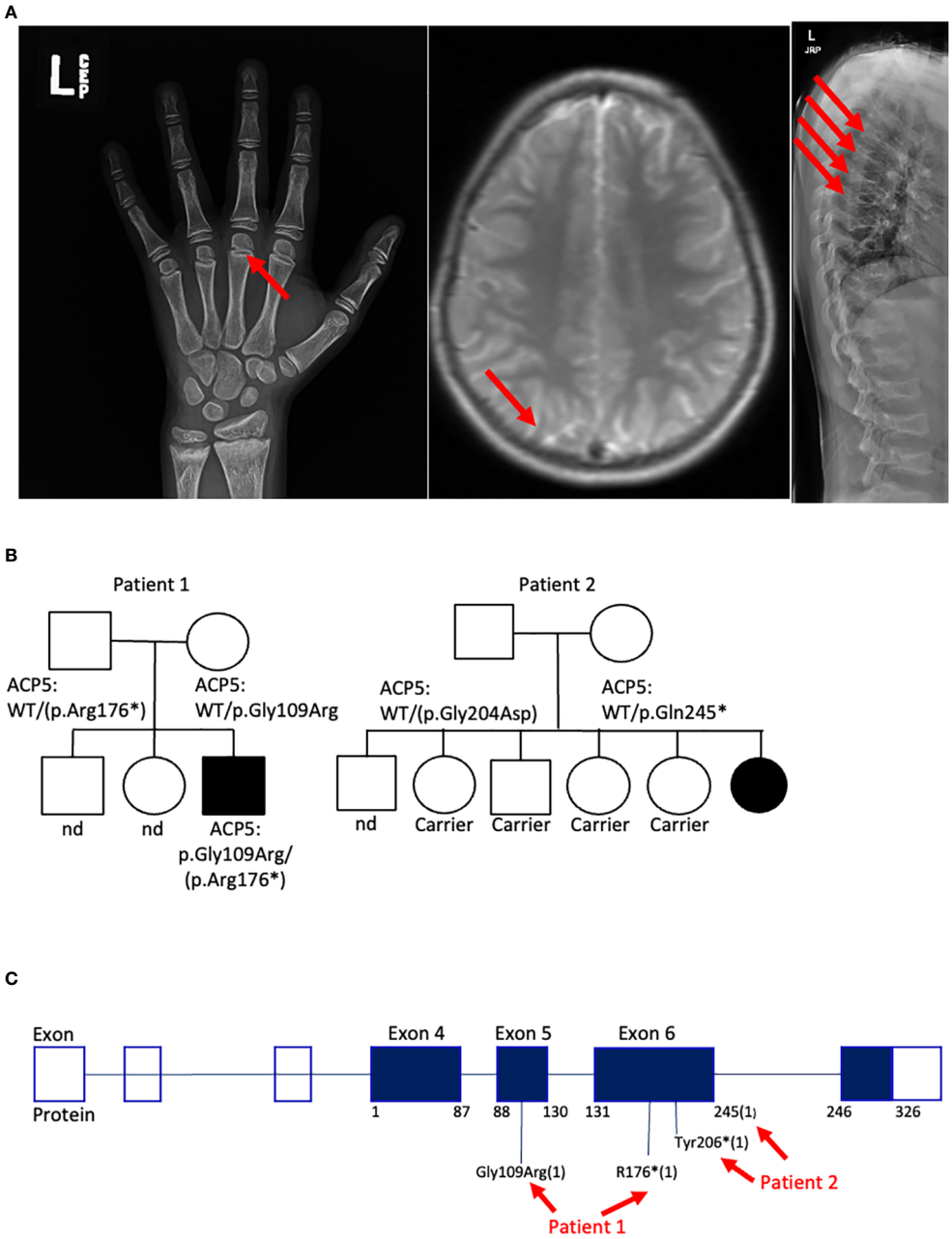



FIGURE 2
Genetic and clinical characteristics of SPENCDI patients. **(A)** Xray of the left hand (patient #1). Well-defined metaphyseal irregularity (indicated by red arrow) and sclerosis of the distal radius and ulna consistent with bone growth abnormality. Brain MRI (patient #1): nonspecific calcifications of the globus pallidus bilaterally without acute intracranial abnormality (indicated by red arrow). Xray of spine (patient #1): Multilevel compression deformities of the thoraco-lumbar spine (indicated by red arrows). Nd: not determined. **(B)** Family pedigree for patient #1 and patient #2. **(C)** Diagram illustrates the distribution of the reported *ACP5* variants for patient #1 and patient #2. * : stop codon.

interferonopathies (14, 22), a therapeutic trial with the JAK1/JAK2 inhibitor ruxolitinib was initiated (0.4 mg/kg/day). Within a week from initiation of therapy, the patient reported significantly improved energy levels. Within three months, the patient's anemia and thrombocytopenia were brought into remission and he has remained clinically stable with red blood cell indices in the normal range and platelet counts of approximately 100,000 per microliter of blood without any other additional therapies for the following three-and-a-half years (Figure 3A; Supplementary Table 2).

While on treatment with ruxolitinib, the patient has not experienced any significant infections. His shorter stature compared to his siblings is likely a sequela of his underlying disease, possibly confounded by early and prolonged glucocorticoid use. He remains neurologically asymptomatic and is performing well academically. Upon transfer to our care, an

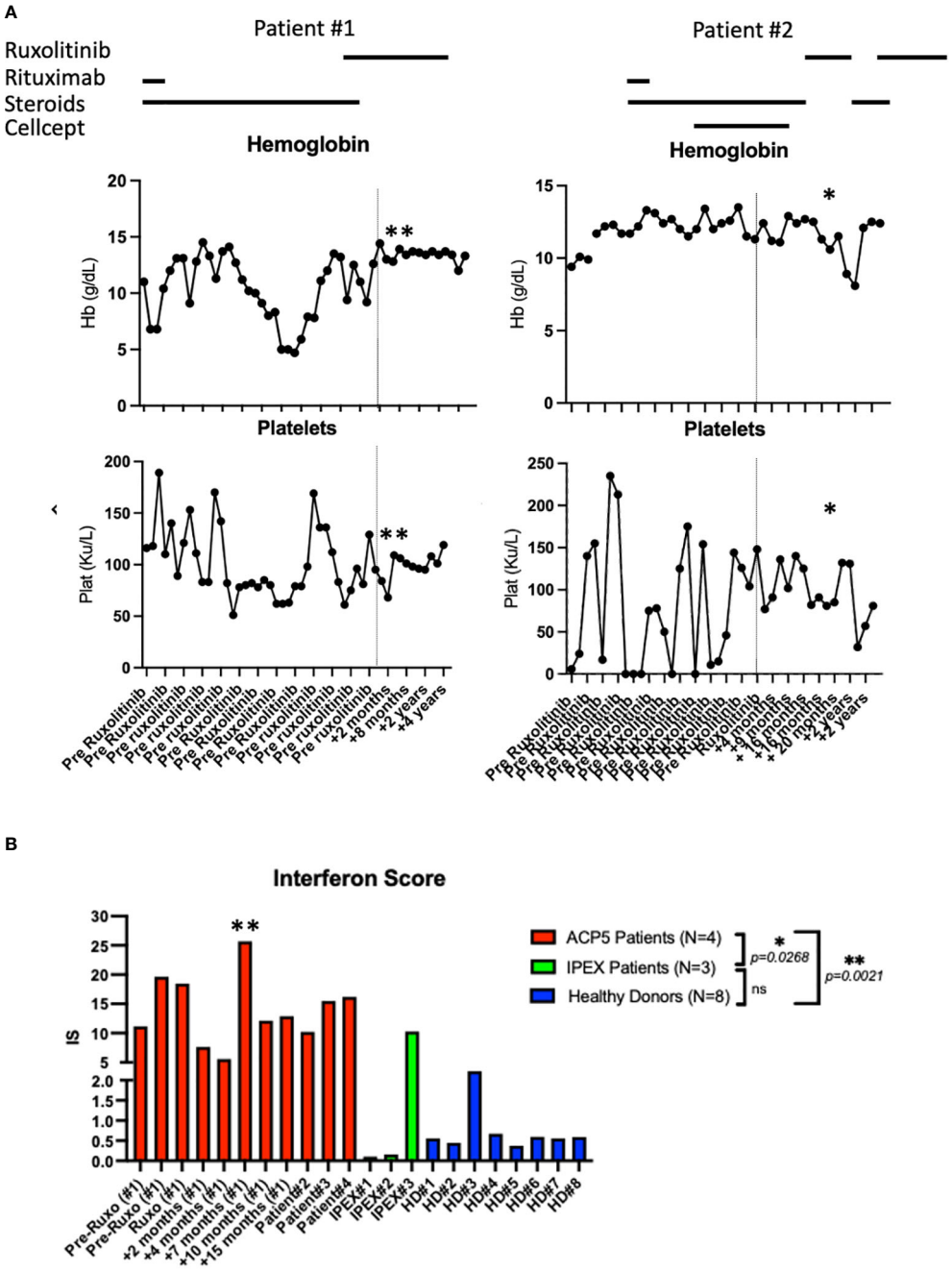



FIGURE 3
Laboratory parameters and interferon scores pre- and post-ruxolitinib therapy. **(A)** Hemoglobin and platelet count pre and post therapy with ruxolitinib in patient #1 and patient #2. Asterix (*) indicates time of hospital admission for acute viral and bacterial pneumonia complicated by acute SPENCDI flare. Asterix (**) indicates ISG expression in patient #1 transiently spiked during an infectious trigger while he remained clinically symptom free **(B)** Interferon Score of a panel of interferon stimulated genes in 4 SPENCDI patients at various time points throughout treatment, three subjects with IPEX and eight healthy donors. Dashed lines indicate the start of ruxolitinib. HD: healthy donors, Pat: patient, pre: pre ruxolitinib, post: post ruxolitinib, ruxo: ruxolitinib, IS: Interferon Score. Grouped statistical analysis performed using One-Way ANOVA (Kruskal-Wallis test) with Dunn's multiple comparison test. p-value between groups indicated on the graph. Overall p-value: <0.0001. Level of significance (p)=0.05. Additional information on ACP patient #3 and #4 is detailed in Supplementary Table 3.

initial screening MRI brain was obtained which showed nonspecific findings, including calcifications of the globus pallidus bilaterally, but no acute intracranial abnormalities. A subsequent brain MRI three years later showed stable calcifications but no additional abnormal findings. He was immunized with the mRNA COVID-19 vaccine and did not experience any side effects. Despite being fully vaccinated and boosted against COVID-19, he contracted the infection but remained asymptomatic without flaring of his autoimmunity.

In the context of a slowly but steadily rising serum IgG level over 36 months, a bone marrow biopsy screening was obtained which revealed a monotypic population of kappa light-chain

restricted plasma cells without an overall increase in blasts. This monotypic population, which lacked cytogenetic abnormalities, encompassed 20% of all bone marrow cells. The patient was subsequently referred to an oncologist and diagnosed with smoldering multiple myeloma. These findings prompted a review of the literature that revealed that approximately half of the patients with SPENCDI also report hypergammaglobulinemia (2, 4, 12, 13, 20, 22).

## Patient 2

is an 8-year-old female who was diagnosed with systemic lupus erythematosus (SLE) at the age of 5 years old. The patient presented with short stature and developmental delay. At diagnosis, the patient suffered from mucocutaneous disease (petechia, purpuric rash), anemia, thrombocytopenia, and splenomegaly. The patient also had, elevated inflammatory markers [ESR: 78 mm/h (normal range (NR):0-15mm/h); CRP:1.2 mg/dL(NR:<0.3 mg/dL)], severely decreased complement levels [CH50: 0 (NR: 42-95 U/mL); C3: 41 mg/dL (NR: 89-173 mg/dL); C4: <2.9mg/dL (NR: 17.0-42.0 mg/dL)], hypergammaglobulinemia, positive ANA titer (>1:1280), elevated dsDNA antibodies (>300 IU/mL), and elevated myeloid peroxidase (MPO) antibodies (Table 1). There was no evidence of renal involvement. Cytopenias were moderately responsive to glucocorticoid therapy, but refractory to rituximab and IVIG. At the time of initial assessment in immunology clinic, the patient was treated with glucocorticoids and MMF. Further details on presentation and treatment are listed in the Supplementary Materials.

Genetic analysis revealed that the *ACP5* gene had a pathogenic variant with a premature stop codon (c.733C>T, p.Gln245*) and a variant of unknown significance (VUS) resulting in an amino acid substitution (c.611G>A, p.Gly204Asp). Both parents were identified as heterozygous asymptomatic carriers of one of these variants establishing that the patient was compound heterozygote for these two variants (Figures 2B, C; Supplementary Materials; Supplementary Table 1). Given these findings, the patient was assessed for the presence of metaphyseal dysplasia. X-rays of hands and spine showed metaphyseal dysplasia and platyspondyly. Additionally, characteristic radiolucent metaphyseal and vertebral lesions were identified. Apart from an episode of pneumonia at age 4 years, there was no significant history of infections. Due to unclear developmental delay, the patient underwent a screening MRI of the brain which was normal. Considering the positive outcome observed in patient #1, we initiated treatment with ruxolitinib at a dosage of 0.4 mg/kg/day and this patient also showed significantly improved energy levels within one week and improved platelet counts within less than one month from starting treatment. She remained clinically stable and was steroid-free for the next 2-and-a-half years until she developed acute respiratory failure due to parainfluenza and rhinoviral pneumonia with bacterial superinfection and sepsis. Ruxolitinib was discontinued and the patient experienced, after a few days, an acute flare of ITP treated with glucocorticoids. After resolution of sepsis and following the reinitiation of ruxolitinib therapy, the patient's platelet count improved within 4 weeks (Figure 3A).

There is no specific biomarker for tartrate-resistant acid phosphatase activity, however, increased expression in interferon stimulated genes (ISG) has consistently been found in SPENCDI patients. The interferon score of both patients with SPENCDI in our study (patient 1 and 2) was significantly elevated at baseline compared to healthy controls and patients with IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, where autoimmunity is caused by a regulatory T cell defect (Figure 3B; Supplementary Figure 1). As previously reported by Fremond et al., we only observed a minimal decrease in interferon score in patient #1 following the initiation of ruxolitinib therapy (Figure 3B) (23). However, the resolution of cytopenias, combined with the increase in energy, academic performance and general wellbeing associated with ruxolitinib treatment in both patients suggests that interferon scores fail to adequately capture the clinical response. Notably, ISG expression in patient #1 transiently spiked during an infectious trigger while he remained clinically symptom free (Figures 3A, B; Supplementary Figure 1).

## Discussion

There is growing evidence that SPENCDI is a type I interferonopathy that shares clinical features with other interferonopathies, including autoimmune and autoinflammatory manifestations (1–9). Specifically, a clinical presentation consistent with SLE, in patient #2, should prompt consideration for further genetic testing as monogenic forms of SLE have been described in association with variants in *C1Q, C1R, C1S, CA, DNASE1*, *TREX1* and *ACP5* (11, 12, 24). Genetic testing was pursued for this patient because of the severe and refractory nature of Evans's syndrome (25–28).

The long-term prognosis and quality of life in patients with SPENCDI is influenced by multiple factors. The severity of the immune dysregulation and the side effects of conventional immunosuppressive therapies play an important role. The use of JAK inhibition in interferonopathies (14) aims at achieving immunomodulation, i.e., a normalization of the augmented immune response by downregulating the signal that is downstream of the type I interferon receptor; which is expected to ameliorate both, autoinflammatory and adaptive autoimmune manifestations alike. Patient #1 has experienced multiple vertebral compression fractures, likely associated with his primary disease but possibly confounded by the long-term glucocorticoid use. The two patients reported in our study were refractory to conventional immunosuppressive therapies but responded to ruxolitinib within only a few weeks from starting treatment, while their interferon score remained elevated. One plausible explanation for this discrepancy could be the consequence of JAK inhibitors on the B cell differentiation by blocking the effects of pro-inflammatory cytokines. JAK inhibitors are known to inhibit the differentiation of human B cells into plasmablasts in response to type I interferon stimuli, thereby reducing the levels of autoantibodies (29, 30). While JAK inhibitor treatment did yield significant improvements in autoimmune cytopenias, it is possible that genes associated with type I interferonopathy remain activated in immune cells with cell-intrinsic defects. Importantly, both patients are tolerating ruxolitinib well, with no significant adverse effects, except for

mild neutropenia in patient #1 which constitutes a manageable dose limiting toxicity. Ruxolitinib has been associated with various side-effects including myelosuppression, increased risk of viral infections, transaminitis and non-melanoma skin malignancy. Patients on prolonged ruxolitinib treatment can also develop treatment resistance (31). Both patients were regularly monitored for Epstein-Barr virus, cytomegalovirus, JC, and BK virus reactivation by PCR. which remained negative throughout treatment with ruxolitinib. Ruxolitinib discontinuation syndrome has been documented among myelofibrosis patients, manifesting after the cessation of ruxolitinib treatment. The reported rebound effects vary significantly in severity, ranging from mild to potentially life-threatening symptoms. Abrupt discontinuation of ruxolitinib in myelofibrosis patients may lead to conditions such as worsening of cytopenia, splenomegaly, spleen rupture or acute respiratory syndrome, affecting approximately 15% of individuals (32). The patients and their families have been educated about the risk of rebound if ruxolitinib is abruptly discontinued.

An increase in IgG levels in patients with SPENCDI has been observed by us and others (2) and ultimately lead to the diagnosis of smoldering multiple myeloma in patient #1. We therefore recommend SPENCDI patients should be monitored prospectively for the development of monoclonal gammopathy and regular assessment of immunoglobulin levels, free kappa/lambda light chain ratio and 24 hours urine analysis for Bence-Jones proteinuria should be considered. Any abnormal findings may warrant a referral to the hematologist to assess the need for a bone marrow biopsy.

To the best of our knowledge, there have been no reports of multiple myeloma in patients with SPENCDI. It's important to highlight that MM and MGUS have also been observed in individuals with VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome, a condition propelled by somatic myeloid mutations resulting in autoinflammatory responses (33, 34). In a comprehensive study involving 116 French patients diagnosed with VEXAS syndrome, MDS (myelodysplastic syndrome) was detected in 58 out of 116 cases (50%). Out of these 58 MDS cases, 12 exhibited MGUS (17%) (35). Nevertheless, there remains uncertainty regarding whether somatic UBA1 variants directly instigate MM's development or whether these variants contribute to conditions like MGUS and plasma cell disorders.

We carefully assessed the potential involvement of the JAK inhibitor therapy in the pathogenesis of multiple myeloma in patient #1. Notably, the patient's hyperglobulinemia predated the initiation of ruxolitinib treatment. Furthermore, multiple myeloma is not a malignancy associated with either primary T-cell immunodeficiency or prolonged immunosuppressive therapy. There is no documented association between STAT-1 loss-of-function and multiple myeloma (36). In contrast, recent clinical approaches have demonstrated some success in treating refractory multiple myeloma using a combination of ruxolitinib, corticosteroids, and lenalidomide (37). Given the scarcity of literature specifically addressing baricitinib in the context of multiple myeloma, we have elected to continue treatment with ruxolitinib in patient #1.

Another important consideration for the long-term prognosis in patients with SPENDCI is the development of neurologic symptoms in the context of nonspecific brain calcifications. Despite exhibiting bilateral calcification of the globulus pallidus on the brain MRI, patient #1 did not display any neurological symptoms. By contrast, patient #2 exhibited developmental delay but no calcifications noted in the brain MRI. Notably, the neurological status of both patients has remained stable on ruxolitinib treatment for more than 2 years. One might speculate that mitigating systemic inflammation with ruxolitinib could also have beneficial effects on the neurologic manifestations in SPENCDI as has been shown for patients with type I interferonopathy due to Aicardi-Goutières syndrome (38).

The presented cases by us and others (3, 4, 12, 19–21) support the use of JAK-inhibitors as an effective targeted therapy for patients with SPENCDI and severe cytopenias. Lack of effective biomarkers to capture the clinical response to JAK-inhibitors (e.g. IFN scores) highlight the need for further studies to delineate the exact underlying disease mechanism in SPENCDI. SPENCDI patients should be monitored prospectively for the development of monoclonal gammopathy. Further randomized controlled trials will be needed to confirm these findings in larger patient cohorts and evaluate possible neuroprotective benefits of targeted JAK-STAT inhibition in patients with SPENCDI and other interferonopathies.

# Methods

## Laboratory testing

T, B and NK subsets as well as immunoglobulin levels (IgA, IgM and IgG levels) were measured by flow cytometry in the CLIA-certified clinical core laboratory at Stanford (Stanford, CA, USA).

## Cytokines and chemokine testing

IL-18 serum level and CXCL9 were measured by ELISA in a CLIA-certified clinical core laboratory (Cincinnati Children's hospital, Cincinnati, OH, USA). In Table 1, IFNa2, IL-1Ralpha, IL-6, IL-18 and TNF-alpha were measured via Luminex (Human Immune Monitoring Center Stanford, CA, USA). In Supplementary Table 2: IL-1β, IL-2 receptor, IL-6, IL-10, IL-18, IFN-gamma, IFN-α were measured by ELISA method (ARUP, Salt Lake City, UT, USA).

## Interferon score

Six out of 15 ISGs were selected based on their expression level in a previous study (15) and measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR) (Supplementary Figure 1. In brief, 2.5 mL of blood was collected into PAXgene tubes (PreAnalytix), and total RNA was extracted from whole blood using a PAXgene RNA isolation kit (MagMAX). qRT-PCR analysis was performed using the TaqMan Universal PCR Master Mix (Applied Biosystems) and cDNA derived from 40 ng of total RNA and TaqMan probes for the ISGs *IFI27* (Hs01086370_m1), *IFI44L* (Hs00199115_m1), *IFIT1*

(Hs00356631_g1), *ISG15* (Hs00192713_m1), *RSAD2* (Hs01057264_m1), and *SIGLEC1* (Hs00988063_m1). Taqman probes for *HPRT1* (Hs03929096_g1) and *18S* (Hs999999001_s1) ribosomal RNA was used for internal normalization of the PCR assay (Applied Biosystems qpcr analysis module). Delta delta Ct method was used for relative quantification (RQ) of gene expression for each of the six probes, against a single reference control sample. Subsequently, Interferon Score (IS) was calculated by the fold change in the median of the six probes per sample compared to the median of all the healthy controls (n=8).

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Stanford, Research of compliance, CA, USA. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) (patient 1) and minor(s)' legal guardian (patient 2) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YG: Data curation, Supervision, Writing – original draft, Writing – review & editing. MN: Writing – review & editing, Data curation. JV: Writing – review & editing. A-MC: Writing – review & editing. EH: Writing – review & editing. KM: Writing – review & editing. BG: Writing – review & editing. DS: Writing – review & editing. BS: Writing – review & editing. LR: Writing – review & editing. AT: Writing – review & editing. KIW: Writing – original draft. DL: Writing – review & editing. RB: Writing – review & editing. KGW: Methodology, Supervision, Writing – review & editing.

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## Conflict of interest

KGW is a scientific advisory board member for Garuda Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1328005/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Interferon signature per gene for 8 healthy controls, 3 IPEX patients, and 4 SPENCDI patients.

SUPPLEMENTARY TABLE 1
ACP5 variants for patients #1 and #2.

SUPPLEMENTARY TABLE 2
Clinical phenotype and biological parameters of patient #1 pre and post ruxolitinib therapy.

SUPPLEMENTARY TABLE 3
Clinical phenotype and biological parameters for ACP5 patient #3 and #4.

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# A case of IgG4-related ophthalmic disease after SARS-CoV-2 vaccination: case report and literature review

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Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is affecting the world with a surge in cases. A variety of autoimmune diseases occur after SARS-CoV-2 infection or vaccination, of which IgG4-related disease (IgG4-RD) is an important type. IgG4-RD can involve multiple organs of the body. The ocular manifestation of IgG4-RD is called IgG4-related ophthalmic disease (IgG4-ROD). We herein report a patient diagnosed with IgG4-ROD. The patient developed ptosis and vision loss after SARS-CoV-2 vaccination, and the symptoms worsened after SARS-CoV-2 infection. After excluding other diseases like myasthenia gravis and Eaton-Lambert syndrome that may cause ptosis, the diagnosis of IgG4-ROD was confirmed by pathological examination. We discussed the predisposing factors, diagnosis and treatment of this patient to provide a more empirical and theoretical basis for clinical diagnosis and treatment. We conducted a literature review of previously reported cases of IgG4-RD following SARS-CoV-2 infection or vaccination. We retrieved a total of 9 cases, of which 5 developed symptoms after vaccination and 4 after infection. Demographic and clinical characteristics were summarized. In conclusion, our case represents the first case of proven IgG4-ROD after COVID-19 vaccination. We believe that IgG4-ROD and SARS-CoV-2 infection or vaccination are closely related, and the immune system disorder caused by SARS-CoV-2 infection or vaccination may be a key factor in the pathogenesis of IgG4-RD. But for now, there is no direct evidence that there is a causal relationship between SARS-CoV-2 infection or vaccination and IgG4-ROD, which still needs more research and exploration to confirm.

KEYWORDS

**autoimmunity, case report, COVID-19, IgG4, IgG4-related ophthalmic disease, SARS-CoV-2**

**Abbreviations:** COVID-19, Coronavirus disease 19; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; IgG4-RD, IgG4-related disease; IgG4-ROD, IgG4-related ophthalmic disease; TLRs, Toll-like receptors.

# 1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious coronavirus, which causes an acute respiratory disease called coronavirus disease 19 (COVID-19) (1). COVID-19 does not only cause inflammatory symptoms such as fever and cough but also has a huge impact on the immune system. Vaccination is one of the most effective interventions to substantially reduce severe disease and death due to SARS-CoV-2 infection. At present, there is some evidence that a variety of different autoantibodies appear in patients after SARS-CoV-2 infection or vaccination, and a number of them develop autoimmune diseases, such as autoimmune hemolytic anemia, Guillain-Barre syndrome, and so on (2–4).

IgG4-related disease (IgG4-RD) is an autoimmune disease with undetermined pathogenesis, in which multiple organs and tissues can be involved (5). IgG4-RD is characterized by infiltration of IgG4-immunopositive plasmacytes and elevated serum IgG4 concentration accompanied by enlargement and mass in various organs (6). Several previous case reports had reported the development of IgG4-RD after SARS-CoV-2 infection or vaccination, patients showed different symptoms. The ocular manifestation of IgG4-RD is called IgG4-related ophthalmic disease (IgG4-ROD). IgG4-ROD most commonly affects the lacrimal gland, but orbital soft tissue, orbital nerves, sclera, choroid, and orbital adnexa can also be involved. It presents insidiously, with symptoms of painless proptosis, eyelid swelling, decreased vision with tearing, pain, redness, and photopsia (7). IgG4-ROD may involve a single structure or multiple structures within the orbit, and may also exhibit bilateral disease (8).

There are currently no internationally standardized diagnostic criteria for IgG4-ROD. The most recent diagnostic criteria proposed by Japanese researchers in 2015 are: (1) Imaging studies show enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscle as well as masses, enlargement, or hypertrophic lesions in various ophthalmic tissues; (2) Histopathologic examination shows marked lymphocyte and plasmacyte infiltration, and sometimes fibrosis. A germinal center is frequently observed. $IgG4^+$ plasmacytes are found and satisfy the following criteria: ratio of IgG4+ cells to $IgG4^+$ cells of 40% or above, or more than 50 $IgG4^+$ cells per high-power field (×400); (3) Blood test shows elevated serum IgG4 (≥135 mg/dl). Diagnosis is classified as "definitive" when (1), (2), and (3) are satisfied; "probable" when (1) and (2) are satisfied; and "possible" when (1) and (3) are satisfied (9). In terms of treatment, intravenous glucocorticoid therapy is the first-line treatment for IgG4-ROD, which is effective and well-tolerated (10). Rituximab is also a treatment option for some refractory patients (11).

We herein report a patient diagnosed with IgG4-ROD. The patient developed ptosis and vision loss after SARS-CoV-2 vaccination, and the symptoms worsened after SARS-CoV-2 infection. We admitted her to the ophthalmic ward of the Third Medical Center of Chinese PLA General Hospital. We recorded the changes in her condition and reviewed the previous literature.

# 2 Case description

The patient, a previously healthy 22-year-old female, received an inactivated COVID-19 vaccine in May 2021 and reported fever within the next few days. After a month, the patient noticed a slight ptosis in the left eye and a mild loss of vision in the right eye, and these symptoms gradually worsened. In January 2022, the patient felt that the above symptoms had progressed to the point where they were affecting her life and went to the local hospital. Orbital CT showed soft tissue swelling in the left lacrimal gland region. The funduscopy examination revealed macular edema in the right eye. Fundus fluorescein angiography showed tortuous fundus veins in the right eye, anastomosed vessels in the optic disc and retina, and extensive peripheral retinal vessel dilation and leakage. During hospitalization, compound anisodine was injected into the left superficial temporal artery, together with oral mecobalamin, Mongolian medicine, acupuncture, and electromagnetic therapy, the patient felt that the symptoms were worse than before.

The patient was admitted to our hospital in August 2022. After admission, the visual acuity of the right eye was 0.3 and the left eye was 0.8, the ptosis of the left eye covered the pupil more than 1/2 (Figure 1). Initially, we considered a diagnosis of myasthenia gravis and central retinal vein occlusion in the right eye. Serial tests were performed to identify the differential diagnosis. Electromyography showed that repetitive nerve electrical stimulation did not show characteristic changes. The fatigue test and the neostigmine test were negative. Serum specific antibodies for neuromuscular disease were all negative. The diagnosis of neuromuscular diseases like myasthenia gravis and Eaton-Lambert syndrome can be ruled out. However, we noted that serum IgG4 was 280 mg/dl and ocular ultrasound suggested uneven enlargement of the left lacrimal gland and fullness of the right lacrimal gland. To investigate the presence of neuropathy, an MRI of the head was performed, which revealed the optic nerve in the right orbit was slightly thinner than normal with hyperintensity on T2WI and abnormal enhancement of the optic nerve and its surrounding sheath. On August 23, 2022, a biopsy of the left lacrimal gland, orbital septal tissue, and orbital fat was performed by us. The result of histopathology was inflammatory pseudotumor. Immunohistochemical showed that the ratio of $IgG4^+$ plasmacytes to $IgG^+$ plasmacytes was more than 40% and more than 50 $IgG4^+$ cells per high-power field (×400) (Figure 2). We performed a staining of the CD4 cells (Supplementary Figure 1) and CD8 (Supplementary Figure 2) cells in the biopsy. This patient satisfied diagnostic criteria (1), (2), and (3) for a definite diagnosis of IgG4-ROD. After diagnosis, the patient was given high-dose intravenous methylprednisolone pulse therapy and tacrolimus. After five days of treatment, the patient reported opening the eye more easily, but there was no significant change in the ptosis and vision loss. The patient asked to be discharged. After discharge, the patient continued to take methylprednisolone orally until November 2022 and tacrolimus orally until August 2023.

Unfortunately, the patient was infected with COVID-19 in December 2022. Although the patient remained on oral

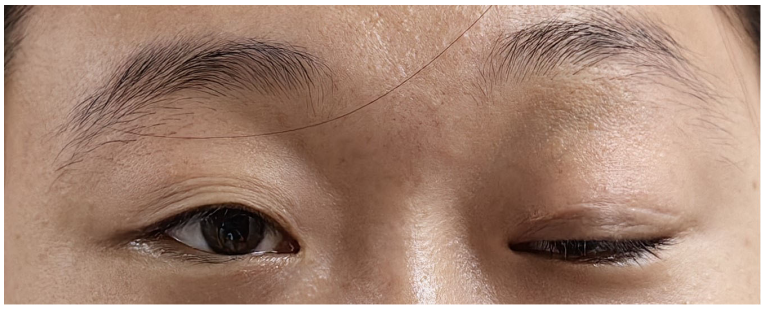


FIGURE 1
Photograph of the patient on admission.

tacrolimus, the symptoms of ptosis in her left eye and vision loss in her right eye worsened after infection, and she was readmitted in August 2023. The visual acuity of the right eye was 0.15 and the left eye was 1.0, the ptosis of the left eye covered the entire pupil. The serum IgG4 was 240 mg/dl. Given the poor response to steroids therapy and the patient's request for surgery to improve ptosis, we performed ptosis correction of left eye and bilateral double eyelid plasty on August 15, 2023 (Figure 3). During the ptosis correction, we performed a pathologic examination of a piece of the levator palpebrae superioris muscle, which showed fibrosis. The patient recovered well after the operation, and the eyelid margins of both eyes were symmetrical.

## 3 Discussion

The SARS-CoV-2, responsible for COVID-19, has spread across the world. The clinical manifestations of COVID-19 vary greatly, but it is worth noting that some patients can develop long-term complications, including the respiratory system, cardiovascular system, and nervous system (12). There is growing evidence that COVID-19 can cause autoimmune diseases. It has been suggested that common pathogenetic and clinical-radiological aspects between hyperinflammatory diseases and COVID-19 may indicate that SARS-CoV-2 may be a trigger for rapid autoimmune or autoinflammatory dysregulation (13). Several mechanisms, including molecular mimicry, bystander activation of T-cells, and epitope spreading, as for explaining how viral infection can trigger a response leading to autoimmune disease (14).

As the most important means to prevent SARS-CoV-2 infection, the COVID-19 vaccine has been widely used worldwide. Although it is well tolerated by most people, adverse reactions after vaccination should not be ignored. Vaccines induce adaptive immune responses to exert their protective effects, but may induce a hyperinflammatory state. A few cases of new or recurrent autoimmune disease have been reported after COVID-19 vaccination. Pichi et al. reported nine eyes presenting with ocular adverse events after the first inoculation of inactivated COVID-19 vaccine (15). It is assumed that COVID-19 vaccine can trigger autoimmunity through molecular mimicry, the production of

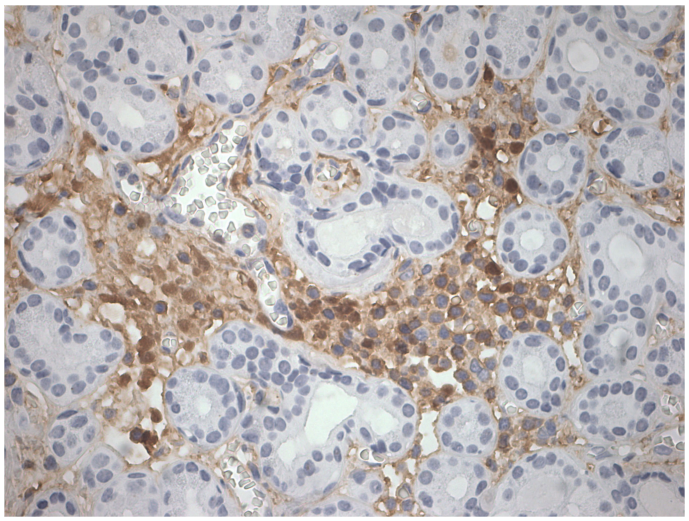


FIGURE 2
$IgG4^+$ cells (×400).

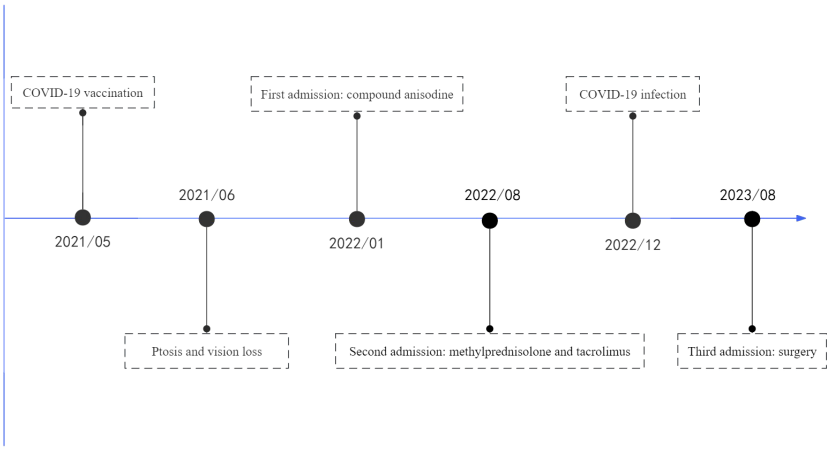



FIGURE 3
Timeline of treatment.

particular autoantibodies, and the role of certain vaccine adjuvants (16).

We conducted a literature review of previously reported cases of IgG4-RD following SARS-CoV-2 infection or vaccination (Table 1) (17–25). We retrieved a total of 9 cases, of which 5 developed symptoms after vaccination and 4 after infection. Of the vaccinated patients, 4 received mRNA vaccine, including 3 who received the mRNA BNT162b2 vaccine. The interval between the onset of IgG4-RD symptoms and SARS-CoV-2 infection or vaccination ranged from one day to three and a half months. IgG4-RD can affect a wide range of organs, and patients can be clinically manifested as hepatopathy, lung disease, pancreatitis, sialadenitis, rhinosinusitis, lymph node enlargement, and parotid enlargement. After surgery and prednisone therapy, most patients' symptoms were relieved or even recovered.

In our literature review, we found four patients who developed IgG4-RD after mRNA vaccination, whereas the patient we report here received an inactivated vaccine. Based on the available evidence, it is not clear whether different COVID-19 vaccine types have an effect on IgG4-RD pathogenesis. The mRNA in mRNA vaccines can present as either an antigen or an adjuvant,

TABLE 1 Demographic and clinical characteristics of previously reported IgG4-related disease following COVID-19.

| Author | Year | Age | Sex | SARS-CoV-2 | Vaccine Type | Interval time | Clinical Manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Rodrigues | 2022 | 66 | Male | Vaccination | mRNA BNT162b2 | 2 weeks | Autoimmune pancreatitis | Prednisone | Recovered |
| Patel | 2022 | 63 | Male | Vaccination | mRNA | 2 months | Autoimmune pancreatitis | Prednisone | Recovered |
| Tasnim | 2022 | 71 | Male | Vaccination | mRNA BNT162b2 | 2 weeks | Lung disease | Thoracoscopic drainage Decortication | Further treatment |
| Aochi | 2022 | 78 | Female | Vaccination | mRNA BNT162b2 | 2 weeks | Sialadenitis Autoimmune pancreatitis | Prednisone | Recovered |
| Kuno | 2023 | 84 | Female | Vaccination | / | 1 day | Hepatopathy | No treatment | Recovered |
| Roncati | 2020 | 67 | Male | Infection | / | 3.5 months | Subglottic stenosis | Surgery | Symptom relief |
| Harb | 2021 | 70 | Male | Infection | / | 1 week | Rhinosinusitis | Prednisone Surgery | Recovered |
| Xu | 2023 | 50 | Male | Infection | / | 2 months | Pleura lymph node enlargement | Not mentioned | Not mentioned |
| Gurunathan | 2023 | 36 | Female | Infection | / | 3 months | Sinusitis Parotid enlargement | Prednisolone Mycophenolate mofetil Rituximab | Symptoms controlled |

COVID-19, coronavirus disease 19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

and can be recognized and bound by endosomal Toll-like receptors (TLRs) and inflammasomes to induce inflammation and immune responses (26). It has been found that TLRs play an important role in the pathogenesis of IgG4-RD. M2 macrophages expressing TLR7 in diseased organs recognize the COVID-19 mRNA or their own RNAs released by stressed or injured cells and promote the production of a variety of fibrotic cytokines through TLR7/IRAK4/NF-κB signaling, leading to severe fibrosis in diseased organs (27). Furthermore, after injection of the COVID-19 mRNA vaccine, the mRNA enters the muscle cells and the ribosomes perform cellular translation to produce the spike protein (16). Multiple amino acid fragments on the SARS-CoV-2 spike protein have been identified as molecular mimics of human proteins, which can induce the immune system to produce autoantibodies (28). Although the inactivated COVID-19 vaccine cannot be translated *in vivo* like the mRNA vaccine, it carries the spike protein itself. When individuals are exposed to antigens for prolonged period of time, the humoral immune response eventually switches to IgG4. The proportion of IgG4 in immunoglobulin would increase significantly after multiple vaccination or breakthrough infection with SARS-CoV-2 (29). Recently revealed a novel subset of IL-10$^+$LAG3$^+$ T follicular cells infiltrating the affected organs of IgG4-RD patients, it may play an important role in driving IgG4 class switching (30). CD4$^+$ helper T cells are the most abundant cells in tissues affected by IgG4-RD and are thought to be the driver of IgG4-RD pathogenesis (31). Under some unknown conditions, CD4$^+$ helper T cells are activated in response to long-standing COVID-19 spike protein or other antigenic stimulation, thereby promoting the differentiation of IL-10$^+$LAG3$^+$ T follicular cells, driving IgG4 class switching.

IgG4-RD is an immune-mediated fibro-inflammatory disease, which usually leads to tumefactive lesions and fibrosis (32, 33). We considered the following two possible causes of this patient's ptosis: the first was the compression of the oculomotor nerve by the swelling of the orbital soft tissue caused by IgG4-ROD, and the second was the fibrosis of the levator muscle of the upper eyelid caused by IgG4-ROD. It has been suggested that serum IgG4 levels are useful in assessing dynamic disease severity and monitoring relapse (34). This is essential for physicians to treat IgG4-RD clinically. Kobak et al. reported a patient with IgG4-RD, who had a good response to treatment, but eventually causing IgG4-RD recurrence after infection with SARS-CoV-2 (35). Relapse of IgG4-RD is not only secondary to COVID-19 but may also be secondary to mRNA vaccination (36). Egashira et al. reported the development of cerebral venous sinus thrombosis in a patient with IgG4-ROD during recovery from COVID-19 (37). Cerebral venous sinus thrombosis is an important complication of COVID-19, which suggests that IgG4-ROD patients are more likely to have complications of COVID-19. A prospective study reported that serum IgG4 levels may predict the prognosis of COVID-19, a concentration of serum IgG4>700 mg/dl and an IgG4/IgG1 ratio>0.05 were associated with a significantly increased mortality at 30 days (38).

As to the cause of this patient's vision loss in the right eye, the central retinal vein occlusion was confirmed on examination. Ocular vascular embolism after COVID-19 vaccination is a rare complication (39). The exact mechanisms have yet to be ascertained. Leung et al. raised three possible mechanisms: vaccine-induced immune thrombotic thrombocytopenia, COVID-19 vaccine as a trigger in homocysteinaemia, and retinal vasculitis (40). There are a few reports of vision loss caused by central retinal vein thrombosis after COVID-19 vaccination, and vision can return to normal after timely treatment (41, 42). However, a self-controlled case series found no evidence of an association between retinal vein thrombosis and COVID-19 vaccination (43).

In conclusion, our case represents the first case of proven IgG4-ROD after COVID-19 vaccination. We believe that IgG4-ROD and SARS-CoV-2 infection or vaccination are closely related, and the immune system disorder caused by SARS-CoV-2 infection or vaccination may be a key factor in the pathogenesis of IgG4-RD. But for now, there is no direct evidence that there is a causal relationship between SARS-CoV-2 infection or vaccination and IgG4-ROD, which still needs more research and exploration to confirm.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

PZ: Writing – original draft. QWu: Writing – review & editing. XX: Writing – review & editing. MC: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1303589/full#supplementary-material

SUPPLEMENTARY FIGURE 1
CD4 cells (×100).

SUPPLEMENTARY FIGURE 2
CD8 cells (×100).

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# Successful treatment of acrodermatitis continua of Hallopeau coexisting with generalized pustular psoriasis with spesolimab: a case report

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Generalized pustular psoriasis (GPP) is a rare chronic inflammatory pustular dermatosis that presents as painful erythema with sterile pustules on nonacral skin. No unified standard and guideline for the treatment of GPP has been established. Several biologics have been tried for GPP, with varying success. Acrodermatitis continua of Hallopeau (ACH) is a very rare disabling variant of pustular psoriasis characterized by sterile pustules on the fingers and toes, including the nail bed. Comparatively, treating ACH is highly challenging due to its commonly therapy-resistant disease course. The pathogenic role of IL-36 signaling axis has been currently identified in GPP development. Spesolimab, the first anti-interleukin-36 receptor biologic, has been approved for treating GPP flares and shown promising results. In view of a shared pathogenesis between GPP and ACH, specolimab may be an effective treatment for ACH. Currently, there is no case and clinical trial data exist on this condition. Therefore, this case was aim to describe real-world experience of spesolimab use in ACH coexisting with GPP. We report an Asian patient with a 16-year-history of GPP and ACH with marked pustulosis on the nail bed and onychodystrophy. He received conventional systemic regimen acitretin, cyclosporine and biologics adalimumab and secukinumab, but experienced relapse for skin lesions and refractory for nail lesions. He was then treated with a single dose of spesolimab in combination with secukinumab, which resulted in skin clearance and nearly complete resolution of nail lesions over a 32-week period. Our observation suggests that spesolimab should be considered for the treatment of ACH, especially in the patients with intractable nail lesions and concomitant GPP.

KEYWORDS

**generalized pustular psoriasis, acrodermatitis continua of Hallopeau, spesolimab, treatment, IL-36**

## Introduction

Generalized pustular psoriasis (GPP) is a rare, chronic, and recurring condition characterized by painful erythema and sterile pustules on nonacral skin (1). It is commonly accompanied by systemic symptoms such as fever and malaise, with severe flares potentially leading to mortality. Acrodermatitis continua of Hallopeau (ACH) is an exceptionally rare and debilitating variant of pustular psoriasis, characterized by sterile pustules on the fingers, toes, and even the nail bed, along with erythematous atrophic skin (2). ACH may precede, coincide with, or follow the onset of GPP in some cases (3, 4).

Given that both GPP and ACH are chronic and incurable conditions, achieving long-term therapeutic control becomes crucial to prevent complications. At present, there is a lack of standardized treatment guidelines for both ACH and GPP. Various biologics have been attempted for GPP, but their success rates have been inconsistent (5–7). On the other hand, managing ACH poses significant challenges as it commonly exhibits resistance to therapy. Notably, even within the same patient, the treatment response of ACH tends to be inferior to that of GPP (3, 8).

Recent studies have indicated that innate immune inflammation primarily underlies the pathogenesis of GPP, with a crucial role played by the activation of the IL-36 signaling axis (9, 10). Overactivation of IL-36 signaling and dysregulation of inflammatory cytokines released by keratinocytes contribute to the recruitment of neutrophils in the epidermis (11). Notably, mutations in the IL-36RN gene, responsible for encoding the IL-36RA, are commonly observed in both GPP and ACH patients (12, 13). Furthermore, a few GPP patients have also been found to have variants in AP1S3, a gene encoding the adaptor-related protein complex 1, sigma-3 subunit, leading to hyperactivation of tumor necrosis factor (TNF) and increased IL36α expression (14, 15). Interestingly, these variants are also observed in some ACH patients (13, 16), suggesting a shared pathogenesis between GPP and ACH, with the IL-36 signaling pathway being a potential therapeutic target. The recent approval of spesolimab, the first anti-interleukin-36 receptor (IL-36R) biologic, for the treatment of GPP flares in 2022 has shown promising results (17, 18). In this context, we present a case study of a Chinese male with concurrent ACH and GPP, who exhibited successful treatment outcomes with spesolimab after prior treatment failures with adalimumab and secukinumab.

## Case presentation

A 22-year-old Chinese male with a 7-year smoking history was referred to our department due to recurring episodes of generalized bright erythema and pustules on the trunk, limbs, fingers, toes, and nails that had been persistent for 16 years. The patient was initially diagnosed with GPP when he experienced his first flare at the age of 6. While the application of acitretin resolved the skin lesions, there was limited or no improvement in the lesions on the distal fingertips, toes, and nails. Based on the repeated pattern of relapse and remission of the finger, toe, and nail lesions, a clinical diagnosis of ACH was suspected. Histological examination of a skin biopsy from the abdomen revealed an accumulation of neutrophils in the epidermis and a moderate perivascular lymphocytic infiltrate in the dermis. The patient was administered acitretin at a daily dose of 40mg, in combination with cyclosporine at 125mg twice daily (4 mg/kg) for 24 weeks, which resulted in a slight improvement in the nail lesions. However, due to intolerable mucosal dryness, the patient discontinued the use of acitretin and cyclosporine on his own.

In August 2020, the patient was hospitalized with a diagnosis of GPP, as generalized pustules reappeared accompanied by leucocytosis and elevated C-reactive protein (CRP) levels (Figures 1A–D). A loading dose of 80mg of adalimumab was prescribed, followed by a subsequent dose of 40mg every 4 weeks, which led to a significant improvement in skin lesions within 3 weeks. Despite occasional recurrences of the psoriasis rash due to stress or respiratory infection during 15 months of treatment, the nail lesions persisted (Figure 1B). Adalimumab was then discontinued, and the patient's treatment was switched to a loading dose of 300 mg of secukinumab every week for 5 weeks, followed by a monthly dose of 150 mg, in accordance with the Chinese guidelines for the use of biologic agents in the treatment of psoriasis (19). Improvement was observed 2 weeks after the initial injection, and after three months of treatment, the skin lesions were nearly completely resolved (Figure 1C). However, the patient's nail lesions remained unresponsive to treatment. As a result, secukinumab treatment was discontinued six months later due to its high cost, and the patient was switched back to adalimumab. Within 2 months, he experienced a worsening of the skin lesions and was transferred to our hospital.

The physical examination revealed severe erythema accompanied by mild scales on the scalp, trunk, and upper limbs. Pustules and areas filled with pus were clearly visible at the center of several erythematous areas. Distinct demarcation lines could be observed along with erythema and pustules on most swollen distal fingers and the first toes. These areas also had erosions that were covered in thick yellow crusts. The nails on these affected digits showed signs of dystrophy and were adorned with pustules (Figures 2A–D). The patient's generalized pustular psoriasis area and severity index (GPPASI) and modified nail psoriasis severity index (mNAPSI) scores were 21.9 and 10, respectively. Laboratory investigations indicated leukocytosis with neutrophilia, as well as elevated levels of CRP (Figure 1). Notably, the patient tested negative for rheumatoid factor, antinuclear antibody, and anti-cyclic citrullinated peptide.

In light of the notable resistance to treatment, particularly in the context of the finger and toe nails, a single intravenous dose of 900 mg of spesolimab was administered. The patient's GPPASI and mNAPSI scores were evaluated on Day 1 (Figures 2E–H), Day 5 (Figures 2I–L), week 9 (Figures 2M–P), and week 32 (Figures 2Q–T). Following the infusion of spesolimab, pustules were significantly alleviated on the trunk and upper limbs. However, within 24 hours, several new erythematous patches emerged, extending to the patient's forearms and a substantial portion of their trunk (Figures 2E, F). By Day 5, the erythema had darkened on the trunk while subsiding on the upper limbs, leaving behind scaling

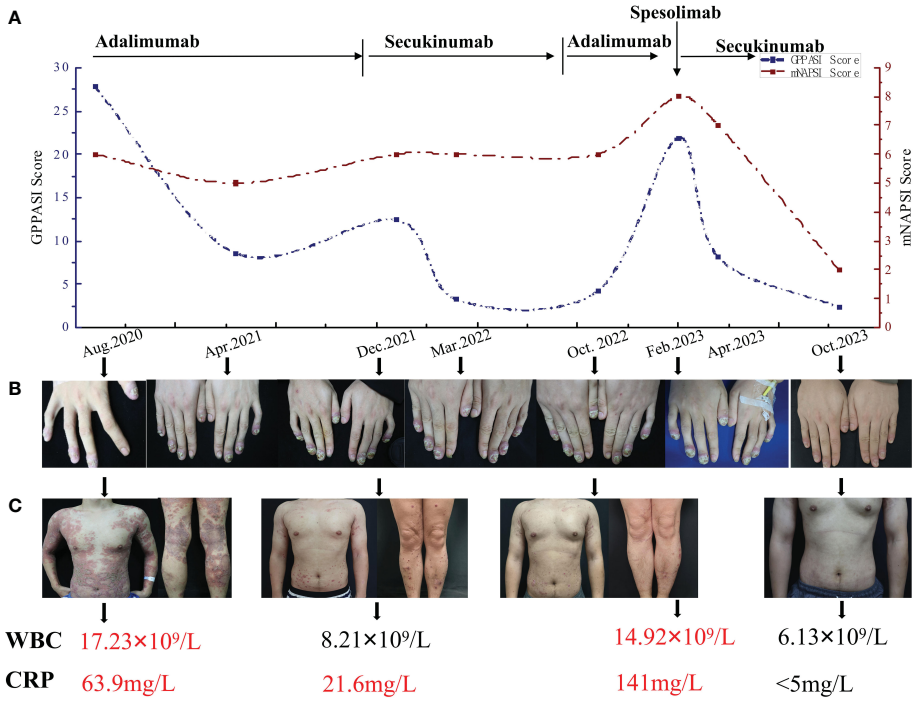



FIGURE 1
**(A)** The timeline of the GPPASI score and mNAPSI score during treatment with different biologics. **(B)** Periungual erythema, periungual and subungual pustules and onychodystrophy on swollen distal fingers in different periods. **(C)** Skin lesions on the trunk and both lower limbs and variation in the WBC and CRP. GPPASI, generalized pustular psoriasis area and severity index; mNAPSI, modified nail psoriasis severity index; WBC, white blood cells; CRP, C-reactive protein.

(Figures 2I, J), with no observed changes in the nail lesions (Figures 2K, L). After a month of spesolimab treatment, the erythema on the patient's arm faded, and no new lesions manifested. However, erythema and pustules persisted on the distal fingers and the first toes. Consequently, the patient was prescribed secukinumab (150 mg every 4 weeks) at a local hospital. At week 9, a remarkable improvement was witnessed, with a 63% reduction in the GPPASI score (Figures 2M, N). Periungual inflammation diminished, and all affected fingernails began to regenerate (Figures 2O–P). After 32 weeks of spesolimab use, the patient's skin and nail lesions had largely disappeared (Figures 2Q–T). Their GPPASI and mNAPSI scores were reduced by approximately 90% and 80%, respectively. Laboratory findings conducted at week 32 post-treatment revealed no abnormalities, and there were no reported adverse effects.

## Discussion

ACH and GPP commonly manifest as chronic and recurrent conditions that often do not respond well to conventional treatment approaches, such as acitretin, methotrexate, and cyclosporine. Biologic agents, initially used for plaque psoriasis and psoriatic arthritis (PsA), have been extensively explored as potential treatments for GPP and have shown greater efficacy compared to non-biologic systemic agents (20). Nonetheless, it is important to note that the use of TNF-α and IL-17 inhibitors has been associated with paradoxical flares of GPP and the development of new pustular lesions in some cases (21–23).

In limited case reports and small case series, encouraging effects have been observed with TNF-α and IL-17 inhibitors in managing nail lesions for ACH. Studies have shown complete resolution of nail changes within different time frames ranging from 12 to 55 weeks (24–26). It is important to note that the development of anti-drug antibody (ADA) is a significant factor contributing to treatment failure with TNF-α inhibitors (27–29). Additionally, the treatment with IL-17 inhibitors has been associated with the emergence of psoriasiform eruptions involving the fingers and nails (23), and there have been reported cases where no significant improvement was observed even after 4-8 months of therapy (30). This underscores the complex relationship of cytokines like TNF-α and IL-17 in the pathogenesis of different psoriasis subtypes, with their dominant role in plaque psoriasis not necessarily reflected in pustular psoriasis.

The IL-36 signaling pathway has emerged as a key player in the pathogenesis of GPP. Upregulation of the IL-36 cascade induces the proliferation of IL-17 and $CD4^+$ Th17 cells, which in turn stimulates the expression of IL-36 and other cytokines, thereby amplifying the inflammatory response in GPP (31, 32). Numerous studies have highlighted the presence of IL-36RN mutations in patients with GPP and concomitant ACH, and loss of IL-36RN function leads to unregulated IL-36 activity (9, 12, 33). Spesolimab, targeting IL-36R $^2$, effectively inhibits the activation of pathogenic IL-36 pathways and downstream inflammasome pathways. Clinical trials have

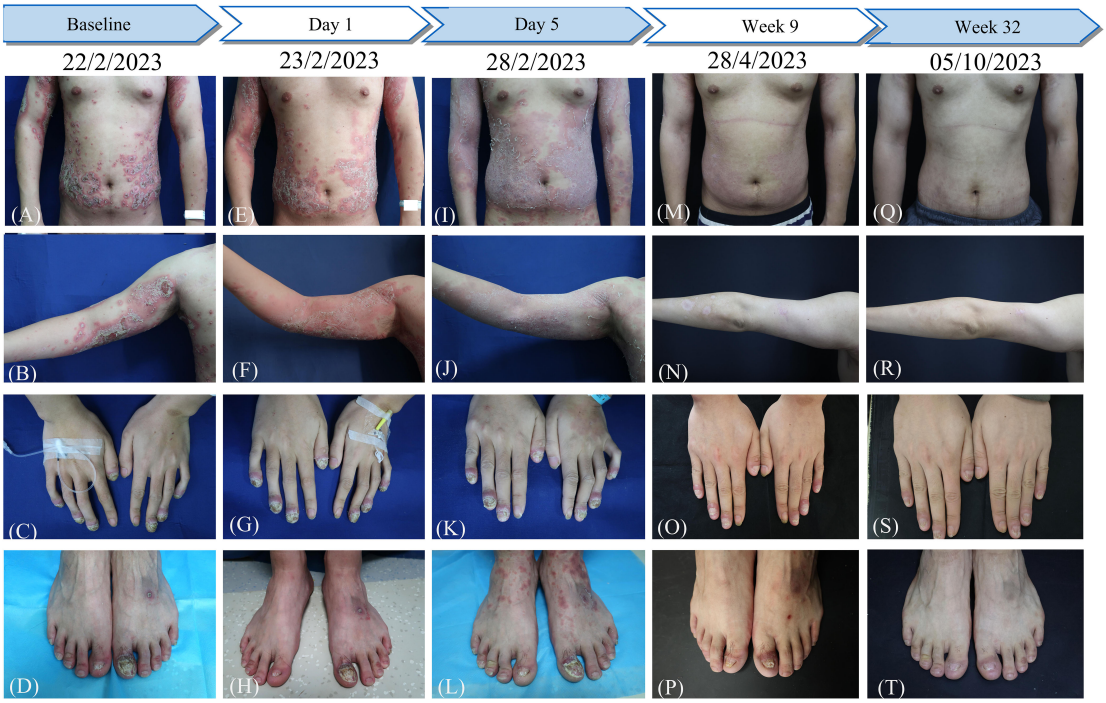



FIGURE 2
The flowchart of the patient before and after a single dose of spesolimab treatment and GPPASI and mNAPSI scores at baseline, Day 1, Day 5, week 9 and week 32. **(A-D)** Clinical appearance of the trunk, right arm, hands and toes before treatment; **(E-H)** Clearance of existing pustules and enlarged erythema on the trunk and right arm on Day 1 after treatment; clinical appearance 5 days **(I-L)**, 9 weeks **(M-P)**, and 32 weeks **(Q-T)** After treatment with spesolimab.

confirmed the efficacy and safety of spesolimab in GPP (17, 34). The phase 1 proof-of-concept Effisayil™ 1 study demonstrated that a single dose of spesolimab at 900 mg significantly reduces GPP severity over 20 weeks (34). Additionally, the phase 2 randomized trial revealed rapid pustular and skin clearance within one week of spesolimab treatment, with an acceptable safety profile (17). Furthermore, the Effisayil™ 2 study evaluated the efficacy and safety of spesolimab in preventing GPP flares, and recent results indicate that subcutaneous administration of spesolimab (600 mg loading dose, followed by 300 mg every 4 weeks) effectively prevents GPP flares and reduces the risk of recurrence over 48 weeks (35). Currently, phase II and III trials of spesolimab are underway in palmoplantar pustulosis, atopic dermatitis (AD), and ulcerative colitis (36–39).

To objectively assess the effectiveness of spesolimab in treating GPP lesions, we employed the GPPASI score in this particular patient. The GPPASI score is a physician-based evaluation of the severity of pustules, erythema, and scaling, with scores ranging from 0 to 72 (40, 41). Consistent with previous studies exploring the use of spesolimab in GPP treatment, a rapid clinical response was observed, with near-complete clearance of pustules within 24 hours of treatment. On Day 5, the patient demonstrated a 16.0% improvement in the GPPASI score, which falls below the previously reported range of 47.2-83.5% improvement seen one week after administration (18). Nonetheless, the patient's skin lesions improved over the following week, eliminating the need for a second injection. The GPPASI score exhibited a remarkable decrease at week 9 and maintained this improvement until week 32.

The mNAPSI score was a reliable tool to evaluate the psoriatic nail disease in the current patient (42, 43). Since nails take 5-7 months to complete a growth cycle, assessing the efficacy of treatment for nail lesions requires a longer follow-up period compared to skin lesions (44). After 32 weeks, the patient exhibited significant improvement in nail lesions, as indicated by a 75% reduction in the mNAPSI score compared to baseline. This level of improvement had not been achieved with any previous treatments. Given the lack of response to secukinumab therapy over nearly a year, the credit for this improvement can be attributed to spesolimab rather than secukinumab. This finding suggests that IL-36 receptor antagonists hold promise as a potential therapeutic approach for the treatment of ACH.

Several limitations of the present study should be acknowledged. Firstly, a larger number of cases and longer-term follow-up are required to accurately evaluate the efficacy of spesolimab in ACH. Furthermore, it is important to recognize that concurrent PsA is estimated to be present in approximately 20.5% of ACH patients (45). Another limitation of this study was the lack of assessment of joint injuries in the patient during

treatment. It is worth noting the significance of evaluating the effectiveness of spesolimab in ACH patients with concurrent joint involvement.

## Conclusion

Despite numerous proposed treatment strategies, effectively managing ACH and GPP remains a significant challenge. Given the pivotal role played by the IL-36 signaling pathway in GPP's pathogenesis, we administered spesolimab, an anti-IL-36R biologic, to our patient. Not only did we witness a rapid regression of skin lesions, but more significantly, we achieved outstanding therapeutic outcomes for the nail lesions. To the best of our knowledge, this is the first documented case where spesolimab has been successfully employed in the treatment of coexisting ACH and GPP. Our observation strongly suggests that considering spesolimab as a treatment option for ACH, particularly in patients with challenging nail lesions in conjunction with GPP, is warranted.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Ethics Committee on Clinical Trial, West China Hospital of Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

PFW: Writing – original draft, Data curation, Methodology, Visualization. CL: Writing – original draft, Data curation, Investigation. TW: Writing – review & editing. XJ: Writing – review & editing, Supervision. PW: Supervision, Writing – review & editing, Resources. SW: Supervision, Writing – review & editing, Validation.

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## Conflict of interest

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# Case report: Rapid recovery after intrathecal rituximab administration in refractory anti-NMDA receptor encephalitis: report of two cases

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**Background:** Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most prevalent etiologies of autoimmune encephalitis. Approximately 25% of anti-NMDAR encephalitis cases prove refractory to both first- and second-line treatments, posing a therapeutic dilemma due to the scarcity of evidence-based data for informed decision-making. Intravenous rituximab is commonly administered as a second-line agent; however, the efficacy of its intrathecal administration has rarely been reported.

**Case summary:** We report two cases of severe anti-NMDAR encephalitis refractory to conventional therapies. These patients presented with acute-onset psychosis progressing to a fulminant picture of encephalitis manifesting with seizures, dyskinesia, and dysautonomia refractory to early initiation of first- and second-line therapeutic agents. Both patients received 25 mg of rituximab administered intrathecally, repeated weekly for a total of four doses, with no reported adverse effects. Improvement began 2–3 days after the first intrathecal administration, leading to a dramatic recovery in clinical status and functional performance. At the last follow-up of 6 months, both patients remain in remission without the need for maintenance immunosuppression.

**Conclusion:** Our cases provide evidence supporting the intrathecal administration of rituximab as a therapeutic option for patients with refractory anti-NMDAR encephalitis. Considering the limited penetration of intravenous rituximab into the central nervous system, a plausible argument can be made favoring intrathecal administration as the preferred route or the simultaneous administration of intravenous and intrathecal rituximab. This proposition warrants thorough investigation in subsequent clinical trials.

KEYWORDS

**case report, anti-N-methyl-D-aspartate receptor, encephalitis, refractory, intrathecal rituximab**

# 1 Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, first described in 2007 (1), is one of the most prevalent etiologies of autoimmune encephalitis, with an annual incidence of 1.5 per million population (2). Predominantly afflicting young women, this condition is usually characterized by early-stage psychiatric and/or behavioral disturbances (2). As the condition evolves, patients may exhibit various neurological symptoms, including seizures, dyskinesias, cognitive dysfunction, and autonomic dysfunction (2).

A distinctive feature of anti-NMDAR encephalitis lies in its association with ovarian teratomas in a subset of cases. Approximately 37% of patients with this condition are reported to harbor ovarian teratomas, playing a role in the pathogenesis by hosting dysmorphic neurons expressing NR1/NR2A/NR2B antigens (3). This elicits the activation of germinal centers, leading to the production of NMDAR antibodies, resulting in the internalization and reversible reduction in the number of NMDAR, thus giving rise to the clinical manifestations of anti-NMDAR encephalitis (3).

Approximately 25% of anti-NMDAR encephalitis cases prove refractory to both first- and second-line treatments (4), posing a therapeutic dilemma due to the scarcity of evidence-based data for informed decision-making. In this context, we present two cases of severe and refractory anti-NMDAR encephalitis, characterized by an inadequate response to first- and second-line agents. These cases exhibited a rapid and striking clinical improvement after the intrathecal administration of rituximab, offering a novel and promising alternative for cases resistant to conventional treatments.

# 2 Case description

## 2.1 Case 1

A previously healthy 35-year-old woman presented to the emergency department with acute-onset behavioral changes following an upper respiratory tract infection. That same day, she woke up with new-onset delusions about imminent death, accompanied by disorientation, labile mood swings, and inappropriate laughter and crying. A brain MRI revealed a non-enhancing high T2 FLAIR signal in the left hippocampus. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (95 WBCs, 95% lymphocytic) with normal protein and glucose levels. Tentatively diagnosed with viral encephalitis, intravenous acyclovir was initiated, despite negative cultures and a negative herpes simplex virus (HSV) PCR.

Over the subsequent 2 days, her condition deteriorated, progressing to hallucinations, mutism, diffuse rigidity, and catatonia in addition to new-onset seizures. Based on the suspicion of autoimmune encephalitis, a 5-day course of 1-g methylprednisolone intravenously daily was administered while awaiting CSF and serum autoimmune antibody titers. However, her condition worsened and progressed to unresponsiveness with prominent orofacial dyskinesias and recurrent bouts of sympathetic hyperactivity in addition to frequent electrographic seizures identified on EEG. Intravenous immunoglobulin (IVIg) at a dose of 2 g/kg over 5 days failed to improve her clinical condition, necessitating intubation due to central hypoventilation syndrome. At that time, NMDAR antibody titers in the CSF returned positive with a titer of 1:32 on the day of admission and 1:128 on day 3 (Bioscientia Laboratories). Repeat brain MRI showed progression of the high FLAIR signal, involving the left parahippocampal gyrus. A pelvic MRI revealed a complex left adnexal mass, subsequently resected with pathology diagnostic of a mature cystic teratoma. Owing to the lack of clinical improvement, the patient underwent five sessions of plasma exchange therapy. Subsequently, she received two doses of 500 mg of intravenous rituximab, with each dose administered 1 week apart. Despite these interventions, there was evidence of clinical deterioration over the next 2 weeks, as she remained comatose with hypoventilation, worsening orofacial dyskinesias, and bouts of severe sympathetic hyperactivity, and required a tracheostomy.

At that point (day 38 of admission), the patient received 25 mg of rituximab intrathecally, repeated weekly for a total of four doses with no reported adverse effects. A remarkable clinical improvement ensued, with spontaneous eye opening on the second day after administration of the first dose, obeying simple commands on day 3, and complete resolution of orofacial dyskinesias. She attempted to verbalize on day 5 and showed daily improvement. The NMDAR antibody titer in the CSF drawn at the time of her third intrathecal rituximab administration was 1:16. The patient was discharged to a rehabilitation center on day 58 of her admission. At her last follow-up visit, approximately 7 months from symptom onset, the patient had a normal sensorimotor examination with a modified Rankin scale of 1. However, mild cognitive deficits in memory, attention, ability to calculate, and executive function were noted.

## 2.2 Case 2

A previously healthy 16-year-old woman presented to the emergency department with generalized convulsive status epilepticus accompanied by high-grade fever. Ten days before presentation, she began experiencing mood swings, anxiety, and fear, along with delusions and hallucinations. Her symptoms subsequently progressed to include memory difficulties and focal impaired awareness seizures initially misdiagnosed as functional seizures by an outside physician. A brain MRI revealed mild increase FLAIR signal over both mesial temporal areas and CSF analysis showed lymphocytic pleocytosis (50 WBC cells; 80% lymphocytes), with normal protein and glucose levels. Despite benzodiazepines, loading doses of levetiracetam, and valproate, the status epilepticus persisted, eventually being controlled with propofol infusion. Treatment with intravenous acyclovir was initiated in addition to a 5-day course of 1-g methylprednisolone intravenously based on suspicion of anti-NMDAR encephalitis while awaiting antibody titers.

Following the pulse steroid therapy, the patient's condition worsened with persistent hallucinations, prominent orofacial dyskinesias, autonomic dysfunction, and breakthrough seizures

following attempts of propofol taper despite the introduction of various antiseizure medications including phenytoin, lacosamide, perampanel, and clonazepam. Following IVIg administration at a dose of 2 g/kg over 5 days, there was no improvement in her overall clinical condition with persistence of the super refractory status epilepticus that failed to respond to the ketogenic diet. A total body CT scan and ultrasound of the ovaries were negative. Three weeks after presentation, the patient received a single intravenous infusion of cyclophosphamide, totaling 1,600 mg, concomitant with the intravenous administration of 500 mg of rituximab. Subsequently, the patient received three additional doses of intravenous rituximab, each at a dosage of 500 mg, spaced 1 week apart. However, because of the development of high-grade fever and sepsis, the patient did not receive any further cyclophosphamide administration. The NMDAR antibody titer in the CSF drawn on the day of admission was 1:32. The patient received 25 mg of rituximab intrathecally, repeated weekly for a total of four doses with no reported adverse effects. Two days following the first intrathecal injection, the patient was successfully weaned off the anesthetic with no seizure recurrence. In addition, the orofacial dyskinesias and autonomic dysfunction subsided. She gradually regained full alertness and was discharged to a rehabilitation center for the management of her critical care neuromyopathy. At her last follow-up, 6 months from symptoms onset, the patient was found to have a mild distal, symmetric sensorimotor deficit secondary to critical care neuropathy and mild memory deficit. She remained seizure free on levetiracetam administered as monotherapy.

## 3 Discussion

Our findings substantiate the efficacy and safety of intrathecal rituximab administration in patients with refractory anti-NMDAR encephalitis who fail to respond to first- and second-line therapeutic agents. Our two patients, who were in a comatose state and failed to respond to pulse steroids, IVIg, intravenous rituximab (patients 1 and 2), and oophorectomy and plasmapheresis (patient 1), exhibited a rapid and remarkable improvement in their mental status following the initial intrathecal rituximab administration. The intervention also led to the resolution of the severe orofacial dyskinesias (patients 1 and 2), dysautonomia (patient 1), and super refractory status epilepticus (patient 2), within 48 h.

Our results align with a few previously documented cases (Table 1) where intrathecal rituximab administration to refractory anti-NMDAR encephalitis patients resulted in a swift and substantial recovery (5–7). This underscores the therapeutic potential of intrathecal rituximab in cases where its intravenous administration has failed or when systemic administration is hindered by factors such as severe infections.

The recommended initial therapeutic approach for anti-NMDAR encephalitis involves tumor removal when applicable, high-dose intravenous steroids, IVIg, and plasmapheresis. Approximately 53% of patients respond to first-line treatment, typically within 4 weeks of initiating therapy (8). For non-responders, second-line agents such as rituximab, targeting CD20-positive B cells, or cyclophosphamide, an immunosuppressive agent, improve symptoms in a proportion of patients by modulating the immune response (4). Nevertheless, up to 25% of patients remain refractory despite second-line therapies (4).

For patients unresponsive to second-line agents, no established guidelines exist, and recommendations are based on expert opinions, small series, or isolated case reports. Third-line agents are categorized into cytokine-based drugs (e.g., tocilizumab, interleukin-2, basiliximab, anakinra, and tofacitinib), plasma cell-depleting agents (e.g., bortezomib and daratumumab), and treatments targeting intrathecal antibody synthesis (e.g., intrathecal methotrexate, natalizumab, and intrathecal rituximab) (9).

In our patients, the decision to proceed with intrathecal rituximab administration was carefully made after thorough consideration of all alternative off-label treatments (9). A crucial consideration was the observation from previous published cases that the efficacy of intrathecal rituximab could be assessed within a matter of days, whereas the efficacy of other off-label treatments might not be evident for several weeks. Therefore, our rationale was to administer intrathecal rituximab initially and monitor for response within approximately a week after the first administration. If no response was observed within this time frame, we planned to transition to tocilizumab, as this agent appeared to hold the most promising efficacy among the off-label treatments (9).

In addition, several other key factors lead to the choice of intrathecal rituximab administration in our patients including the presumed pathophysiology of CNS manifestations in anti-NMDAR encephalitis, the pharmacokinetics of rituximab, and its safety following this route of administration. Plasma cells located within the perivascular, interstitial, and Virchow Robin spaces of the brain are believed to play a pivotal role in the intrathecal synthesis of antibodies associated with anti-NMDAR encephalitis (3). Additionally, the fact that only 1% of intravenously administered rituximab crosses the blood–brain barrier (BBB) stands as a critical factor influencing its efficacy as it will not be able to target B cells that have crossed the BBB to become antibody-secreting plasma cells that perpetuate the disease process (3, 10). The safety profile of intrathecal rituximab administration, a crucial consideration, was previously established across various clinical conditions. In patients with CNS lymphoma, lymphomatous meningitis, and some cases of progressive multiple sclerosis, the safety of intrathecal rituximab was demonstrated when it was administered in weekly or biweekly doses of 25 mg (11–13). Adverse effects at this low dosage were of mild intensity and included nausea, vertigo, and paresthesia (5, 11–13).

The rapid clinical improvement seen in our patients following intrathecal rituximab administration is surprising since after systemic administration, it typically manifests a therapeutic effect over a span of weeks. It is purported that the mechanism of action of rituximab involves several pathways, including direct signaling, complement-dependent cellular cytotoxicity, and antibody-dependent cellular cytotoxicity (14). For instance, studies have demonstrated a direct local anti-lymphoma effect of rituximab when injected directly into the CSF in patients with central

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TABLE 1 Characteristics of patients who received intrathecal rituximab for refractory anti-NMDA encephalitis.

| | Casares et al. (5) | Krishnan et al. (6) | Krishnan et al. (6) | Santiago et al. (7) | Santiago et al.* (7) | Case 1 (current report) | Case 2 (current report) |
|---|---|---|---|---|---|---|---|
| **Gender, age (years)** | F, 20 | F, 15 | F, 16 | F, 4 | F, 5 | F, 35 | F, 16 |
| First-line agents | | | | | | | |
| **IVMP + IVIG** | √ | √ | √ | √ | √ | √ | √ |
| **PLEX** | – | √ | √ | – | √ | √ | – |
| Second-line agents | | | | | | | |
| **IV rituximab** | √ | √ | √ | √ | √ | √ | √ |
| **IV cyclophosphamide** | – | √ | √ | √ | √ | – | √ |
| Persistent symptoms after second line | | | | | | | |
| **Uncontrolled seizures** | – | √ | √ | – | – | – | √ |
| **Dyskinesia** | √ | – | √ | – | – | √ | √ |
| **Dysautonomia** | – | – | – | – | – | √ | √ |
| **Encephalopathy** | √ | √ | √ | – | – | √ | √ |
| **Need for mechanical ventilation** | – | – | – | – | – | √ | √ |
| **mRS** | – | – | – | 3 | 5 | – | – |
| **Dose of IT rituximab** | 25 mg weekly for 4 doses | 25 mg weekly for 4 doses | 25 mg weekly for 4 doses | 25–100 mg repeated in 2–4 weeks | 25–100 mg repeated in 2–4 weeks | 25 mg weekly for 4 doses | 25 mg weekly for 4 doses |
| **Time to 1st clinical improvement after 1st dose of IT rituximab (days)** | 2 | 2 | 3 | NA | NA | 3 | 2 |
| Improvement after IT rituximab | | | | | | | |
| **Full seizure control** | – | √ | √ | – | – | √ | √ |
| **Resolved dyskinesia** | √ | – | √ | – | – | √ | √ |
| **Resolved dysautonomia** | – | – | – | – | – | √ | √ |
| **Improvement of mental status** | √ | √ | √ | – | – | √ | √ |
| **mRS** | – | – | – | 1 | 5* | – | – |
| **Duration of follow-up (months)** | 11 | 8 | 8 | 6 | 12 | 7 | 6 |
| **Maintenance immunosuppression** | Mycophenolate | None | None | None | None | None | None |
| **Relapse** | None | None | None | **None** | **None** | None | None |

F, female; IV, intravenous; IT, intrathecal; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; mRS, modified Rankin Score; NA, no available data; PLEX, plasma exchange therapy. * This patient was ultimately found to have a potential alternate etiology for her symptoms (compound heterozygous variants in VPS13D) (NM_015378.2) (p.S2199G) and (p.R2433H) (OMIM #607317).

nervous system lymphoma (14), suggesting a direct effect on targeted lymphocytes, possibly mediated by complement augmentation (14). Moreover, systemic infusion of rituximab in autoimmune nephritis resulted in a profound depletion of total B cells within 48 h in most cases (15). In the context of autoimmune encephalitis, the pathogenic mechanisms of anti-NMDAR antibodies involve crosslinking, internalization, and reversible reduction in NMDA receptor density (16). *In vitro* studies have shown that this reduction is reversible, with levels returning to baseline within 4 days after antibody removal (3).

In our cases, it is therefore plausible that intrathecal rituximab administration induced a rapid depletion of CD20 lymphocytes, potentially amplified by inflammatory cytokines or complement due to a leaky BBB. This swift depletion of a small B-cell compartment may have led to an initial increase in NMDA receptor clusters and synaptic currents, thus correlating with the

observed rapid clinical improvement. Subsequently, sustained changes occurred after completion of treatment, with restoration of the NMDA receptor's density and reduction in autoantibody levels. Therefore, the prompt response observed following intrathecal rituximab administration may be attributed to complex interactions between rituximab, B-cell depletion, inflammatory mediators, and NMDA receptor dynamics. The exact mechanism will need to be elucidated with further research to delineate the precise mechanisms underlying the therapeutic effects of intrathecal rituximab in anti-NMDAR encephalitis.

However, given that the autoimmune mechanism in anti-NMDAR encephalitis is likely initiated and promoted outside the CNS, the first- and second-line therapeutic agents administered to our patients might have contributed to their clinical recovery. Nonetheless, it remains uncertain whether a sequential or concurrent use of therapies targeting both the central and the peripheral components of the autoimmune response would achieve a synergistic therapeutic effect, potentially enhancing treatment efficacy and leading to a more comprehensive disease control. Therefore, further research is warranted to delineate the specific contributions of each therapeutic approach.

It is important to note that both patients' families were extensively informed on all available options for refractory cases, including intrathecal rituximab, which had only been employed in a limited number of cases of anti-NMDAR encephalitis patients. Detailed explanations regarding why intrathecal rituximab was preferred over alternative treatments were provided during discussions with both families, alongside a thorough examination of potential adverse effects. Written informed consent was obtained from the families of both patients following these discussions.

## 4 Conclusion

In conclusion, our cases provide evidence supporting the administration of intrathecal rituximab as a therapeutic option for patients with refractory anti-NMDAR encephalitis. This recommendation is based on its efficacy, swift onset of action, cost-effectiveness, and favorable safety profile. Given the limited penetration of intravenous rituximab into the central nervous system, a plausible argument can be made favoring intrathecal administration as the preferred route or the simultaneous administration of intravenous and intrathecal rituximab. This proposition warrants thorough investigation in subsequent clinical trials.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MR: Writing – review & editing, Writing – original draft. RJ: Writing – original draft, Writing – review & editing. AH: Writing – review & editing. FJ: Writing – review & editing. NE: Conceptualization, Writing – review & editing. ON: Writing – review & editing. AB: Conceptualization, Supervision, Visualization, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Autoimmune nodopathy with anti-contactin 1 antibody characterized by cerebellar dysarthria: a case report and literature review

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**Background:** Autoimmune nodopathy (AN) has emerged as a novel diagnostic category that is pathologically different from classic chronic inflammatory demyelinating polyneuropathy. Clinical manifestations of AN include sensory or motor neuropathies, sensory ataxia, tremor, and cranial nerve involvement. AN with a serum-positive contactin-1 (CNTN1) antibody usually results in peripheral nerve demyelination. In this study, we reported a rare case of AN with CNTN1 antibodies characterized by the presence of CNTN1 antibodies in both serum and cerebrospinal fluid, which is associated with cerebellar dysarthria.

**Methods:** A 25-year-old man was admitted to our hospital due to progressive dysarthria with limb tremors. The patient was initially diagnosed with peripheral neuropathy at a local hospital. Three years after onset, he was admitted to our hospital due to dysarthria, apparent limb tremor, and limb weakness. At that time, he was diagnosed with spinocerebellar ataxia. Eight years post-onset, during his second admission, his condition had notably deteriorated. His dysarthria had evolved to typical distinctive cerebellar characteristics, such as tremor, loud voice, stress, and interrupted articulation. Additionally, he experienced further progression in limb weakness and developed muscle atrophy in the distal limbs. Magnetic resonance imaging (MRI), nerve conduction studies (NCS), and autoimmune antibody tests were performed.

**Results:** The results of the NCS suggested severe demyelination and even axonal damage to the peripheral nerves. MRI scans revealed diffuse thickening of

bilateral cervical nerve roots, lumbosacral nerve roots, cauda equina nerve, and multiple intercostal nerve root sheath cysts. Furthermore, anti-CNTN1 antibody titers were 1:10 in the cerebrospinal fluid (CSF) and 1:100 in the serum. After one round of rituximab treatment, the patient showed significant improvement in limb weakness and dysarthria, and the CSF antibodies turned negative.

**Conclusion:** Apart from peripheral neuropathies, cerebellar dysarthria (central nervous system involvement) should not be ignored in AN patients with CNTN1 antibodies.

KEYWORDS

contactin-1, autoimmune nodopathy, cerebellar dysarthria, nerve conduction studies, magnetic resonance imaging

## Introduction

Autoimmune nodopathy (AN) is a spectrum of motor-sensory peripheral neuropathies mediated by antibodies associated with adhesion molecules at the nodes of Ranvier and paranodes, including contactin-associated protein 1 (CASPR1), contactin-1 (CNTN1), neurofascin 155 (NF155) and neurofascin isoforms 140/186 (NF140/186) (1). AN has been considered a variant of chronic inflammatory demyelinating polyradiculopathy (CIDP). Emerging evidence supports the idea that AN has a specific clinical phenotype, with no significant macrophage-mediated demyelination and a poor therapeutic response to corticosteroid therapy and intravenous immunoglobulin (IVIg). In 2021, the European Academy of Neurology/Peripheral Nerve Society proposed the designation AN for these antibody-related disorders (2). Specifically, anti-CNTN1 AN was the first documented disease subtype, mainly in elderly individuals (3). Instead of the obvious inflammation or traditional macrophage-mediated demyelination resembling CIDP, anti-CNTN1 AN was found to cause detachment of terminal myelin from the axolemma in the paranode region, resulting in nerve conduction abnormalities similar to the diagnostic criteria for CIDP (4). Clinical manifestations of AN patients with CNTN1 antibodies mainly include symmetrical limb weakness, paresthesias, tremors, and sensory ataxia (5). Respiratory system and cranial nerve involvement (mainly facial paralysis, ophthalmoplegia, and diplopia) may also be noted (6, 7).

Reports of involvement of the central nervous system (CNS) in AN patients with anti-CNTN1 antibodies are rare. In our case, cerebellar dysarthria was noted in AN patients with anti-CNTN1 antibody, with positive CNTN1 antibody in the cerebrospinal fluid (CSF) providing strong evidence for possible CNS involvement. The patient, who was very young, also experienced distal limb weakness, sensory disturbances, postural dizziness, diminished tendon reflexes, irregular nystagmus, and ataxia. Nerve conduction studies (NCS) found chronic progressive peripheral nervous system damage involving myelin to axons. We followed the above with a review of the literature, which provided novel insights and values for early identification and in-depth investigation of AN with anti-CNTN1 antibodies in the future.

## Case presentation

A 20-year-old man was admitted to our hospital due to progressive dysarthria, slurred speech, and limb tremors for more than 8 years. He had no remarkable medical history. His first clinical symptoms were noted in April 2015, characterized by limb tremors, slurred speech, and mild limb weakness. He was initially evaluated for peripheral neuropathy at a local hospital and underwent a 5-day treatment of daily IVIg at a dose of 20g and methylprednisolone pulse therapy (initial dose 500mg). However, there was no significant improvement in clinical symptoms.

In 2018, the patient presented to our hospital with dysarthria, apparent limb tremor, and limb weakness. Dysarthria is specifically characterized by slurred speech, pauses in speech, and pronounced interruptions in pronunciation, and is accompanied by certain plosive sounds and abnormal intonation. The subject had no dysphagia, water aspiration during drinking, abnormal pharyngeal sensation, glossopharyngeal neuralgia, difficulty with tongue extension, or tinnitus. The NCS revealed that the conduction of multiple motor and sensory nerves was impaired (Table 1). At that time (before AN was widely recognized), a clinical diagnosis of CIDP was considered. However, the patient's symptoms did not improve significantly following corticosteroid therapy and IVIg. Therefore, careful evaluation should be performed to rule out spinocerebellar ataxias (SCA) associated with peripheral neuropathy.

In the following five years, the patient developed worsening lower limb weakness, postural dizziness, muscle atrophy, and paresthesia in the lower limbs, along with distal numbness. Therefore, he was admitted to our hospital in March 2023. A neurological examination was performed on admission: the patient's uvula and

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TABLE 1 Nerve conduction studies (NCS)/Electromyogram(EMG) results from a patient with anti-CNTN1 autoimmune nodopathy.

| Nerve detection | Time point detection | | | Normal value |
|---|---|---|---|---|
| Ulnar nerve | Detection 3 years after onset April 2018 Left/Right | Detection 8 years after onset March 2023 Left/Right | Eight months after rituximab treatment November 2023 Left/Right | |
| Motor nerve conduction velocity (m/s) Upper elbow - Wrist | 43.4/30.0 | 19.3/16.6 | 21.8/15.5 | ≥50 |
| Compound muscle action potential amplitude (mV) Upper elbow - Wrist | 7.3/8.4 | 2.2/2.2 | 3.0/2.1 | ≥7.0 |
| Motor terminal latency (ms) Wrist - ADM | 5.35/5.07 | 6.27/5.21 | 6.87/5.81 | ≤4.0 |
| Sensory nerve action potential amplitude (μV) Upper elbow - Wrist | Not elicited | Not elicited | Not elicited | ≥7.1 |
| Sensory nerve conduction velocity (m/s) Upper elbow - Wrist | Not recordable | Not recordable | Not recordable | ≥50 |
| F-wave latency (ms) Wrist - ADM | 62.9/65.5 | 85.3/96.6 | 80.3/88.5 | ≤30 |
| F-wave occurrence rate (%) Wrist - ADM | 90.0/90.0 | 90.0/90.0 | 85.0/80.0 | ≥75 |
| Median nerve | | | | |
| Motor nerve conduction velocity (m/s) Elbow - Wrist | 28.8/30.8 | 15.7/15.5 | 17.5/16.1 | ≥50 |
| Compound muscle action potential amplitude (mV) Wrist - APB | 9.7/8.1 | 4.0/1.2 | 4.1/1.1 | ≥6.0 |
| Motor nerve distal latency (mS) Wrist - APB | 6.04/6.42 | 8.85/9.00 | 9.06/11.6 | ≤4.2 |
| Sensory nerve action potential amplitude (μV) Index finger - Wrist | Not elicited | Not elicited | Not elicited | ≥9.5 |
| Sensory nerve conduction velocity (m/s) Index finger - Wrist | Not recordable | Not recordable | Not recordable | ≥50 |
| F-wave latency (ms) Wrist - APB | 60.1/65.7 | 89.4/131.0 | 91.6/111 | ≤30 |
| F wave occurrence rate (%) Wrist - APB | 90.0/90.0 | 95.0/40.0 | 95.0/75.0 | ≥75 |
| Tibial nerve | | | | |
| Motor nerve conduction velocity (m/s) Popliteal fossa - Ankle | 30.1/31.8 | Not recordable/13.3 | 28.2/31.7 | ≥40 |
| Compound muscle action potential amplitude (mV) Ankle - AH | 1.10/1.09 | Not elicited/1.04 | 1.0/1.83 | ≥7 |
| Motor nerve distal latency (ms) Ankle - AH | 9.77/9.55 | Not elicited/11.5 | 11.9/9.3 | ≤5 |
| Sensory nerve action potential amplitude (μV) | Not checked | Not checked | Not checked | ≥0.4 |
| Sensory nerve conduction velocity (m/s) | Not checked | Not checked | Not checked | ≥35.1 |
| F-wave latency (ms) Ankle - AH | Not elicited | Not elicited | 131.0/94.6 | ≤51.0 |

*(Continued)*

TABLE 1 Continued

| Nerve detection | Time point detection | | | Normal value |
|---|---|---|---|---|
| Ulnar nerve | Detection 3 years after onset April 2018 Left/Right | Detection 8 years after onset March 2023 Left/Right | Eight months after rituximab treatment November 2023 Left/Right | |
| **Tibial nerve** | | | | |
| F wave occurrence rate (%) Ankle - AH | Not elicited | Not elicited | 50.0/75.0 | ≥75.0% |
| **Common peroneal nerve** | | | | |
| Motor nerve conduction velocity (m/s) Capitulum fibulae - Ankle | 33.9/35.2 | Not elicited | 32.8/31.9 | ≥45 |
| Compound muscle action potential amplitude (mV) Ankle - EDB | 0.57/0.24 | Not elicited | 0.44/0.33 | ≥3 |
| Motor nerve distal latency (ms) Ankle - EDB | 9.35/10.4 | Not elicited | 8.45/9.34 | ≤5 |
| **Sural nerve** | | | | |
| Sensory nerve conduction velocity (m/s) Middle leg - Lateral malleolus | Not elicited | Not elicited | Not elicited | ≥50 |
| Sensory nerve action potential amplitude (μV) Middle leg - Lateral malleolus | Not elicited | Not elicited | Not elicited | ≥3.3 |
| **Electromyogram** | | | | |
| **Left abductor digiti minimi** | | | | |
| Average amplitude (μV) | 502 | 1843 | Not checked | ≤1000 |
| Average time limit (ms) | 10.2 | 13.0 | Not checked | ≤9.5 |
| Resting potential | Not elicited | Not elicited | Not checked | – |
| **Left tibialis anterior muscle** | | | | |
| Average amplitude (uV) | 2408 | 1377 | 1118 | ≤1000 |
| Average time limit (ms) | 16.0 | 15.0 | 16.0 | ≤12.1 |
| Resting potential | Not elicited | Lead out P++, F+ | Lead out P+ | – |

μV, microvolt; mV, millivolt; m/s, meter per second; ms, millisecond; ADM, abductor digiti minimi; APB, abductor pollicis brevis; AH, abductor hallucis; EDB, extensor digitorum; Resting potential: P, positive shape potential; F, fasciculation potential. Compound muscle action potentials were measured from peak to peak.

tongue extension were centered, the soft palate could be raised, the pharyngeal reflex was present, and there was no facial paralysis with normal hearing. Dysarthria was observed, and both eyes showed irregular nystagmus. His lower limb muscle strength was graded at 3/5. The tendon reflex of the upper limbs was weakened, while the knee reflex, distal pain, and vibratory sensation were decreased. Both the nose-finger and heel-shin tests were inaccurate. Bilateral Babinski and Kernig signs were negative.

The NCS revealed the presence of motor and sensory nerve conduction abnormalities in multiple peripheral nerves. The Electromyogram (EMG) from five years earlier revealed denervation in the tibialis anterior muscle of the lower limb. However, after five years with no treatment, new findings of spontaneous potentials in the lower limbs and signs of denervation of the abductor digiti minimi in the upper limbs were identified in addition to the previously observed features. This indicated a wider extent and further progression of the denervation damage, suggesting that both the myelin sheath and the nerve axons were damaged. A lumbar puncture was performed and the CSF protein level was found to be 3009 mg/L (normal range: 150-450mg/L). The number of nucleated cells was $12*10^6$/L (normal range: $0-8*10^6$/L). CSF IgG: 247mg/L (normal range: 0-34mg/L); CSF IgA: 29mg/L (normal range: 0-5.0mg/L); CSF IgM: 16.6mg/L (normal range: 0-1.3mg/L). Anti-CNTN1 antibody titers were 1:10 in CSF and 1:100 in serum (Figure 1). Cervical Spine MRI revealed diffuse thickening of bilateral posterior cervical plexus segments, while thoracic MRI showed nerve root sheath cysts on the left anterior rib at thoracic disc plane 6-7 and bilateral anterior ribs at thoracic disc plane 7-8. Lumbar MRI showed diffuse thickening of the lumbosacral nerve roots (Figure 2). His cranial MRI revealed no abnormalities (Figure 3). In addition, antinuclear antibodies were positive with a titer of 1:200. Genetic screening for SCA was conducted, and the results were negative. In addition, the following urinalysis results were higher than normal values: urine protein: 1 + 0.3g/L, urine KAP light chain: 12.6mg/L

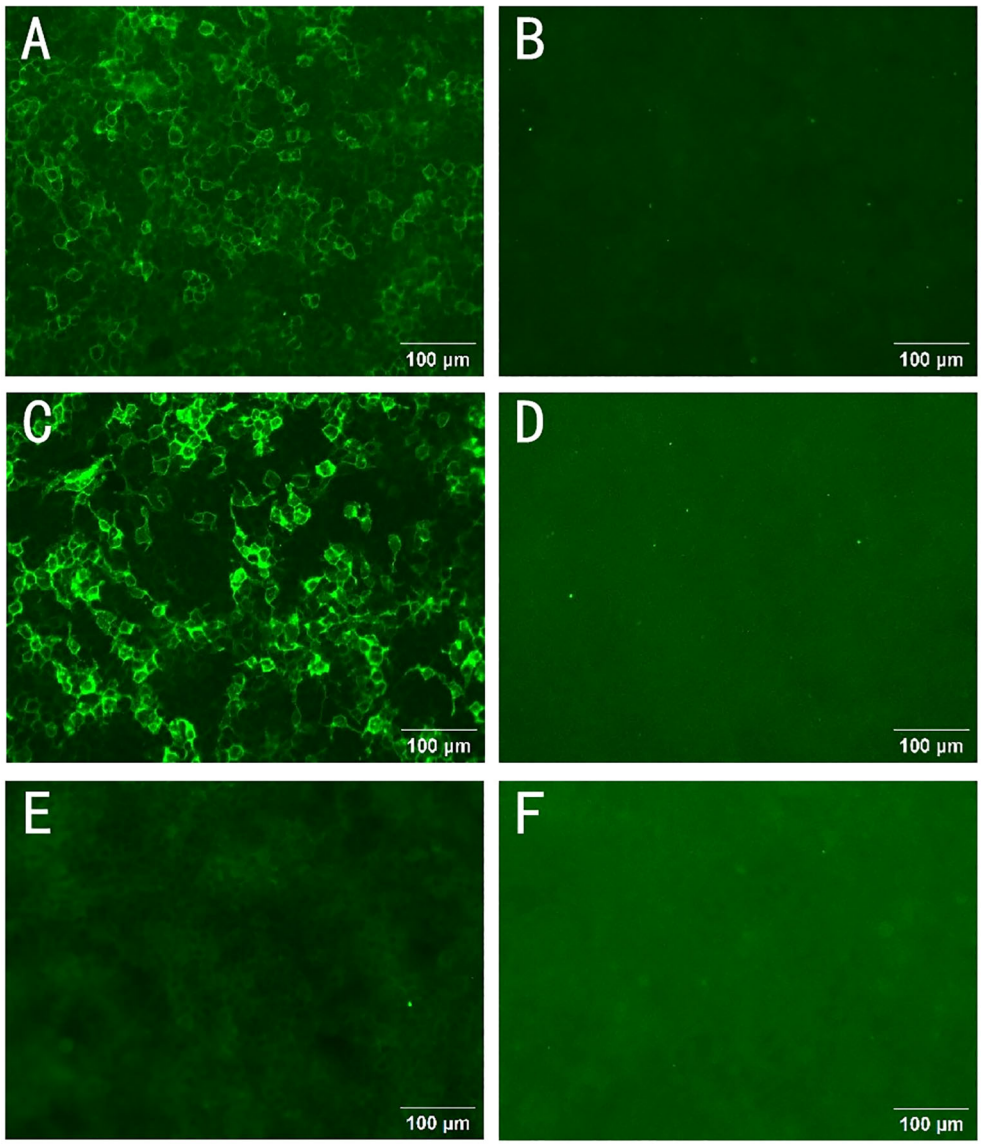



FIGURE 1
Autoantibodies to CNTN1 in serum and cerebrospinal fluid. The presence of anti-CNTN1 antibodies was confirmed using a cell-based assay (CBA) with CNTN1-transfected Human Embryonic Kidney (HEK) 293 cells. Cells overexpressing CNTN1 antigen on cell slides were able to bind to the patient's anti-CNTN1 autoantibody IgG4. The antibody bound to the cells on the slides could be detected by a Fluorescein Isothiocyanate (FITC) labeled anti-human IgG4 secondary antibody. Finally, its reactivity was observed and analyzed by immunofluorescence microscopy. A positive CNTN1 antibody reaction was noted in the cerebrospinal fluid (CSF) **(A)**, the CSF control was negative **(B)**, the positive serum CNTN1 antibody was detected **(C)**, and the serum control was negative **(D)**. After one round of rituximab treatment, the patient's CSF CNTN1 antibody tests were negative **(E)**. Negative control group **(F)**. Scale bar:100 μm.

(normal range 0-7.13mg/L), urinary LAM light chain: 6.2mg/L (normal value 0-3.94mg/L), 24-hour urine protein quantification: 5109mg/24h (normal range 0-300mg), urine total protein: 1890.05mg/L (normal range 0-150mg/L), urine immunoglobulin: 29.0mg/L (normal range 0-9.6mg/L), urine transferrin: 23.80mg/L (normal range 0-2.2mg/L), urine microalbumin: 523.0mg/L (normal range 0-30mg/L), suggesting that the patient had impaired renal function.

A diagnosis of anti-CNTN1 positive AN was made. Despite three rounds of plasma exchange being used, there was no significant improvement. As an alternative, we administered a single low dose of 500mg Rituximab. Eight months later, the patient returned to our hospital. It was observed that his tremor, gait stability, and walking speed had improved. Muscle strength in the distal extremities improved from grade 3 to 4. Residual mild dysarthria (characterized by mild syllable prolongation and uneven pitch intensity) was noted, while postural dizziness and nystagmus essentially recovered. Additionally, anti-CNTN1 antibodies in the CSF became negative. Repeat urinalysis showed that the urine protein had become negative (Figure 1). NCS suggested partial improvement in the conduction of the tibial and common peroneal nerves in the lower limbs compared to before. The EMG indicated a

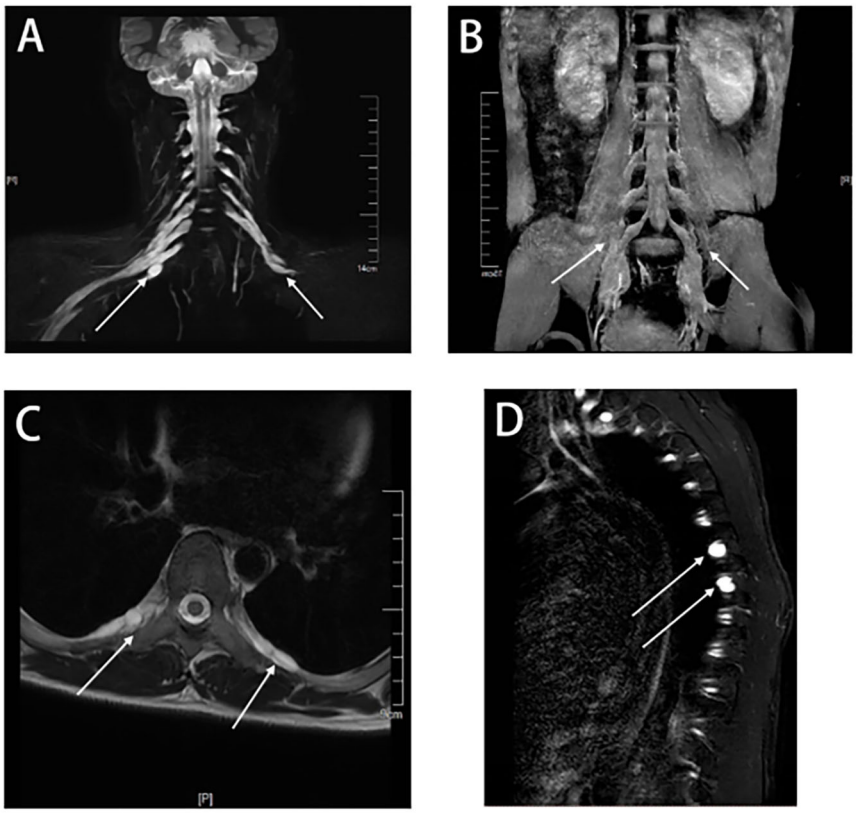



FIGURE 2
MRI of the cervical, thoracic, and lumbar spines of this patient. The principle of selective excitation technique (PROSET) of thin coronal MRI **(A)** showed diffuse thickening of nerve roots in the posterior segment of the cervical plexus, and three-dimensional short-time inversion recovery (3D-STIR) magnetic resonance imaging **(B)** showed diffuse thickening of nerve roots in the posterior segment of the lumbar plexus. A thoracic axial T2-weighted plain scan **(C)** showed nerve root sheath cysts in the intercostal nerves. Multiple nerve root sheath cysts were observed in T2-weighted fat-suppressed sequences **(D)**.

decrease in spontaneous muscle activity (Table 1). These findings suggested that the patient experienced a partial recovery of nerve function.

## Discussion

A unified understanding of AN has emerged in the last three years. In 2021, the European Academy of Neurology/Peripheral Nerve Society issued guidelines that proposed four types of antibody-related disease subtypes including CNTN1, NF155, Caspr1, and NF140/186 (8). Previous studies suggested that anti-CNTN1 positive AN leads to peripheral nerve damage with subacute or acute CIDP-like manifestations, accompanied by sensory ataxia, tremor, or cranial nerve involvement (1, 9). In this study, we report a rare case that presented with typical cerebellar dysarthria at the onset of the disease, which has not been reported in the literature. Generally, dysarthria can be divided into atony, spasticity, hypokinesia, hyperactivity, ataxia, and mixed dysarthria (10). Among them, ataxic dysarthria can usually be observed in cerebellar diseases, manifesting as syllable explosions, impaired rhythms, and pauses after syllable. The expression of CNTN1 is not only limited to the paranode, but it can also be found in dorsal root ganglion neurons and cerebellar granule neurons. A previous study indicated that CNTN1 can be detected in the retina, spinal cord, cerebral cortex, hippocampus, and cerebellum (11, 12). There is no evidence of intrathecal synthesis of autoantibodies against accessory nodules (12), whereas increased levels of protein in the CSF are common in patients with anti-CNTN1 positive AN. This is most likely caused by the disruption of the blood–brain barrier and peripheral circulating proteins may be infiltrated into the CNS (12). In animal and basic experiments, the CNTN1 antibody was confirmed to bind to the hippocampal neurons and the cerebellum of rats (3, 13), which provides certain theoretical support for our case. We summarized the specific clinical characteristics of anti-CNTN1 antibody-positive patients from previous relevant literature (details are in Table 2). It is worth noting that our case initially presented with dysarthria and limb tremors, along with irregular nystagmus, postural dizziness, and nerve root sheath cysts. These manifestations are rarely observed in cases with positive anti-CNTN1 antibodies previously reported in the literature. Research has shown that long-term exposure to anti-CNTN1 autoantibodies results in reduced expression of CNTN1 in cerebellar granule neurons and has identified a cytotoxic effect on

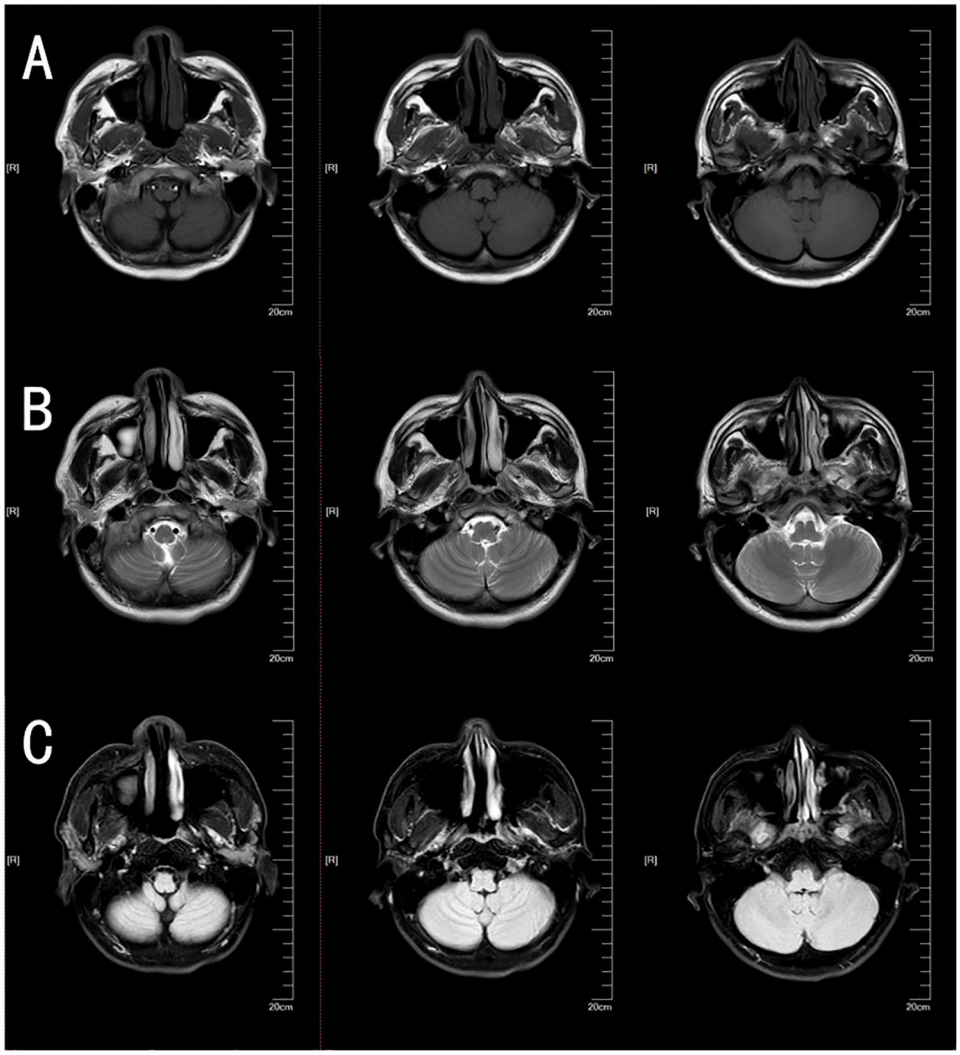



FIGURE 3
Brain MRI of this patient. The patient's brain T1 plain scan sequence **(A)**, T2 plain scan sequence **(B)**, and fluid-attenuated inversion recovery (FLAIR) **(C)** did not reveal obvious cerebellar atrophy or other abnormal findings.

cerebellar neurons (12, 32). Regarding the mechanism of anti-CNTN1 affecting the cerebellum, studies have shown that CNTN1 controls synaptic interactions between cerebellar interneurons, and the presence of antibodies may lead to disruption of this process (33). CNTN1 can facilitate the activity of the non-receptor tyrosine kinase Fyn (which is predominantly expressed in the cortex, cerebellum, hippocampus, and other areas of the central nervous system) by binding to the PTPα (receptor protein tyrosine phosphatase) protein, thereby promoting the development, function, and synapse formation of the central nervous system (11, 34, 35). However, the presence of CNTN1 antibodies can disrupt this process. Furthermore, studies have shown that the PTPα protein can also increase the activity of the non-receptor tyrosine kinase Src (34, 36). The literature indicates that concurrent deficiency of Src and Fyn kinases can lead to damage in cerebellar Purkinje cells, resulting in cerebellar injury (37). Therefore, we hypothesized that CNTN1 antibodies might cause cerebellar damage by inhibiting the interaction between CNTN1 and PTPα protein, thereby suppressing the activities of Fyn and Src kinases.

Patients with anti-CNTN1 AN were prone to kidney involvement and nephrotic syndrome (22). In our case, the 24-hour urinary protein level was significantly elevated. Additional elevated urine-related protein indicators suggested renal glomerular damage. In support of this, CNTN1 can also be expressed in podocytes, with IgG4 and CNTN1 antigens coexisting in glomerular deposition (21, 22).

When the patient presented to our hospital for the first time, a diagnosis of SCA was considered based on the results of NCS and his clinical presentation, suggesting that we should pay attention to the differentiation of NCS between anti-CNTN1 positive AN and SCA. The NCS of SCA with peripheral neuropathy is non-specific and may manifest as sensory and axonal neuropathy, sensorimotor axonal neuropathy, demyelinating sensorimotor neuropathy, and

TABLE 2 Detailed clinical features and imaging features of anti-CNTN1 antibody-positive cases.

| Author/ References | Time | Total Number | Age /sex | Clinical features | | | | | | | | | Elevated CSF protein | Serum Anti-CNTN1 antibody | CSF Anti-CNTN1 antibody | Imaging features | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Ataxia (Number of cases) | Weakness of the limbs (Number of cases) | Paresthesia (Number of cases) | Muscle atrophy (Number of cases) | Difficulty swallowing (Number of cases) | Tremor (Number of cases) | Postural dizziness (Number of cases) | Nystagmus (Number of cases) | Cerebellar dysarthria (Number of cases) | | | | Nerve root thickening on MRI | Nerve root cyst |
| Appeltshauser et al. (14) | 2020 | 3 | 67 (median)/ F | 2 | 3 | 3 | – | – | – | – | – | – | 3 | 3 | – | – | – |
| Xu et al. (15) | 2021 | 1 | 57/M | 1 | 1 | 1 | – | – | – | – | – | – | – | 1 | – | – | – |
| Hashimoto et al. (16) | 2018 | 1 | 70/M | – | 1 | 1 | 1 | – | – | – | – | – | / | 1 | / | 1 | – |
| Hou et al. (17) | 2022 | 2 | 52 (median)/ M | 2 | 2 | 2 | – | 1 | 2 | – | – | – | 2 | 2 | 1 | 2 | – |
| Doppler et al. (13) | 2015 | 4 | / | – | 4 | 4 | / | – | 3 | – | – | – | 4 | 4 | / | / | / |
| Tan et al. (18) | 2022 | 1 | 37/M | 1 | 1 | 1 | – | – | – | – | – | – | 1 | 1 | – | / | / |
| Tang et al. (19) | 2023 | 4 | 38 (median)/ 2/2(F/M) | 3 | 4 | 4 | – | – | – | – | – | – | 3 | 4 | – | / | / |
| Li et al. (5) | 2023 | 1 | 62/M | 1 | 1 | 1 | – | 1 | – | – | – | – | 1 | 1 | 1 | 1 | – |
| Fukushima et al. (20) | 2022 | 1 | 77/M | – | – | 1 | – | – | – | – | – | – | 1 | 1 | – | / | – |
| Santoro et al. (21) | 2022 | 1 | 73/F | 1 | 1 | – | – | – | – | – | – | – | / | 1 | – | / | / |
| Taieb et al. (22) | 2019 | 1 | 75/M | 1 | 1 | 1 | – | – | – | – | – | – | 1 | 1 | – | – | – |
| Delmont et al. (23) | 2020 | 10 | 63 (median)/ 2/8 (F/M) | 9 | 8 | 10 | / | / | / | – | – | – | – | 10 | – | – | – |
| Carrera-García et al. (24) | 2019 | 1 | 2/M | – | 1 | – | – | – | – | – | – | – | 1 | 1 | 1 | – | – |
| Lin et al (25) | 2018 | 1 | 20/F | 1 | 1 | 1 | 1 | – | – | – | – | – | 1 | 1 | – | 1 | – |
| Dubey et al. (26) | 2020 | 10 | 61 (median)/ 5/5 (F/M) | 9 | 8 | 9 | / | – | 1 | – | – | – | 7 | 10 | / | / | / |
| Liberatore et al. (27) | 2022 | 4 | 53 (median) 1/3 (F/M) | 3 | 4 | 4 | / | – | – | – | – | – | 4 | 4 | / | / | / |

*(Continued)*





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TABLE 2 Continued

| Author/ References | Time | Total Number | Age /sex | Clinical features | | | | | | | | | Elevated CSF protein | Serum Anti-CNTN1 antibody | CSF Anti-CNTN1 antibody | Imaging features | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Ataxia (Number of cases) | Weakness of the limbs (Number of cases) | Paresthesia (Number of cases) | Muscle atrophy (Number of cases) | Difficulty swallowing (Number of cases) | Tremor (Number of cases) | Postural dizziness (Number of cases) | Nystagmus (Number of cases) | Cerebellar dysarthria (Number of cases) | | | | Nerve root thickening on MRI | Nerve root cyst |
| Pascual-Goñi et al. (6) | 2021 | 15 | 58 (median)/ 5/10 (F/M) | 12 | 15 | 8 | / | 6 | 10 | – | – | – | 15 | 15 | – | / | / |
| Plaisier et al. (28) | 2021 | 1 | 61/M | 1 | 1 | 1 | / | – | – | – | – | – | 1 | 1 | / | – | – |
| Fehmi et al. (29) | 2023 | 15 | 59 (median)/ 12/3 (F/M) | 14 | 14 | 8 | / | / | 14 | / | / | / | 11 | 15 | – | / | / |
| Miura et al. (30) | 2015 | 13 | 61 (median)/ 3/10 (F/M) | 13 | 13 | 13 | – | 1 | 2 | – | 1 | – | 1 | 13 | – | – | – |
| Cortese et al. (9) | 2020 | 3 | 56 (median)/ M | 3 | 2 | 3 | 2 | – | 1 | – | – | – | – | 3 | – | – | – |
| Papantoniou et al. (31) | 2023 | 2 | 60 (median)/ M | 2 | 2 | 2 | – | – | – | – | – | – | – | 2 | – | – | – |
| Dong et al. (7) | 2022 | 1 | 62/M | – | 1 | 1 | – | – | – | – | 1 | – | – | 1 | 1 | – | – |
| Querol et al. (3) | 2013 | 3 | 71 (median)/ 2/1 (F/M) | 1 | 3 | 2 | / | – | – | – | – | – | 3 | 3 | – | / | / |
| Our case | 2023 | 1 | 23/M | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

CNTN1, contactin-1; F, female subject; M, male subject; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; -, none;/, unknown.





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sensorimotor polyneuropathy with axonal and demyelinating sensations (38). NCS features of anti-CNTN1 positive AN include prolonged distal motor latency, slow nerve conduction velocity, conduction block, prolonged or absent F wave latency, decreased compound muscle action potential amplitude, slow nerve conduction velocity, and decreased sensory nerve action potential amplitude (39). Notably, the 5-year interval of NCS results in this case suggested progressive motor and sensory nerve damage, possibly due to secondary axonal damage after severe myelin sheath injury. After retreatment, NCS showed partial improvement in some lower limb nerves, suggesting that the treatment may be effective.

On an MRI of the spinal nerve roots in AN, the enhancement or thickening of the lumbosacral nerve roots can usually be noted (1). Our case showed enhancement not only in the lumbar nerve root, but also in the cervical plexus. At the same time, the patient had multiple nerve root sheath cysts in intercostal nerve roots near the thoracic vertebrae, which had not been previously reported in the condition of anti-CNTN1 positive AN. Previously, the disease was reported to mainly occur in middle-aged and elderly people (1). However, our case is a patient who had clinical symptoms at the age of 17, suggesting that anti-CNTN1 positive AN may also occur in young people. Further investigation is warranted to explore the possible divergent pathogenesis between middle-aged and elderly individuals.

Previous studies have shown that the majority of anti-CNTN1 antibodies belong to the IgG4 subclass (1). Notably, animal studies conducted by Labasque and colleagues have demonstrated that patient-derived IgG4 antibodies disrupt paranodal junction formation in an *in vitro* myelination assay in the absence of complement or inflammatory cells, suggesting that Anti-CNTN1 IgG4 antibodies may themselves be pathogenic (40). Anti-CNTN1 antibodies are produced by activated B cells. Rituximab is a monoclonal antibody directed against B cells that express high levels of CD20. The study has shown that patients treated with rituximab have a significant decrease in the proportion of circulating $CD20^{+}$B cells, accompanied by a reduction in specific IgG4 antibodies of CNTN1 (17), which may be an important reason for the improvement of patients treated with rituximab in our case. Other studies have shown that CNTN1 patients have IgG3 antibodies instead of IgG4, and that they respond well to treatment with IVIg (41, 42). This may be because IVIg regulates the immune response mainly by binding to a variety of Fc receptors and activating the complement pathway, whereas IgG4 neither binds to the Fc receptor nor activates the complement pathway (43), so the action of IVIg fails.

In conclusion, in addition to peripheral neuropathies, cerebellar dysarthria (central nervous system involvement) should not be ignored in AN patients with CNTN1 antibodies.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Ethics Committee of the First People's Hospital of Yunnan Province. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

JC: Writing – original draft. LL: Data curation, Resources, Writing – review & editing. HZ: Writing – review & editing. JH: Resources, Supervision, Validation, Writing – review & editing. RL: Writing – review & editing. XG: Formal analysis, Writing – review & editing. HF: Writing – review & editing. JL: Writing – review & editing. HL: Writing – review & editing. QM: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Novel compound heterozygous *IL1RN* mutations as the likely cause of a lethal form of deficiency of interleukin-1 receptor antagonist

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Undiagnosed monogenic diseases represent a challenging group of human conditions highly suspicious to have a genetic origin, but without conclusive evidences about it. We identified two brothers born prematurely from a non-consanguineous healthy couple, with a neonatal-onset, chronic disease characterized by severe skin and bone inflammatory manifestations and a fatal outcome in infancy. We conducted DNA and mRNA analyses in the patients' healthy relatives to identify the genetic cause of the patients' disease. DNA analyses were performed by both Sanger and next-generation sequencing, which identified two novel heterozygous *IL1RN* variants: the intronic c.318 + 2T>G variant in the father and a ≈2,600-bp intragenic deletion in the mother. *IL1RN* mRNA production was markedly decreased in both progenitors when compared with healthy subjects. The mRNA sequencing performed in each parent identified two novel, truncated *IL1RN* transcripts. Additional experiments revealed a perfect intrafamilial phenotype–genotype segregation following an autosomal recessive inheritance pattern. The evidences shown here supported for the presence of two novel *loss-of-function* (LoF) *IL1RN* pathogenic variants in the analyzed family. Biallelic LoF variants at the *IL1RN* gene cause the deficiency of interleukin-1 receptor antagonist (DIRA), a monogenic autoinflammatory disease with marked similarities with the patients described here. Despite the non-availability of the patients' samples representing the main limitation of this

study, the collected evidences strongly suggest that the patients described here suffered from a lethal form of DIRA likely due to a compound heterozygous genotype at *IL1RN*, thus providing a reliable genetic diagnosis based on the integration of old medical information with currently obtained genetic data.

KEYWORDS

**case report, interleukin-1, interleukin-1 receptor antagonist (IL-1 ra), autoinflammatory diseases (AID), whole-genome sequencing (WGS)**

# Introduction

Autoinflammatory diseases (AIDs) represent a special group among inborn errors of immunity (IEI) since they are characterized by recurrent episodes of sterile inflammation, with no increased risk to severe infections (1). Over the past 20 years, ≈60 different monogenic AIDs have been identified, and different successful treatments have been reported (1, 2). The deficiency of interleukin-1 (IL-1) receptor antagonist (IL-1Ra), abbreviated as DIRA, is a rare monogenic AID, with less than 25 families described worldwide, provoked by biallelic *loss-of-function* variants at *IL1RN*. These variants typically lead to the loss of IL-1Ra production, the endogenous inhibitor of the proinflammatory cytokines IL-1α and IL-1β (3, 4). DIRA starts typically during early infancy with sterile inflammation mainly affecting skin, joints, and bones. Daily treatment with anakinra, the recombinant form of human IL-1Ra, resulted in terrific clinical responses and normalization of laboratory parameters (3, 4).

Herein we describe an undiagnosed and devastating inflammatory disease observed in two siblings born in 1970–1980s from a non-consanguineous healthy couple. Genetic investigations performed four decades later identified two novel *IL1RN* variants in their family, and additional studies demonstrated their deleterious consequences at the *IL1RN* mRNA production by different mechanisms. These evidences strongly suggest that the patients herein described probably suffered from DIRA as a consequence of a compound heterozygous genotype at *IL1RN* and died as a consequence of the natural course of the disease. We also discussed the limitations of our study to unequivocally establish DIRA as their definitive diagnosis mainly due to the non-availability of the patients' samples.

# Subjects and methods

## Subjects

The patients' clinical data and laboratory results were collected from medical charts. Written informed consents to participate in the study and to publish the results were obtained from each enrolled alive individual. The Ethical Review Board of Hospital Clínic, Spain approved the study (code HCB/2022/0855). All investigations were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

## DNA analyses

DNA samples were prepared from peripheral blood using QIAmp DNA Blood Mini Kit (QIAgen, Germany). The next-generation sequencing methods employed included a targeted gene panel (TGP; Supplementary Table S1) and whole genome sequencing (WGS). TGP was generated in an Access Array System 48.48 platform (Fluidigm, USA), whereas WGS was prepared using the lllumina DNA PCR-Free Library Prep kit (Illumina, USA). Library preparation and control quality were performed according to the manufacturers' instructions, and sequencing was performed on NextSeq or NovaSeq 6000 platforms (Illumina, USA). Reads were mapped against the GRCh37 using the BWA software (5), and their analyses were performed using the SeqNext software (JSI Medical Systems, Germany). Detected variants were classified according to previously published recommendations (6).

For the Sanger method of DNA sequencing, amplicons of *IL1RN* gene (RefSeq NM_173842.3) were in-house designed and PCR-amplified, purified with Illustra ExoStar 1-Step kit (GE Healthcare, USA), bidirectionally sequenced using ABI BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA), and run on the ABI 3730XL DNA analyzer (Applied Biosystems, USA). Reads analysis was performed using the SeqPilot software (JSI Medical Systems, Germany).

## RNA analyses

RNA samples from family members and healthy individuals were prepared from peripheral blood collected in Tempus™ tubes (Thermo Fisher Scientific, USA). To evaluate *IL1RN* mRNA production, cDNA was generated by the Superscript II reagent kit (Invitrogen, USA). Quantitative polymerase chain reaction (qPCR) was performed using two different TaqMan (Thermo Fisher Scientific, USA) probes for *IL1RN*: CustomEx1 probe, targeting

exon1 of *IL1RN*, and Hs00893626_m1, targeting a region covering the end of exon 3 and the beginning of exon 4 of *IL1RN*, on a QuantStudio 12K Flex Real-Time PCR System (Thermo Fisher Scientific, USA). Gene expression levels were calculated according to the $\Delta\Delta C_t$ method and normalized against two endogenous controls (*GAPDH*, probe Hs0786624_g1; *ACTB*, probe Hs01060665_g1; Thermo Fisher Scientific, USA).

To characterize the sequence of the different *IL1RN* transcripts, RNA libraries were prepared from total mRNA using NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (New England Biolabs, USA) with the rRNA depletion configuration. RNA libraries were validated using TapeStation (Agilent Technologies, USA), pooled and quantified by qPCR, and sequenced on a NextSeq platform (Illumina, USA) using the NextSeq 500 High-Output 150-paired-end 2 × 75 cycles kit (Illumina Inc, USA). Sequence reads were aligned to GRCh38 using the Ensembl annotation version 109 with STAR (version 2.7.0d). Gene expression quantification at the exon level and differential exon usage analysis were performed using the DEXSeq package in R. To identify novel transcripts, the sequence reads were aligned to the same reference using Bowtie2 (version 2.3.4.1) and Tophat (version 2.1.1). Subsequently, we employed specific applications from Cufflinks (v2.2.1) for further analysis. Initially, BAM files obtained from previous steps were filtered based on our region of interest. Cuffcompare was used to predict transcripts for each group, and gffread was utilized to generate the FASTA files of the predicted transcripts.

# Results

## Patients

We identified a non-consanguineous healthy couple of Spanish ancestry with four children, two of which were affected by an undiagnosed and lethal inflammatory disease (Figure 1A). One of these patients (patient II-1) was previously reported (7). Both patients were born prematurely at 36 weeks of gestation in 1977 and 1983, respectively. Their disease started during the first week of life, with similar clinical manifestations and laboratory perturbations (Table 1). The disease had a chronic course and a fatal outcome in both cases: patient II-1 died at the age of 13 months as a consequence of a complicated varicella infection, whereas patient II-2 died at the age of 3 years due to a cerebral thrombosis.

Their main clinical features included recurrent fever and skin and musculoskeletal manifestations. Skin lesions were characterized by generalized, severe vesiculo-pustular lesions, often over-infected, refractory to all administered treatments. Musculoskeletal manifestations included marked pain with movement and painful swelling at clavicles, ribs, femur, and mandibula. The radiographic findings included periosteal elevations of long bones and widening of clavicles and multiple ribs. On the basis of these lesions, patient II-1 was diagnosed as having Caffey–Silverman syndrome, and corticosteroid treatment led to a transient relief. Additional manifestations included hypotonia, irritability, marked development and growth retardation, conjunctivitis, aseptic

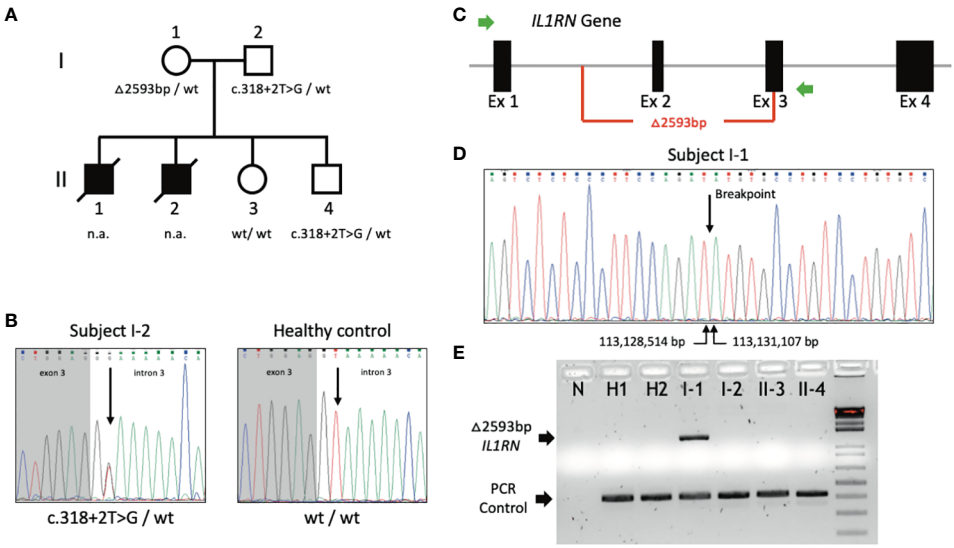



FIGURE 1
*IL1RN* variants detected in enrolled individuals. **(A)** Pedigree of the family. Black-filled symbols, affected subjects; open symbols, unaffected subjects; squares, male subjects; circles, female subjects; slash, deceased subjects. *IL1RN* genotypes are shown below each analyzed subject. n.a., not analyzed; wt, wild-type. **(B)** Sense Sanger chromatograms from subject I-2 carrying the heterozygous genotype for the c.318 + 2T>G *IL1RN* variant (left box) and from a healthy subject (right box). The arrows indicate the position where the nucleotide variant is located. **(C)** Genomic organization of isoform 1 of *IL1RN* gene (NM_173842.3). Green arrows represent the forward and reverse primers designed to generate a PCR amplicon specific of the genomic deletion. **(D)** Sense Sanger chromatogram showing the breakpoint and boundaries of the genomic deletion at *IL1RN* locus identified in subject I-1. The arrows indicate the nucleotides located at each side of the breakpoint site, and shown below are the respective genomic coordinates according to GRCh38. **(E)** Agarose gel electrophoresis of PCR products generated with the use of primers designed for genomic deletion. N, negative control; H1 and H2, healthy subjects. Black arrows indicate the specific bands of PCR amplicons of the *IL1RN* allele containing the deletion (top) and a positive control of PCR reaction (bottom).

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TABLE 1 Clinical manifestations and genetic data of enrolled patients and reported patients with DIRA. .

| | | Patient II-1 | Patient II-2 | Reported DIRA patients (*n* = 28) |
|---|---|---|---|---|
| | Sex | Male | Male | 15 male/13 female |
| Gestational age[a] | Premature | Yes (36 weeks) | Yes (36 weeks) | 88.9% (16/18) |
| | At term | – | – | 11.1% (2/18) |
| Age at disease onset[b] | 0–1 month | Yes | Yes | 69.2% (18/26) |
| | 2–6 months | – | – | 15.4% (4/26) |
| | >6 months | – | – | 15.4% (4/26) |
| Clinical outcome | Alive | No | No | 78.6% (22/28) |
| | Deceased | Yes | Yes | 21.4% (6/28) |
| | Age at death[c] | 13 months | 3 years | 12.5 months (range: intra-uterus–9.5 years) |
| | Cause of death | Varicella infection | Cerebral thrombosis | Multiorgan failure secondary to SIRS (*n* = 2)<br>Pulmonary hemosiderosis (*n* = 1)<br>Medical pregnancy interruption (*n* = 1)<br>CMV-induced hemophagocytosis (*n* = 1)<br>Not specified (n:1) |
| | Fever | Yes | Yes | 34.6% (9/26) |
| | Pustulosis | Yes | Yes | 92.3% (24/26) |
| Musculo-skeletal manifestations | Arthritis | No | No | 53.8% (14/26) |
| | Sterile multiple osteolytic lesions | No | No | 74.1% (20/27) |
| | Ribs involvement | Yes | Yes | 67.8% (19/28) |
| | Clavicles involvement | Yes | Yes | 21.0% (4/19) |
| | Long bones involvement | Yes | Yes | Not systematically specified |
| | Periosteal elevations | Yes | Yes | 73.1% (19/26) |
| | Hepatomegaly | No | No | 26.3% (5/19) |
| | Splenomegaly | No | No | 26.3% (5/19) |
| | Irritability | Yes | Yes | Not specified |
| | Sleep disturbance | Yes | Yes | Not specified |
| | Conjunctivitis | Yes | Yes | 15.4% (4/26) |
| | Lung disease | No | No | 19.2% (5/26) |
| | Thrombosis | No | Yes | 26.7% (4/15) |
| Other manifestations | Growth retardation | Yes | Yes | Common, but not systematically specified |
| | Hypotonia | Yes | Yes | Occasionally reported |
| | Recurrent Infections | Yes | Yes | 15.4% (4/26) |
| | Cardiac Insufficiency | Yes | Yes | Not specified |
| Genetics | | | | |
| *IL1RN* Genotype[d] | Homozygous | No | No | 91.3% (21/23) |
| | Compound Heterozygous | Yes | Yes | 8.7% (2/23) |
| *IL1RN* variants[e] | Missense | No | No | None |
| | Nonsense | No | No | |

*(Continued)*

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TABLE 1 Continued

| | | Patient II-1 | Patient II-2 | Reported DIRA patients (*n* = 28) |
|---|---|---|---|---|
| | Sex | Male | Male | 15 male/13 female |
| Genetics | | | | |
| | | | | *n* = 7<br>S21X (*n* = 2), R26X (*n* = 2), R29X (*n* = 2), Q45X (*n* = 1), Q54X (*n* = 6), E77X (*n* = 11), Q119X (*n* = 4) |
| | Frameshift deletion | No | No | *n* = 6<br>N18KfsX4 (*n* = 4), T47TfsX4 (*n* = 1), N52KfsX25 (*n* = 2), D72_I76 del (*n* = 6), T133PfsX118 (*n* = 2) |
| | Splice site | Yes | Yes | None |
| | Large genomic deletions | Yes | Yes | *n* = 2<br>22.2kb del (*n* = 2), 175 kb del (*n* = 8) |

SIRS, severe inflammatory response syndrome; CMV, cytomegalovirus.
[a]Data available for 18 patients.
[b]Data available for 26 patients.
[c]Median age at death of reported DIRA patients.
[d]IL1RN genotypes identified in the 23 different families reported as suffering from DIRA.
[e]IL1RN variants identified in the reported DIRA families. The number of alleles with the IL1RN variants is shown among brackets.

meningitis, hydrocephaly, cardiac insufficiency, and a tendency to mild-to-moderate infections (oral thrush, otitis, urinary infection, and gastroenteritis).

The results of laboratory tests revealed increased leukocyte (20.1–55.5 × $10^9$/L; reference range [RR] 6–17 × $10^9$/L) and platelet (620 × $10^9$/L; RR 150–450 ×$10^9$/L) counts, decreased hemoglobin concentration (7.4–10.7 g/dL; RR 10.7–14.7 g/dL), and a marked increase of erythrocyte sedimentation rate (>75 mm/h; RR <10 mm/h). All analyses evaluating the immune system performed at that time (complement, circulating immunoglobulins, oxidative burst test, PHA-stimulated lymphocytic test, PPD test, and thymic shadow) were normal or negative (7).

## DNA analyses

On the basis of the patients' features and familial pedigree, we hypothesized for the presence of an early-onset, severe monogenic inflammatory disease inherited either as a recessive or as an X-linked trait. As biological samples from patients were not currently available, we genetically analyzed the patients' first-degree healthy relatives (see Figure 1A to identify the analyzed individuals). We first performed a screening of monogenic AID-associated genes using a TGP, which detected in the patients' father the heterozygous c.318 + 2T>G transversion in the donor splice site at intron 3 of *IL1RN* (Figure 1B). This variant has not been previously reported, and bioinformatics analyses suggested that it may impair the normal mRNA production (Supplementary Table S2).

DIRA diagnosis might fit with the patients' clinical features, but the absence of *IL1RN* variants in the patients' mother apparently excluded a confirmatory genotype for this recessively inherited disease. Considering the intrinsic limitations of the methods employed thus far, we performed additional analyses in the patients' mother to identify a potential second hit at *IL1RN*. WGS analysis was performed in a DNA sample from the patients' mother, which revealed a heterozygous intragenic *IL1RN* deletion (Supplementary Figure S1). A specific PCR with primers at each side of the breakpoint was designed (Figure 1C), and the amplicon sequencing revealed a 2,593-bp deletion encompassing from intron 1 until exon 3 (Figure 1D, Supplementary Table S2 and Supplementary Figure S2). This genomic deletion has not been reported previously, and neither has it been registered in public databases. Intrafamilial segregation of *IL1RN* variants revealed that the patients' first-degree healthy relatives carried either a single heterozygous *IL1RN* genotype (each of the patients' parent and their brother) or a homozygous genotype for the wild-type allele (patients' sister), thus confirming that none of them carried a confirmatory genotype for DIRA (Figures 1A, E).

## mRNA analyses

Prediction analyses suggested that the novel *IL1RN* variants detected here may provoke a decrease in mRNA production by different mechanisms. The intronic variant is predicted to impair the normal splicing of immature mRNA by destroying one of the canonical splice sites of the gene, whereas the allele containing the genomic deletion is predicted to produce a mRNA transcript smaller than that encoded by the wild-type allele (534 bp in wild-type allele vs. 383 bp in mutant allele). We first evaluated the production of wild-type *IL1RN* mRNA transcript by using qPCR analyses (Figure 2A), which revealed a marked decrease of production in each of the patients' progenitor when compared to healthy subjects (Figure 2B), a result that was subsequently validated by mRNA sequencing (Figure 2C).

To investigate the consequences at the molecular level of the novel *IL1RN* variants, we performed mRNA sequencing in each of the patients' parent. These analyses identified two novel *IL1RN* transcripts predicted to generate truncated IL-1Ra proteins. On one

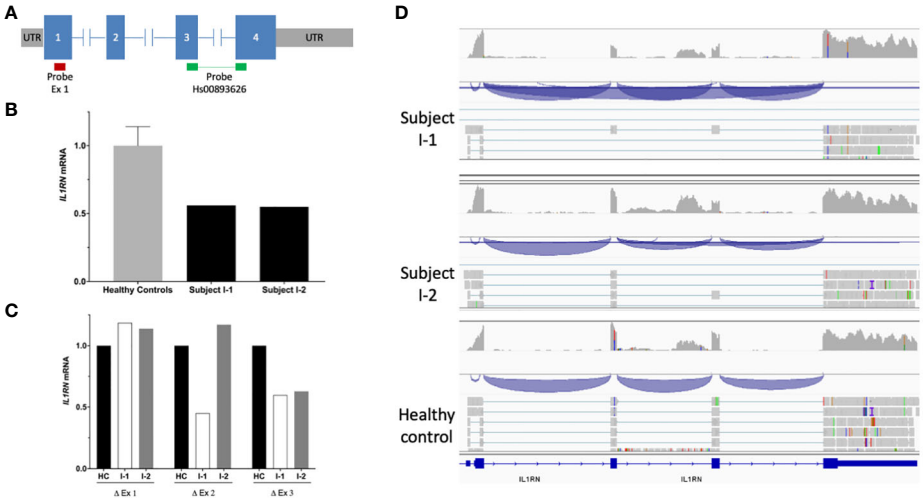



FIGURE 2
| mRNA *IL1RN* analysis. **(A)** Scheme of *IL1RN* gene (isoform 1; RefSeq: NM_173842.3) and location of probes employed in the quantitative PCR assay. The red bar indicates the probe mapping in exon 1, whereas the green bars indicate the probe Hs00893626, which maps in the junction of exons 3 and 4. **(B)** Relative mRNA levels of *IL1RN* in the peripheral blood of healthy subjects ($n$ = 8) and patients' parents determined by quantitative PCR. The bars indicate the ratio of exon 3 *versus* exon 1, while T bars indicate the standard deviations, where applicable. **(C)** Relative quantification of exons of *IL1RN* determined by mRNA sequencing. The bars indicate the mean of the fold change among parents and healthy controls. **(D)** Schemes of novel *IL1RN* mRNA transcripts showing the exon junctions (blue) identified by mRNAseq in subject I-1 (upper panel) and subject I-2 (middle panel) compared with the normal mRNA transcripts identified in a healthy subject (bottom panel).

side, the allele containing the c.318 + 2T>G intronic variant generated a novel transcript with the skipping of exon 3 (Figure 2D), which caused a frameshift mutation, the incorporation of two aberrant amino acid residues, and a premature stop codon (p.Glu69Glyfs*2) (Supplementary Figure S3). On the other side, the allele containing the genomic deletion generated a transcript that lacks exons 2 and 3 of the gene (Figure 2D), which also caused a frameshift, the incorporation of six aberrant amino acid residues, and the appearance of a premature stop codon (p.Ile40Glnfs*6) (Supplementary Figure S4). All these experimental evidences confirmed that the two novel *IL1RN* variants were *loss-of-function*.

## Discussion

In the genetic counseling consult, we identified a lethal inflammatory undiagnosed disease in two siblings who were born 40 years ago from a healthy, non-consanguineous couple. Their familial and clinical data strongly suggested a genetic cause for the disease, being the autosomal recessive and the X-linked modes of inheritance as the most probable. By using different methods of genetic study, we finally identified two novel *IL1RN* variants in this family. Their *loss-of function* behavior was confirmed by different experiments that revealed both a marked reduction of mRNA production by the variant *IL1RN* alleles and the identification of novel transcripts predicted to generate truncated proteins. Considering all collected clinical, laboratory, and genetic evidences, we propose that the most likely option is that both patients suffered from a lethal form of DIRA as a consequence of a compound heterozygous genotype at *IL1RN*. However, the main limitation of this study is the non-availability of the patients' samples due to their death 40 years ago. In a strict sense, this limitation prevented us to unequivocally establish DIRA as their definitive diagnosis despite either clinical manifestations or genetic findings strongly pointing toward it.

Since its description, DIRA has been reported in 23 families of different ethnic backgrounds (3, 4, 8–11). From a clinical perspective, DIRA starts often during neonatal period (≈70%), and sterile inflammatory manifestations involving the musculoskeletal system (100%) and skin (92%) represent their hallmarks (Table 1). The manifestations of the patients here described are in concordance with those previously reported in DIRA, including some occasional features such as a tendency to develop thrombosis (patient II-2) and mild-to-moderate infections (2, 8). From a genetic point of view, 91% of patients with DIRA carried homozygous genotypes as a consequence of parental consanguinity, with only two patients being a consequence of compound heterozygous *IL1RN* genotypes (Table 1). Among all reported *IL1RN* variants causing DIRA, seven variants were single nucleotide exchanges leading to nonsense variants, six were small base pair deletions leading to mRNA frameshift and premature stop codons, and two were large genomic deletions (3, 4, 8–11). The family described here would represent the third known family with DIRA due to a compound heterozygous *IL1RN* genotype, with the additional novelties of the characterization of the first pathogenic variant located in a splice site in the *IL1RN*, and a novel structural variant (intragenic deletion), whose identification required the combination of different techniques.

From a pathophysiological perspective, DIRA represents one of the monogenic AIDs closely related with an increased signaling through the IL-1 pathway (12). The prototypic agonist cytokines driving inflammation in this pathway are called IL-1α and IL-1β.

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Despite the differences in their amino acid sequences and post-translational modifications, both cytokines bind to the same receptor, the IL-1 receptor type 1 (IL-1R1), and recruit the IL-1R accessory protein (IL-1RAcp) to transduce an intracellular signal (13). In contrast, the protein called IL-1Ra also binds to IL-1R1, but it does not recruit the IL-1RAcP nor transduces an inflammatory signal. As a consequence, IL1Ra competitively antagonizes the pro-inflammatory action of IL-1α and IL-1β (13). The relevance of IL-1Ra has been shown by the description of its genetically determined deficiency in mice and humans (3, 4, 14) as well as by the terrific effectiveness of the treatment with the recombinant IL-1Ra in different human diseases including DIRA (3, 4, 8–11, 15–19). At present, different monogenic AIDs have been associated with an overall increase signaling through the IL-1 pathway by different mechanisms. The cryopyrin-associated periodic syndromes (CAPS) represent the prototypic IL-1-mediated disease, and the IL-1β overproduction is a consequence of *gain-of-function NLRP3* variants that ultimately provoke a hyperactivation of the Nlrp3-inflammasome (20, 21). Patients with CAPS exhibit extremely positive responses to all commercially available IL-1 inhibitors, including the blockade of IL-1α and IL-1β and the endogenous IL-1Ra at the IL-1R1 level (anakinra) (15–17) or in the extracellular space (rilonacept) (22, 23) or by using a monoclonal antibody (MoAb) that specifically binds IL-1β in the extracellular milieu (canakinumab) (24, 25). In the recessively inherited DIRA, the increase of the IL-1 signaling pathway is due to the complete loss of the endogenous inhibitor IL-1Ra due to biallelic *loss-of-function IL1RN* variants (3, 4). Interestingly, most patients with DIRA have been well controlled when treated with the recombinant IL-1Ra anakinra (3, 4, 8–11, 15–19). This therapeutic approach would have been extremely useful in the patients described here. Unfortunately, they were born at a time when IL-1Ra was not yet identified. Finally, a dominantly inherited AID named Loss of IL-1R1 Sensitivity to IL-1Ra (LIRSA) has been recently described as a consequence of monoallelic variants at *IL-1R1* (26). In this disease, the mutation characteristically disrupts the interaction of IL-1R1 with IL-1Ra. As a consequence, there is a hyperactivation of the IL-1 signaling related with the functional loss of the endogenous IL-1Ra (26). Patients with LIRSA did not exhibit positive responses to the treatment with the recombinant IL-1Ra anakinra on the basis of the defect in the IL-1R1 that made it unsensitive to this protein. In contrast, these patients are well controlled with the anti-IL-1β MoAb canakinumab (26). In addition, novel evidences also suggest that these patients may be potentially well controlled with rilonacept or with the novel IL-1α/IL-1β trap rilabnacept (26) (see Table 2 for a detailed comparison of these IL-1-mediated diseases).

TABLE 2 Comparative features of IL-1-mediated diseases.

| | CAPS | DIRA | LIRSA |
|---|---|---|---|
| Gene | *NLRP3* | *IL1RN* | *IL1R1* |
| Protein | Cryopyrin | IL-1Ra | IL-1R type 1 |
| Pathophysiological mechanism | *Gain-of-function* variants | *Loss-of-function* variants | Variants causing loss of IL-1R1 sensitivity to IL-1Ra |
| Inheritance pattern | 1. Autosomal dominant (familial cases)<br>2. *De novo* germline variants (sporadic cases)<br>3. *De novo* post-zygotic variants (mosaicism; sporadic cases) | Autosomal recessive | *De novo* germline variants (sporadic cases) |
| **Clinical manifestations** | | | |
| Disease onset | 1. Infancy/first decade<br>2. Occasional reports of adult-onset disease (frequent in mosaicism carriers) | Birth/infancy | First year of life |
| Recurrent fever | Yes | Frequent (≈ 1/3 of patients) | Not reported |
| Skin lesions | Generalized urticaria-like skin rash (often triggered by cold exposure) | Generalized pustulosis | Not reported |
| Articular manifestations | Arthralgias<br>Recurrent arthritis<br>Occasional arthropathy (knees) | Arthralgias<br>Recurrent arthritis<br>Occasional arthropathy (knees)<br>Osteolytic lesions<br>Periosteal elevations<br>Swelling at ribs, clavicles | Arthralgias<br>Recurrent arthritis<br>Chronic pain<br>Osteolytic lesions<br>CRMO |
| Ocular manifestations | Conjunctivitis<br>Papiledema<br>Occasional uveitis | Occasional conjunctivitis (≈1/5 patients) | Not reported |
| CNS manifestations | Headache<br>Recurrent aseptic meningitis | Hypotonia<br>Developmental delay | Not reported |
| Hearing loss | Frequent (≈1/3–1/2 patients) | Not reported | Not reported |

*(Continued)*

TABLE 2 Continued

| | CAPS | DIRA | LIRSA |
|---|---|---|---|
| **Clinical manifestations** | | | |
| AA-amyloidosis | Frequent (≈1/5–1/3 patients) | Not reported | Not reported |
| Tendency to thrombosis | Not reported | Occasionally reported | Not reported |
| **Response to commercially available IL-1 inhibitors** | | | |
| Recombinant IL-1Ra (anakinra) | Positive | Positive | No response |
| IL-1α/IL-1β/IL-1Ra Trap (rilonacept) | Positive | Positive (occasional reports) | Not administered |
| MoAb anti-IL-1β (canakinumab) | Positive | Positive (occasional reports) | Positive |
| Number of reported patients | Hundreds | ≈25–30 | 1 |

CAPS, cryopyrin-associated periodic syndromes; DIRA, deficiency of IL-1 receptor antagonist; LIRSA, loss of IL-1R1 sensitivity to IL-1Ra; IL-1Ra, IL-1 receptor antagonist; IL-1R, IL-1 receptor; CRMO, chronic recurrent multifocal osteomyelitis; CNS, central nervous system.

In all monogenic diseases, the identification of the genetic cause has relevant consequences for the patient in terms of definitive diagnosis and therapeutic management. Moreover, this information may have also consequences for their first-degree relatives due to the moderate-to-high risk of disease recurrence in future pregnancies. This risk of disease recurrence may be present even in those families with undiagnosed diseases but highly suspicious to be monogenic in nature. For all these families, medical advice through an adequate genetic counseling program is highly warranted, even if the patients died many years before as what occurred in the family described here. Indeed this was the scenario in the family analyzed here. We were able to identify and analyze this family until the elucidation of the likely cause of the disease thanks to the request of genetic and medical advices of the patients' healthy sister in a specific consult, thus concluding a 40-year-long journey since the disease onset until the achievement of the patients' diagnosis. It is interesting to note that the first results obtained using standard methods of genetic analyses that did not identify the *IL1RN* deletion did not allow to establish the cause of the disease on the basis of a non-confirmatory genotype of DIRA. In similar apparently "negative" cases, a first approach that is being implemented by many laboratories is the re-analysis of previous analyses mainly performed by whole-exome sequencing methods. This approach may have success rates as high as ≈20% mainly thanks to improved bioinformatic pipelines, specific search for gene mosaicisms, reclassification of detected variants, or new gene associations (27, 28). In this work, we describe the possibility of expanding the analysis of particular families by using complementary technologies such as whole-genome sequencing since these methods may increase the power to identify previously undetected variants, especially structural gene variants such as the *IL1RN* deletion described here. Ideally, if the two pathogenic variants at *IL1RN* would have been detected in samples from the two deceased patients, that would represent a post-mortem genetic analysis (29). In a strict sense, this was not possible due to the non-availability of the patients' samples. However, as a conclusion, the combination of old medical information collected from registries associated with current genetic data obtained in first-degree healthy relatives reasonably provides a reliable diagnosis of DIRA in the analyzed family.

In conclusion, we described two patients who died 40 years ago from an undiagnosed inflammatory disease, of which currently performed studies strongly suggest that they were affected by a lethal form of DIRA. Experimental evidences expand the genetic basis of DIRA by the description of two novel *loss-of-function IL1RN* variants that generate mRNA transcripts predicted to produce truncated proteins. Finally, we highlight the relevance of an adequate genetic counseling in families with undiagnosed but potentially monogenic diseases because this work was possible thanks to the request for medical and genetic advice of the patients' first-degree healthy relative.

## Data availability statement

The data presented in this study are deposited in the NCBI-BioProject database, accession number PRJNA1092963. http://www.ncbi.nlm.nih.gov/bioproject/1092963.

## Ethics statement

The studies involving humans were approved by Ethical Review Board of Hospital Clínic, Spain (code HCB/2022/0855). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

EU: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. NB: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing, Formal Analysis, Software. MS-M: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – review & editing. AM-V: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing, Funding acquisition. IO: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. MT: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing, Software. RL: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing, Project administration. SP: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing. VF: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing. JY: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. FC: Formal Analysis, Investigation, Methodology, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Software, Supervision, Validation. JA: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing, Data curation, Visualization, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1381447/full#supplementary-material

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# Longitudinal cytokine and multi-modal health data of an extremely severe ME/CFS patient with HSD reveals insights into immunopathology, and disease severity

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**Introduction:** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) presents substantial challenges in patient care due to its intricate multisystem nature, comorbidities, and global prevalence. The heterogeneity among patient populations, coupled with the absence of FDA-approved diagnostics and therapeutics, further complicates research into disease etiology and patient managment. Integrating longitudinal multi-omics data with clinical, health, textual, pharmaceutical, and nutraceutical data offers a promising avenue to address these complexities, aiding in the identification of underlying causes and providing insights into effective therapeutics and diagnostic strategies.

**Methods:** This study focused on an exceptionally severe ME/CFS patient with hypermobility spectrum disorder (HSD) during a period of marginal symptom improvements. Longitudinal cytokine profiling was conducted alongside the collection of extensive multi-modal health data to explore the dynamic nature of symptoms, severity, triggers, and modifying factors. Additionally, an updated severity assessment platform and two applications, ME-CFSTrackerApp and LexiTime, were introduced to facilitate real-time symptom tracking and enhance patient-physician/researcher communication, and evaluate response to medical intervention.

**Results:** Longitudinal cytokine profiling revealed the significance of Th2-type cytokines and highlighted synergistic activities between mast cells and eosinophils, skewing Th1 toward Th2 immune responses in ME/CFS

pathogenesis, particularly in cognitive impairment and sensorial intolerance. This suggests a potentially shared underlying mechanism with major ME/CFS comorbidities such as HSD, Mast cell activation syndrome, postural orthostatic tachycardia syndrome (POTS), and small fiber neuropathy. Additionally, the data identified potential roles of BCL6 and TP53 pathways in ME/CFS etiology and emphasized the importance of investigating adverse reactions to medication and supplements and drug interactions in ME/CFS severity and progression.

**Discussion:** Our study advocates for the integration of longitudinal multi-omics with multi-modal health data and artificial intelligence (AI) techniques to better understand ME/CFS and its major comorbidities. These findings highlight the significance of dysregulated Th2-type cytokines in patient stratification and precision medicine strategies. Additionally, our results suggest exploring the use of low-dose drugs with partial agonist activity as a potential avenue for ME/CFS treatment. This comprehensive approach emphasizes the importance of adopting a patient-centered care approach to improve ME/CFS healthcare management, disease severity assessment, and personalized medicine. Overall, these findings contribute to our understanding of ME/CFS and offer avenues for future research and clinical practice.

KEYWORDS

**ME/CFS, EDS/hEDS/HSD, POTS, MCAS, MCS, longitudinal omics, Th2-cytokines, complex chronic condition**

## 1 Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, and debilitating multi-system disease affecting millions of people worldwide (1–3). ME/CFS is characterized by post-exertional malaise, manifested as the worsening of existing symptoms or the onset of new ones following mental or physical exertion, and exposure to environmental risk factors. Persistent symptoms include, but are not limited to, cognitive impairments, hypersensitivity to various stimuli (4–7), headaches, muscle and joint pain, sore throat, tender lymph nodes, gastrointestinal issues, chills, night sweats, multi-chemical sensitivity, shortness of breath, irregular heartbeat, sleep disturbance, pain, and orthostatic intolerance (8–10). Symptoms tend to manifest in various combinations and levels of intensity for each patient, often marked by periods of remission and relapse. This variability, along with the gradual worsening of symptoms can lead to a substantial reduction in patients' ability to engage in previous levels of occupational, educational, social, and personal activities, and quality of life. Around 25% of ME/CFS patients, including children, may become severely affected (11), confined to their homes or beds for extended periods, with some becoming critically ill (12–20).

Critically ill ME/CFS patients may require life-supporting devices like jejunal feeding tubes or central venous catheters (19) for nutrient delivery. Despite their importance, these devices carry significant health risks, contributing to morbidity and mortality, including thrombosis, infections, intestinal perforation, and metabolic complications (21–23), thereby further complicating the management of the patients' health.

Despite decades of research, the precise pathophysiology of ME/CFS remains unclear. The limited understanding of its underlying causes, the FDA-approved diagnostic tests, and treatments, have presented significant challenges in effectively diagnosing and treating ME/CFS patients (9). These substantial hurdles underscore the necessity for innovative research approaches to address the existing gap in disease etiology and enhance patient care and quality of life (24).

A substantial body of research has implicated genetic variations and environmental stressors, such as infections, trauma, and exposure to toxins, in the etiology of ME/CFS (25–30). Additionally, ME/CFS patients and their families exhibit a higher prevalence of conditions like Ehlers-Danlos syndrome (EDS), hypermobility spectrum disorders (HSD) (31), post-treatment Lyme disease (PTLDS) (32), and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) (33–35). Recent investigations into post-COVID syndrome have uncovered significant symptom overlap between ME/CFS and Long COVID (36–38). Studying shared biological systems across these comorbidities holds promise for biomarker and therapeutic discoveries (39).

Within the intricate tapestry of ME/CFS and its comorbidities, a central point of agreement in the scientific community revolves

around immune dysregulation (40) and aberrant cytokine expression. However, a thorough examination of the literature reveals inconsistencies, with some studies indicating an overactive immune response leading to chronic inflammation (41–43), while others propose a scenario of immune system debilitation (44).

The inconsistency in research findings could be due to a myriad of factors including the dynamic nature of ME/CFS (10), characterized by relapse and remission cycles, diverse triggers, and variable durations, as well as medication, lifestyle, and comorbidities (31, 35, 45–48). Adding to the complexity is the subjective nature of symptomatology, spanning across multiple bodily systems, and the inherent limitations in tools available for the quantitative measurement of severity fluctuations.

Currently, to assess clinical severity, researchers rely on methods such as the SF-36 questionnaire, and cardiopulmonary exercise tests, categorizing patients into mild, moderate, and severe groups. Acknowledging the spectrum's breadth, a recent addition of a "very severe" category attempts to capture the extreme end of the scale (5, 20). However, as the condition worsens, some patients transition from ambulatory to bed bound states, rendering conventional assessment tools impractical (49, 50) and highlighting the pressing need for more adaptable approaches. The exclusion of the very severely ill cohort from mainstream ME/CFS studies can also result in misclassification, contributing to research inconsistency and impeding our understanding of disease pathophysiology (49, 50). Recognizing this critical gap, we initiated a comprehensive longitudinal study that integrates clinical, health, pharmaceutical, nutraceutical, textual, and cytokine data, and harnesses the power of artificial intelligence (AI). Our focus on an extremely severe ME/CFS patient in a phase of marginal improvement has provided a unique perspective on the underlying immunopathology and its connections to symptomatology, severity, and comorbidity in ME/CFS. By delving into the intricacies of severity and incorporating the experiences of the most severely affected individuals, our objective is to lay the groundwork for substantial advancements in the quality of care for those navigating the challenges of ME/CFS. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, and debilitating multi-system disease affecting millions of people worldwide (1–3). ME/CFS is characterized by post-exertional malaise, manifested as the worsening of existing symptoms or the onset of new ones following mental or physical exertion, and exposure to environmental risk factors. Persistent symptoms include, but are not limited to, cognitive impairments, hypersensitivity to various stimuli (4–7), headaches, muscle and joint pain, sore throat, tender lymph nodes, gastrointestinal issues, chills, night sweats, multi-chemical sensitivity, shortness of breath, irregular heartbeat, sleep disturbance, pain, and orthostatic intolerance (8–10). Symptoms tend to manifest in various combinations and levels of intensity for each patient, often marked by periods of remission and relapse. This variability, along with the gradual worsening of symptoms can lead to a substantial reduction in patients' ability to engage in previous levels of occupational, educational, social, and personal activities, and quality of life. Around 25% of ME/CFS patients, including children, may become severely affected (11), confined to their homes or beds for extended periods, with some becoming critically ill (12–20).

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# 2 Materials and methods

## 2.1 Study design and participant

Over the course of four years, from June 2017 (when the participant was 34) to January 2021, we collected longitudinal blood samples from an extremely ill male ME/CFS patient. These samples were used for integrative case study on longitudinal plasma cytokine profiling, which incorporated health, clinical, and textual data to identify cytokines associated with disease severity. The patient began experiencing health issues at age 21 and received a diagnosis of ME/CFS almost a decade later. He is entirely bedridden, relying on caregivers for all aspects of his life, and receives nutrition via a G-tube and PICC line. The patient, of Caucasian descent, also has a comorbidity of hypermobility spectrum disorder, with a family history of EDS type III and HSD (refer to Figure 1). Throughout this four-year period, from June 2017 to January 2021, the patient's extreme hypersensitivity and PEM improved to the extent that he could tolerate human presence and regain access to internet use and social media.

This patient met various diagnostic criteria outlined by renowned ME/CFS doctors, such as those from the International Consensus Criteria and Canadian Consensus Criteria. These criteria encompassed Post-Exertional Malaise (PEM), symptom duration (persisting for over six months), multiple symptoms (including gastrointestinal issues, POTS, muscular pain, cold intolerance, sleep impairment, and sensory intolerance), functional impairment (severely affecting daily life), and exclusion of alternative diagnoses (validated through medical investigations) (51).

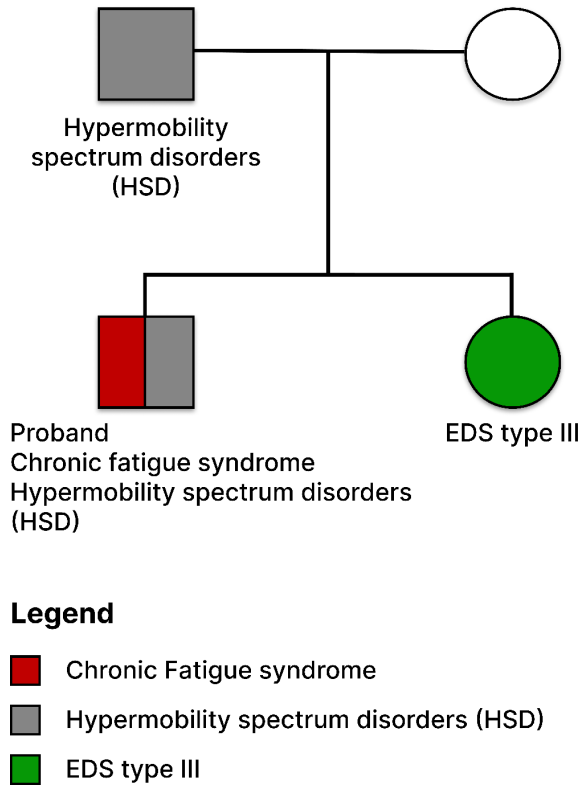



FIGURE 1
Pedigree Structure of the Family with ME/CFS, EDS Type III, and HSD History. The depicted pedigree illustrates an ME/CFS patient of Caucasian descent. The patient presents with the comorbidity of Hypermobility Spectrum Disorder (HSD) and shares a family history of Ehlers-Danlos Syndrome (EDS) Type III. The sister with confirmed EDS Type III is highlighted in green.

## 2.2 Longitudinal plasma sample collection

Over the course of four years (2017-2021), a total of nine plasma samples were collected from an extremely severe ME/CFS patient, transitioning to a marginal improvement in health (Figure 2A; Table 1). Blood samples were obtained using BD-K2EDTA Vacutainer purple top 10 mL tubes (366643) and were immediately mixed by gently and thoroughly inverting the tube five to ten times. Subsequently, plasma was separated through centrifugation at 2500 RPM for 10 minutes at 4°C. The isolated plasma layer was transferred into 15 ml polypropylene conical tubes, thoroughly mixed, and then aliquoted into 1.5 ml DNase- and RNase-free Eppendorf tubes. These aliquoted plasma samples were promptly snap-frozen in liquid nitrogen and stored at −80°C until the time of assay.

## 2.3 Longitudinal plasma cytokine profiling using multiplex cytokine bead array

The analysis was conducted in collaboration with the Stanford Human Immune Monitoring Center, employing the MILLIPLEX Human Cytokine/Chemokine Immunology Multiplex Assay. The assay utilized kits purchased from EMD Millipore Corporation, Burlington, MA, and followed the manufacturer's recommendations with some modifications. The H80 kits consisted of three panels: Panel 1 (Milliplex HCYTA-60K-PX48), Panel 2 (Milliplex HCP2MAG-62K-PX23), and Panel 3 (Milliplex HSP1MAG-63K-06 and HADCYMAG-61K-03, targeting Resistin, Leptin, and HGF) to generate a 9-plex.

Following the recommended protocol, samples were diluted threefold for cytokines measured in Panel 1 & 2 and tenfold for those measured in Panel 3, based on the abundance range of each

cytokine in plasma. A 25 µl volume of the diluted sample was mixed with antibody-linked magnetic beads in a 96-well plate and incubated overnight at 4°C with shaking. Incubation steps were performed on an orbital shaker at 500-600 rpm at both cold and room temperature. After washing the plates twice with a wash buffer using a Biotek ELx405 washer (BioTek Instruments, Winooski, VT), a one-hour incubation at room temperature with biotinylated detection antibody was conducted. Streptavidin-PE was then added for 30 minutes while shaking.

Plates were washed again, and PBS was added to wells for reading in the Luminex FlexMap3D Instrument with a lower bound of 50 beads per sample per cytokine. Control beads (Custom Assay Chex, Radix Biosolutions, Georgetown, Texas) were included in all wells. Wells with a bead count less than 50 were flagged, and data with a bead count less than 20 were excluded. Data analysis was performed using MasterPlex software (Hitachi Software Engineering America Ltd., MiraiBio Group), with both median fluorescence intensity (MFI) and calculated concentration values reported for each analyte.

## 2.4 Statistical analyses

All statistical analyses and visualization were performed in R using custom R scripts. The raw cytokine MFI (median fluorescence intensity) values were log 2 transformed and used for downstream analysis. Hierarchical clustering was done on the samples and cytokines using euclidean distance, and the ward.D2 clustering method. Outliers in cytokine profiling data were identified using the Z-score method, which provides a standardized measure of deviation from the mean, facilitating the detection of biologically meaningful differences. The robustness of the Z-score method to variations in sample size and distribution made it suitable for our study (52). Z-scores were calculated by comparing the latest time-point sample (most improved health state; 01/18/2021) cytokine levels to the average of all the previous time-points. P-values were generated from two-tailed normal distribution samples from each z-score, followed by FDR p-value adjustment for multiple-hypothesis testing. In addition, we conducted an analysis to investigate the correlation between cytokine intensity and the health state over time in the patient. The Pearson correlation coefficient was employed as a statistical measure to assess the strength and direction of the linear association between cytokine levels and health state. We performed a similar analysis to assess the correlation between the change in medication over time and health state.

## 2.5 Patient blog post sentiment analysis

We conducted a thorough analysis on blog posts authored by the extremely severe ME/CFS patient. The extracted dataset included essential details like publication dates and post content. Data preprocessing involved extracting and standardizing publication dates while accounting for time zone variations. The datasets were then filtered for the timeframe spanning 2017 to 2021, aligning precisely with the longitudinal plasma collection phase and coinciding with the period of marginal health improvement. Our exploratory data analysis focused on word frequency at monthly and yearly intervals. We also investigated post lengths over time, calculating and visualizing average post lengths. Employing a pre-trained large language transformer model (SamLowe/roberta-base-go_emotions, available from HuggingFace (53), we conducted sentiment analysis, and the outcomes were visually depicted through monthly and yearly sentiment trends.

To deepen our understanding of linguistic nuances, word cloud analysis was applied, generating visually intuitive representations of word frequencies in all posts, both on a monthly and yearly basis. Furthermore, topic modeling was applied using natural language processing and a latent dirichlet allocation model to uncover hidden thematic structures across the blog posts. The complete pipeline, encompassing data extraction to exploratory analyses, was executed using Python. Leveraging sentiment analysis and topic modeling, the outcomes are encapsulated in a user-friendly Streamlit-powered web application, LexiTime (Lexical and Temporal Insight Mining Exploration). The application is accessible at https://github.com/singjc/lexitime.

## 2.6 Development of a web-based application for real-time symptom tracking and intervention assessment

A web-based application was developed for the active tracking of symptoms for ME/CFS patients. The application was developed using a Node.js frontend and Python backend, interacting with a MongoDB and Postgres data system to save patient responses. The UI/UX design phase focused on creating an intuitive and visually appealing interface for seamless symptom tracking. User feedback and iterative design processes were implemented to enhance user experience, ensuring accessibility and ease of use.

Given the sensitive nature of health data,robust security measures have been implemented at multiple layers of the application to ensure data confidentiality, integrity, and availability. The security design adhered to established principles (54–57) and included end-to-end encryption, input sanitization, server-side authentication, and encryption of usernames and passwords. We employed HTTPS for transport in the web-based application and AES-256 for data encryptions. The application underwent rigorous testing phases, ensuring functionality and usability. User feedback and testing results informed iterative development cycles, ensuring a robust and reliable web-based tool. Upon successful testing, the web-based application was deployed to a secure server, ensuring accessibility for users. Cross-browser compatibility and responsive design were prioritized to facilitate usage across various devices.

# 3 Results

## 3.1 Constructing a comprehensive disease timeline through integration of longitudinal health and clinical data

Individuals with very severe ME/CFS encounter communication challenges, impeding health evaluation and therapeutic assessment.

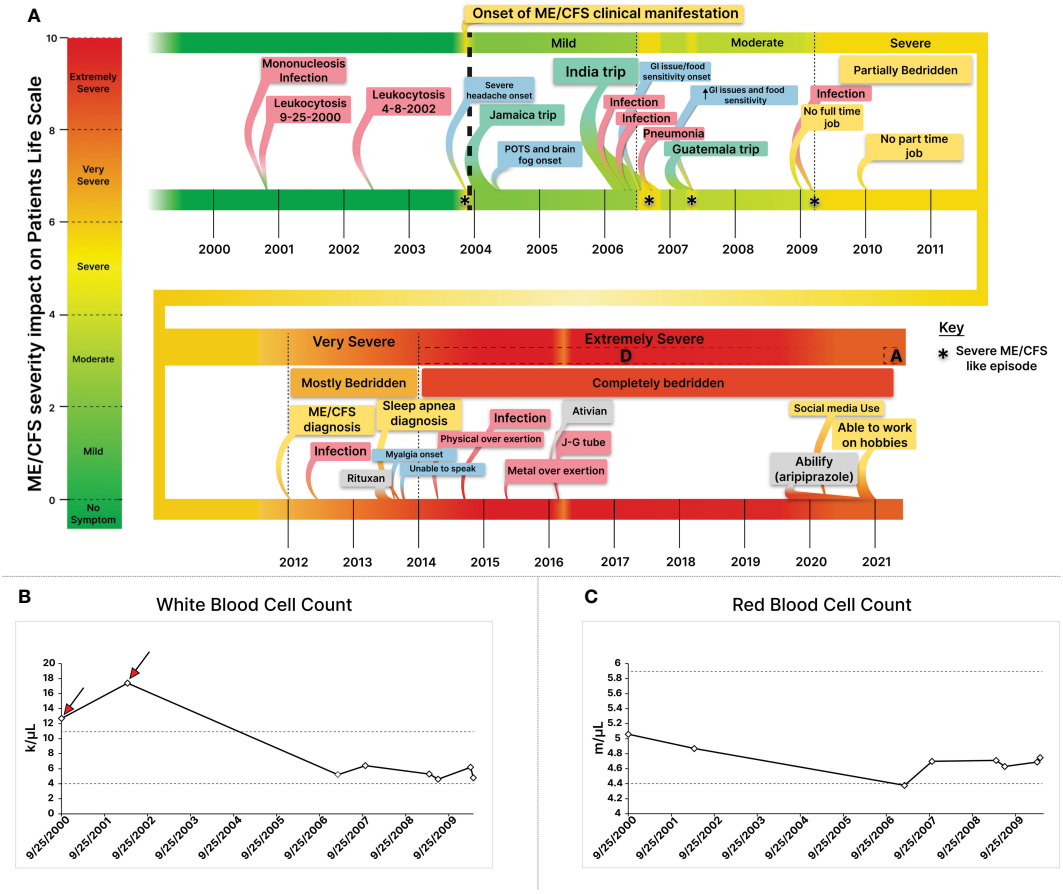



FIGURE 2
Constructing a Comprehensive Disease Timeline through the Integration of Longitudinal Health and Clinical Data for An Extremely Severe ME/CFS Patient. **(A)** Integrating health and clinical data illustrates dynamic severity changes, triggers, contributing factors, and new symptom onsets. Infections like mononucleosis and stressors such as infections, medications, and trauma modulate severity. **(B)** Retrospective analysis of Longitudinal Complete Blood Count (CBC) data from the extremely severe ME/CFS patient during the first decade of his illness revealed two episodes of leukocytosis (red arrows) prior to the onset of health symptom, suggesting infection-derived immune dysregulation as a potential trigger for his ME/CFS. **(C)** Leukocytosis was followed by a lasting red blood cell count reduction. While white blood cell counts normalized, RBC levels declined, remaining low. * Depicts a Severe ME/CFS-like episode.

We took a collaborative approach with patients' caregivers involving meticulous utilization of patient and caregiver notes, alongside clinical health records, to construct a detailed disease timeline and severity assessments (Figure 2, Table 1, Figure 3).

The patient began experiencing health symptoms in 2004 and was diagnosed with ME/CFS in 2012 at the age of 29, after struggling with health issues for nearly a decade (Figure 2A). He had an active life prior to his illness. Longitudinal clinical blood cell count (CBC) analysis indicated two episodes of leukocytosis, characterized by an elevated white blood cell (WBC) count in 2000 and 2002 (Figure 2B), which occurred before the onset of experiencing health symptoms. The initial leukocytosis was attributed to EBV-mediated mononucleosis, as confirmed by a monospot test, and may have potentially acted as a trigger for the condition (Figure 2A). Longitudinal analyses of clinical data revealed mononucleosis as the cause for his initial leukocytosis. Retrospective complete blood count (CBC) analyses also illustrated a consistently diminished red blood cell count subsequent to the

TABLE 1 Longitudinal collection of plasma cytokines, age, and severity score over the 4-Year study period.

| Date | Age | CFS severity |
|---|---|---|
| 6/29/17 | 33 | Severe D |
| 6/18/18 | 34 | Severe D |
| 4/9/19 | 35 | Severe D |
| 8/1/19 | 35 | Severe D |
| 12/19/19 | 36 | Severe D |
| 1/14/20 | 36 | Severe D |
| 2/7/20 | 36 | Severe D |
| 2/13/20 | 36 | Severe D |
| 1/18/21 | 37 | Severe A |

Nine plasma samples were collected using EDTA tubes, capturing the nuanced progression of the patient's health from the extremely severe stage D to A. The collected plasma samples underwent prompt processing and were stored at -80°C.

leukocytosis, persisting at a lower or below-normal range throughout the course of the illness (Figure 2B).

In 2006, during a trip to India, the patient developed a peculiar cold with mild symptoms lasting two weeks. Four months later, he encountered an abrupt onset of symptoms akin to severe ME/CFS cases (Figure 2A). After a slow recovery, regaining about 60% of health (patient self-assessment) (Figure 2A), his disease severity transitioned from mild to moderate (Figure 2A). Subsequently, a similar episode unfolded, starting with mild diarrhea, and escalating to severe ME/CFS, rendering him bedridden, only able to consume liquified white rice soup. Three months later, he ended up with pneumonia in a hospital in India, forcing him to return home. Upon return, although he partially regained health, lingering symptoms including lightheadedness persisted. Seeking a remedy, he traveled to Guatemala, where another severe ME/CFS-like episode occurred, mirroring the India experience. It began with mild diarrhea after a meal, followed by what the patient self-described as a stomach shutdown, possibly indicative of gastroparesis, and fatigue. After a week in this condition, he returned home, and his condition improved. However, his health baseline never fully recovered (patient self-assessment), and issues like gastroparesis, postprandial nausea, cold intolerance, and cold extremities surfaced (Figure 2A).

Throughout the first decade of his ME/CFS journey, the patient's symptom severity gradually worsened from mild to moderate (2004-2006: mild, 2006-2010: moderate) (Figure 2A),

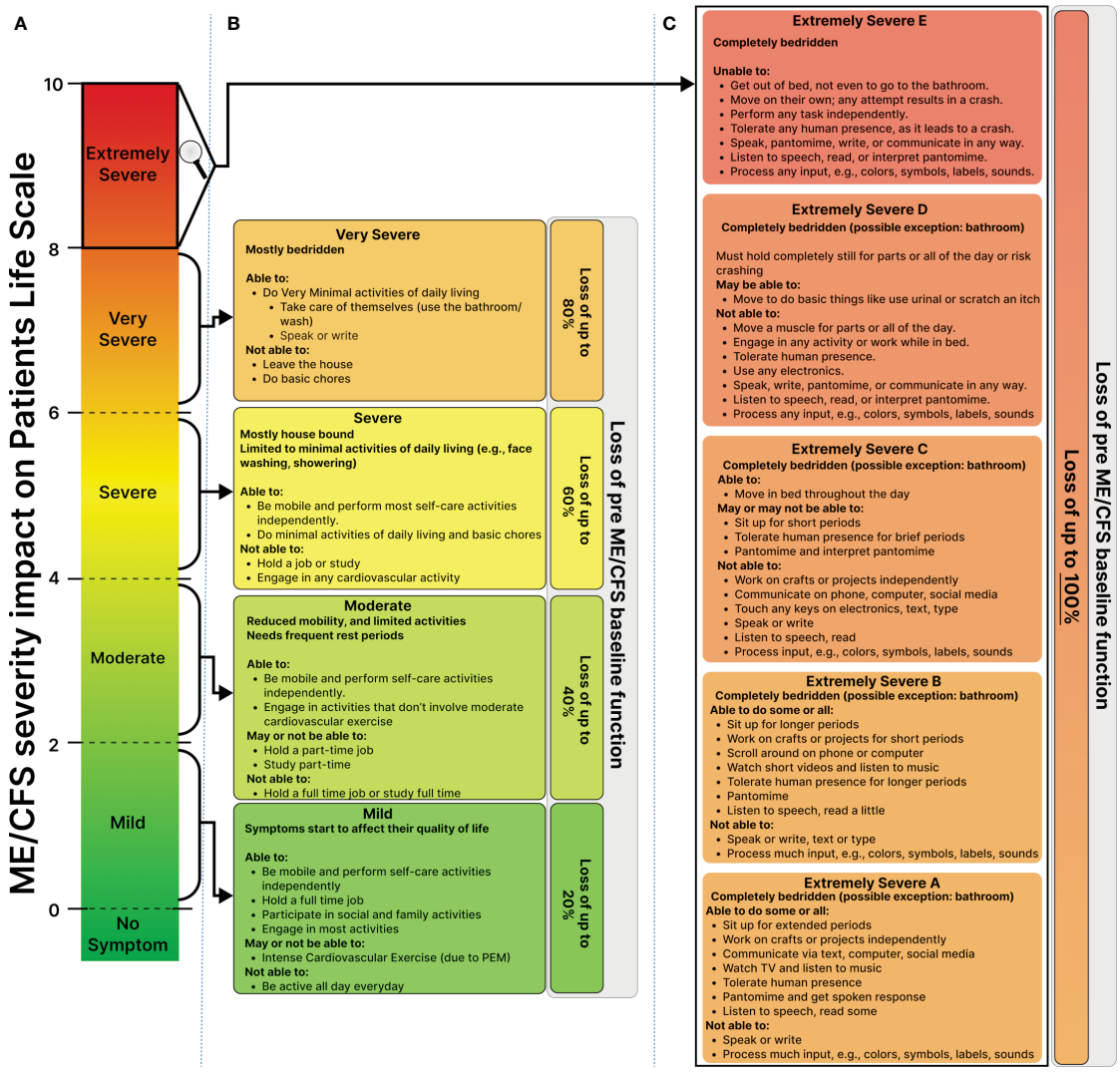



FIGURE 3
Proposed Framework for Personalized Severity Assessment in ME/CFS to Capture Variation in ME/CFS Severity and Life Impairment across Patients and Time. **(A)** Illustrates the dynamic range of the ME/CFS severity scale based on the disease's impact on all aspects of the patient's life, including occupational, educational, social, and personal spheres. **(B)** Depicts the impact of mild to severe ME/CFS on the patient's life. Mild: maintained about 80% of pre-ME/CFS functional capacity, as well as full-time employment with limitations due to post-exertional malaise (PEM). Moderate: pre-ME/CFS functional capacity, unable to hold part-time work, with increased limitations in activity, progressing to severe: inability to hold any job, primarily house and bedbound. **(C)** Shows the patient's functioning ability significantly degrading from extremely severe A to D, highlighting ME/CFS's profound impact at this level. Severe nutritional deficiencies led to Gastrostomy tube (G-tube) and Peripherally inserted central catheter (PICC Line) Line use. Sensory intolerance intensified, making it impossible for the patient to tolerate others in his room. At stage D, communication loss and internet access loss intensified social isolation.

with a notable presence of postural orthostatic intolerance (POTS), which significantly worsened after cardiovascular exercise and reappeared during post-remission periods (Figure 2A). In 2009, while managing only a part time job, the patient encountered another cold episode with initially mild symptoms. This episode triggered a decline in his health, reminiscent of the severe ME/CFS-like states he had previously experienced (Figure 2A). While mostly housebound, he managed short walks for groceries, performed self-care activities, cooked, and was sufficient. His condition further advanced from moderate to severe, rendering him bed bound. Describing his main symptoms as a 'total body shut down,' he emphasized the severity of the debilitating post-exertional malaise (Figure 2A). To articulate the gravity of his condition, he offered the analogy: "To compare the state I was in in 2012 to staying up for two nights in a row while fasting, then getting drunk. The state you would be in on the third day — hangover, not having slept or eaten in 3 days — is close, but still better than many ME/CFS patients feel every day".

In 2013, the patient received Rituximab, after which he experienced an extreme crash and became permanently affected by PEM (Figure 2A). Muscular pain developed in the back of his legs, hindering his ability to stand or walk short distances (Figure 2A). Subsequently, he lost the capacity to speak, and communicated by text messages and a pre-programmed app for basic communication and food requests, ultimately transitioning to a routine food delivery program to minimize the need for texting (18).

During this period, he exerted minimal activity including lying on a lawn chair and listening to music with headphones for a few hours before returning to his room, with 2–3 short trips to the kitchen comprising the extent of his daily walking. Later, he obtained a wheelchair to facilitate movement to the kitchen (Figures 2A, 3A, B). However, a physically demanding event in 2014, coupled with emotional strain, rendered him fully bedridden and intolerant of human contact, escalating his condition to an extremely severe state overnight (Figures 2A, 3C). Transitioning from a very severe to an extremely severe state, heightened sensorial intolerance to noise, human contact, and social media impeded the patient's ability to receive basic necessities. To cope, he resorted to covering his eyes with a folded trowel and wearing earphones and earmuffs to block outside stimuli (18) (Figure 3). The patient coined the term "mental crash" to describe this sensorial intolerance, emphasizing that even stimuli unrelated to any mental links could overwhelm the brain's processing capacity. He subsequently isolated himself from human presence and the external world (Figure 3C) (18).

During emergencies intravenous Ativan administration enabled basic communication (Figure 2A). In the fall of 2019, the patient began a low dose of Abilify (aripiprazole, 0.2 mg), which was gradually increased to 2 mg by February 17, 2020. By June 2020, he reported slight improvement, allowing him to communicate briefly in writing using his cell phone. In one of his posts, the patient attributed this improvement to several factors, including an increase in the doses of Cortef (hydrocortisone) from 10 to 15 (to address potential adrenal insufficiency), and the Abilify treatment. In late 2020, he reported being able to have people in his room without the need for earphones and earmuffs (18) (Figures 2A, 3C).

## 3.2 A proposed framework for assessing the personalized severity of ME/CFS

We built upon the existing classifications of mild to very severe (9), but also introduced the "extremely severe" category, further subdividing it into subclasses (A, B, C, D, and E) (Figure 3). The resulting framework classifies patients on a 1-10 scale and is defined around the impact of symptoms on patients' ability to regain their pre-ME/CFS baseline function at a single symptom resolution.

The mild stage is defined in which the patient maintains 80% of their baseline function and full-time employment, albeit with limitations due to post-exertional malaise. Progressing to a moderate stage reduces their capacity to function to 60% or lower of their baseline, limiting them to part-time work.

Transitioning to the severe stage renders patients house and bed-bound, unable to work. They can perform most self-care activities independently but are unable to hold a job or engage in cardiovascular activity. At a very severe stage, patients become mostly bedridden, only able to perform minimal activities of daily living and self-care, such as bathing. They are unable to leave the house or do basic chores.

Extremely severe ME/CFS significantly interferes with nearly all aspects of the patient's life (Figure 3C). Sensory intolerance and gastrointestinal disorders can cause severe nutritional deficiencies, resulting in a significant weight drop and the potential use of a G-J tube and PICC line for nutritional and medicinal support. From stage B to D, sensory intolerance makes it impossible for the patient to tolerate others in their room. At stage D, they lose communication abilities and internet access, intensifying social isolation.

## 3.3 Development of ME-CFSTrackerApp, a web-based application for real-time symptom tracking and intervention assessment

As a companion to our work, a web-based application was developed to allow patients to create an electronic journal of their symptoms, medications, and life events. The application was built using a stack of a Node.js front end and a Python back end and deployed on a secure server hosted at Stanford. The deployment is configured to guarantee constant uptime and cross-browser compatibility to ensure accessibility. Cross-browser compatibility and responsive design were prioritized to facilitate seamless usage across various devices, enhancing the accessibility and user experience. To promote widespread usage and accessibility, ME-CFSTrackerApp is freely available for use. Users can navigate to the application using the provided link "https://me-cfstrackerapp.su.domains", where they can benefit from its features without any cost. This commitment to open access

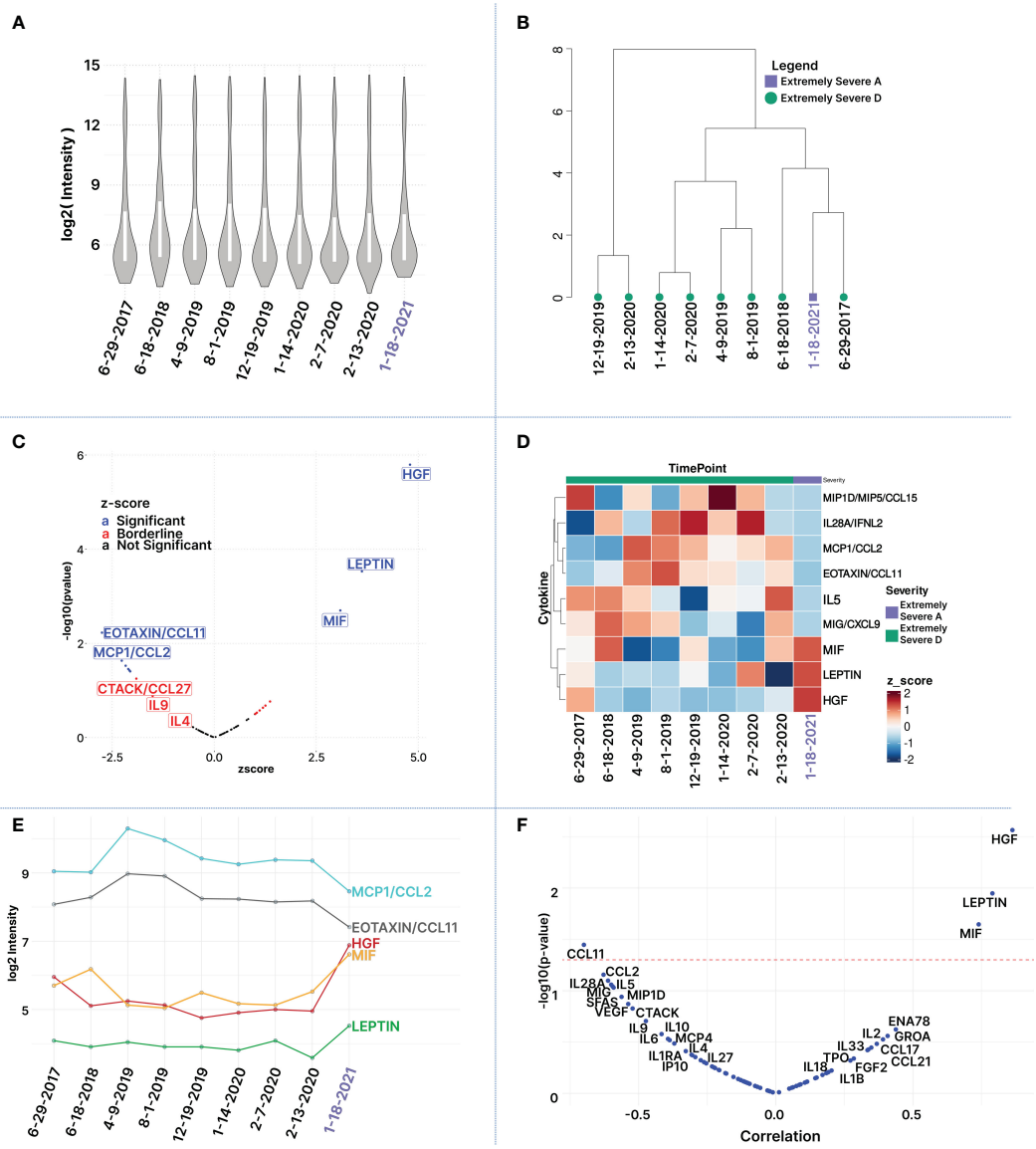



FIGURE 4
Longitudinal Multiplex Cytokine Profiling. **(A)** Distribution of log2-transformed cytokine MFI values per sample: Each boxplot represents a time point (run in 3 cytokine panels). The boxplot is arranged chronologically. **(B)** Hierarchical Clustering of Samples: This panel reveals groupings of similar time points and illustrates relationships between the samples based on clustering of log2-transformed cytokine intensities. **(C)** Volcano Plot of Differentially Expressed Cytokines: Plot illustrates cytokines based on the z-score derived from the last time point (Jan. 21), corresponding to the patient's improved severity to 'extremely severe A,' in comparison to the average of the preceding nine time points. The x-axis represents z-scores, while the y-axis line represents -log (p-value). Black and blue dots marked cytokines with z-score values within -1 and 1, and p-value<0.05, respectively. **(D)** Heatmap of Top Differentially Expressed Cytokines: Columns (sample time points) and rows (cytokines) are clustered using euclidean distance and ward.D2 clustering. Most cytokines are reduced in the healthiest time point (marked in purple) except MIF, HGF, and LEP. Dark blue signifies the lowest z-scores, dark red the highest. **(E)** Log2 intensity levels of top 5 differentially expressed cytokines over time demonstrates cytokines that share similar trends. **(F)** Pearson correlation of cytokines in relation to the health state of the patient at the 9 different timepoints. The red dashed line indicates a 5% p-value cutoff.

ensures that individuals can readily leverage the application for their real-time symptom tracking and intervention assessment needs.

## 3.4 Longitudinal cytokine analyses

For downstream analyses, raw mean fluorescence intensity (MFI) values were log2-transformed. The distribution of log2-transformed cytokine MFI profiles showed remarkable consistency across all 9 time points, with comparable medians (Figure 4A). Hierarchical clustering analysis effectively revealed relationships between samples, resulting in distinct clustering patterns among similar time points (Figure 4B; Supplementary Figure S1).

To investigate cytokines linked with disease severity, Z-scores were computed for the 80 measured cytokines between the patient's improvement to 'Extremely Severe A' (Jan 21) and the average of the preceding eight time points when his health was assessed at

TABLE 2 Top differentially expressed cytokines between healthiest time point (Extremely severe stage A) and average of prior time points (Extremely severe stage D).

| Cytokine | Z score | p-value | fdr |
|---|---|---|---|
| HGF | 4.80 | 1.60E-06 | 0.0001 |
| LEPTIN | 3.62 | 0.0002 | 0.01 |
| MIF | 3.09 | 0.00 | 0.05 |
| EOTAXIN/CCL11 | -2.75 | 0.01 | 0.12 |
| MCP1/CCL2 | -2.27 | 0.02 | 0.35 |
| IL28A/IFNL2 | -2.17 | 0.03 | 0.35 |
| MIG/CXCL9 | -2.11 | 0.04 | 0.35 |
| IL5 | -2.08 | 0.04 | 0.35 |
| MIP1D/MIP5/CCL15 | -2.06 | 0.04 | 0.35 |
| SFAS/TNFRSF6 | -1.91 | 0.06 | 0.45 |
| VEGF | -1.79 | 0.07 | 0.53 |
| CTACK/CCL27 | -1.72 | 0.09 | 0.57 |
| IL9 | -1.51 | 0.13 | 0.81 |
| ENA78/CXCL5 | 1.37 | 0.17 | 0.97 |
| IL6 | -1.29 | 0.2 | 0.97 |
| GROA | 1.25 | 0.21 | 0.97 |
| MCP4/CCL13 | -1.20 | 0.23 | 0.97 |
| IL2 | 1.19 | 0.23 | 0.97 |
| IL10 | -1.18 | 0.24 | 0.97 |
| IL4 | -1.12 | 0.26 | 0.97 |
| TARC/CCL17 | 1.11 | 0.27 | 0.97 |
| 6CKINE/CCL21/EXODUS2 | 1.04 | 0.3 | 0.97 |
| FGF2/FGFB | 1.01 | 0.31 | 0.97 |
| TPO | 1.01 | 0.31 | 0.97 |
| HGF | 4.80 | 1.60E-06 | 0.0001 |

'Extremely Severe D' (Supplementary Table S1). Cytokines of interest were identified based on absolute z-scores deviating by 1 standard deviation or more from the mean (Table 2), enabling the identification of subtle changes in cytokine patterns across time points that may be associated with transitions in health severity from extreme severe D to A. Among 80 cytokines, ten exhibited a Z-score of +1 or more, including HGF (4.80), Leptin (3.61), MIF (3.08), ENA78 (1.37), GROA (1.25), IL2 (1.19), CCL17 (1.10), CCL21(1.04), FGF2 (1.0), and TPO (1.0). Additionally, 14 cytokines showed a z-score value of -1 or less including CCL11 (-2.75), MCP1 (-2.27), IL28A(-2.17), CXCL9 (-2.10), IL5 (-2.08), MIP1D (-2.06), SFAS (-1.90), VEGF (-1.79), CCL27 (-1.71), IL9 (-1.51), IL6 (-1.29), MCP4 (-1.20), IL10 (-1.18), IL4 (-1.11) (Table 2; Supplementary Table S1). Among these 24 cytokines, only nine exhibited statistically significant changes with an absolute z-score > 1 and p-value <= 0.05. These include HGF (z-score: 4.80, p-value: 1.60E-06), Leptin (z-score: 3.61, p-value: 0.0002), MIF (z-score: 3.08, p-value: 0.002), CCL11 (z-score: -2.75, p-value: 0.005), MCP1 (z-score: -2.27, p-value: 0.023), IL28A (z-score: -2.17, p-value: 0.029), CXCL9 (z-score: -2.11, p-value: 0.035), IL5 (z-score: -2.08, p-value: 0.035), and MIP1D (z-score: -2.06, p-value: 0.039) (Figure 4C, Table 2). This limited 9-plex cytokine panel effectively distinguished 'Extremely Severe A' from 'Extremely Severe D' (Figures 4C, D). Out of these 14 cytokines, only HGF, LEPTIN, and MIF withstood an FDR adjustment of 10% (Table 2; Supplementary Table S1).

The color-coded heatmap (Figure 4D) shows cytokines with significant changes in plasma levels as the patient's health improved from Extremely Severe D to Extremely Severe A between June 2017 and January 2021. Key cytokines in this transition, such as HGF, LEPTIN, MIF, IL5, CCL11, CCL2, IL28A, CCL15, are highlighted. The red and blue colors indicate whether the cytokine levels increased or decreased. The change for each cytokine was calculated using a z-score based on log-transformed raw MFI values.

Cytokines were filtered based on an absolute Z-Score of ±1 or more, comparing samples from the healthiest time point (01/18/2021) to the average of the 8 previous time points. Significant differences (denoted in red) between the healthiest and preceding time points were determined using p-values, both before and after adjusting for multiple comparisons (controlling for FDR at 10%).

Analyzing cytokines that demonstrate significant differentiation between the patient's most improved state in January 2021 and the preceding health states revealed distinctive patterns in cytokine deviations. This differentiation is visually represented in the hierarchical clustered heatmap (Figure 4D), where clear clusters of time points emerge, highlighting unique cytokine expression profiles. Moreover, among the top differentially expressed cytokines, some exhibit similar temporal profiles (Figure 4E). Notably, MCP1 and CCL11 demonstrate analogous trends over time, albeit at varying magnitudes, both showing a decline in the latest time point. Similarly, HGF and MIF display comparable temporal patterns, exhibiting an increase in the most recent time point. In contrast, MCP1 and CCL11 display opposite trends compared to those observed for MIF and, to a lesser degree, with HGF (Figure 4E). This intricate interplay underscores the nuanced dynamics of cytokine regulation during the observed period. The analysis of cytokine levels in relation to disease severity indicated a positive correlation for HGF, LEP, and MIF (increase in plasma cytokine level with health improvement and reduced severity) and a negative correlation for CCL11 (decrease in plasma cytokine level with health improvement) during the transition from extremely severe D to extremely severe A. Additionally, negative correlations were observed for MCP1, IL28A, CXCL9, IL5, MIP1D SFAS, VEGF, and CCL27 with health improvement, although statistical significance (p-value < 0.05) was not achieved (Figure 4F; Supplementary Table S2).

## 3.5 Gene set enrichment and ingenuity pathway analyses

In exploring the changes in cytokine expression between the healthiest time point and preceding stages, Ingenuity Pathway

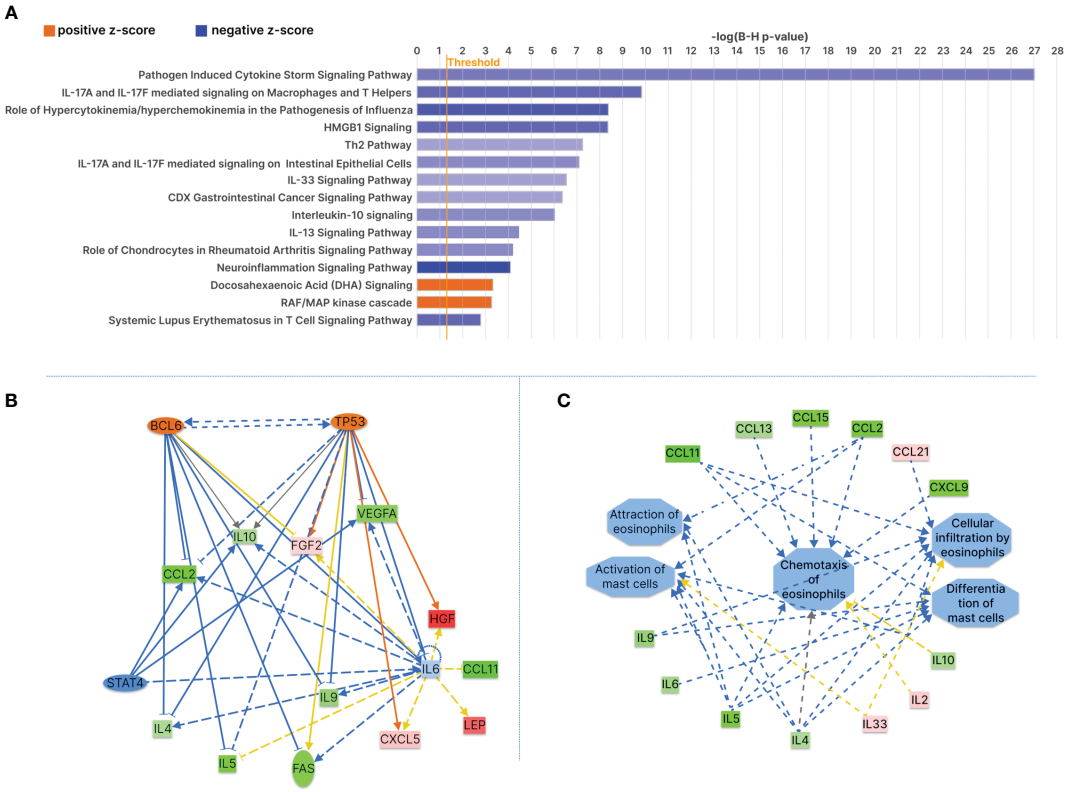
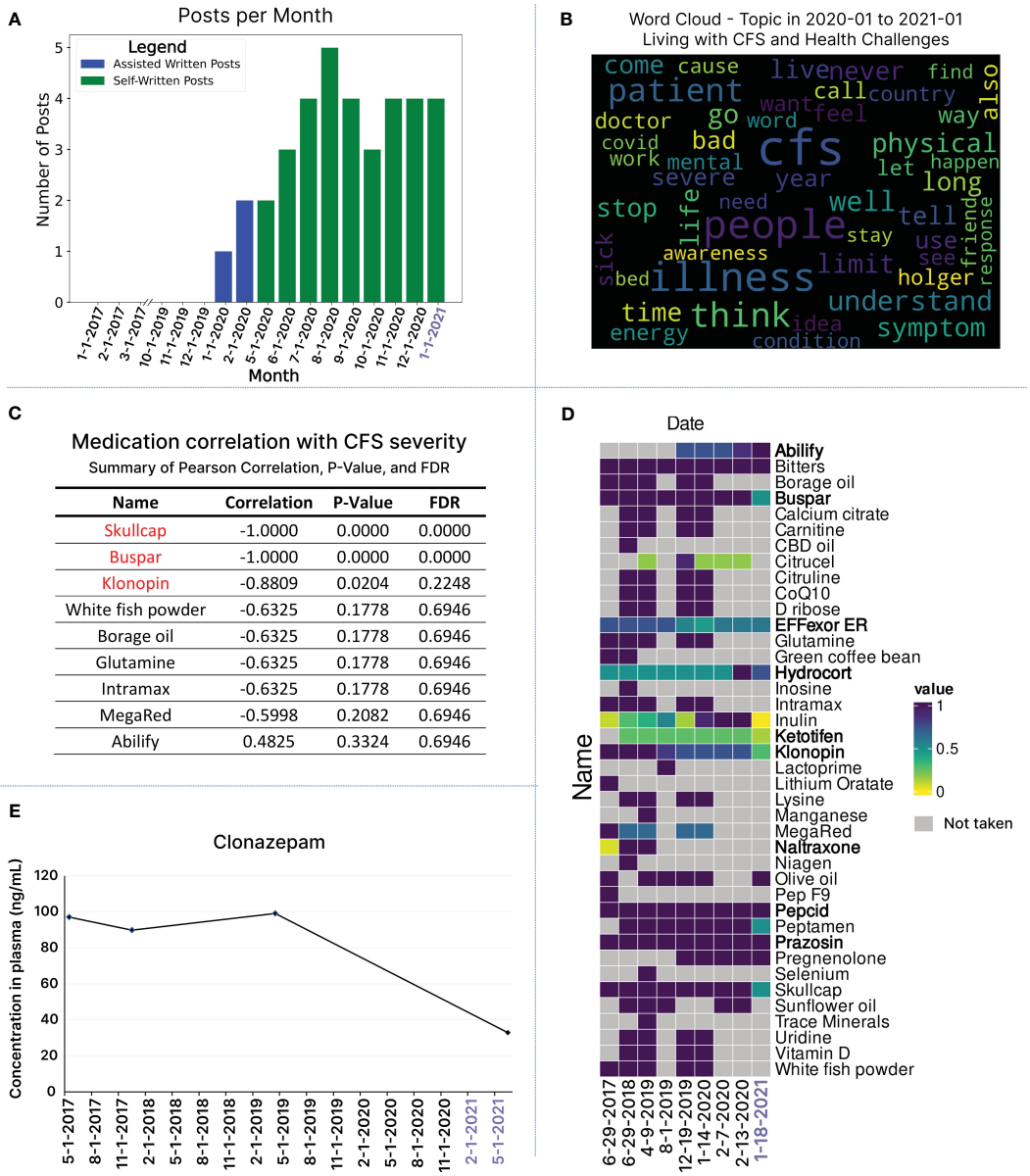



FIGURE 5
Ingenuity Pathway Analysis of Longitudinal Cytokine Profiling During Health Improvement from Extremely Severe Stage D to A. **(A)** Top significant canonical pathways with an absolute z-score value of 0.8 and B-H p-value ≤ 0.05 are shown. Orange and blue bars represent positive or negative z-scores, indicating predicted pathway activation or inhibition, respectively. **(B)** Upstream regulator analysis indicates the activation of BCL6 and TP53 at the healthiest time point. **(C)** IPA diseases and function analyses predict the inhibition of mast cells and eosinophils functions. Green represents cytokines with reduced plasma levels at the healthiest time points, and red indicates increased cytokines. Orange and blue indicate predicted to be activated or inhibited, respectively.

Analysis (IPA) provided insights into pathways potentially associated with health improvement. Canonical pathway analyses on cytokines with z score value of plus minus 1 or more revealed significant inhibition in several pathways, notably the pathogen-induced cytokine storm signaling pathway (-log (B-H p-value)= 27; z-score = -1.15) (Supplementary Table S4), neuroinflammation (-log (B-H p-value)= 4.1; z-score = -2.24), HMGB1 (High Mobility Group Box 1) signaling (-log (B-H p-value)= 8.36; z-score = -1.34), and Systemic Lupus Erythematosus in T cell signaling pathway (-log (B-H p-value)=2.78; z-score: -1.34) (Figure 5A; Supplementary Table S3). The TH2 pathway also exhibited inhibition (-log (B-H p-value) = 5.5; z-score = -1), aligning with the observed reduction in IL4, IL5, and IL9. Notably, DHA (Docosahexaenoic Acid) signaling (-log (B-H p-value) =3.2; z-score = 1) and RAF/MAP kinase cascade (-log (B-H p-value)=3.26, z-score=1) were predicted to be activated (Supplementary Table S3). Canonical pathways analysis on differentially expressed cytokines that passed both the z score value of 1 and more and p value of <0.05 also suggests inhibition of pathogen induced cytokine storm, and IL17 signaling (Supplementary Figure S2).

Upstream regulators analyses indicated predicted inhibition in TNF (activation Z score=-1.6, p-value of overlap=2.56E-27) (Supplementary Figure S3A), TLR4 (Toll-like receptor 4) (activation Z score=-2.2; p-value of overlap=5.18E-10), PLA2G10 (Phosphatidylcholine 2-Acylhydrolase 10) (Supplementary Figure S3A, B) (activation Z score=-2.4, p-value of overlap=5.22E-10), CCL11 (activation Z score=-1.9; p-value of overlap=5.75E-21) (Supplementary Figure S3B) (Supplementary Table S6), KITLG (KIT proto-oncogene ligand) (activation Z score=-2.2, p-value of overlap=1.85E-10), IL9 (activation Z score=-2.4, p-value of overlap=2.92E-10), IL18 (activation Z score=-2.2; p-value of overlap=2.65E-17) and NFkB-RelA (activation Z score=-2.0; p-value of overlap=1.96E-10) (Supplementary Table S5). Notably, BCL6 (activation Z score=2.1; p-value of overlap=5.97E-11) (Figure 5B), EPO (Erythropoietin) (activation Z score=1.99; p-value of overlap=1.29E5), TP53 (activation Z score=1.6; p-value of overlap=1.48E-9) (Figure 5B), HBB (hemoglobin subunit beta) (activation Z score=1.9; p-value of overlap=1.68E-18), IL11 (activation Z score=1.96; p-value of overlap=1.02E-6), and SCGB1A1 (Secretoglobin Family 1A Member 1) (activation Z score=1.9; p-value of overlap=1.51E-8) were predicted to be activated (Supplementary Table S5, Figure S3). Additionally, IPA disease and function analysis predicted

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| Name | Correlation | P-Value | FDR |
|---|---|---|---|
| Skullcap | -1.0000 | 0.0000 | 0.0000 |
| Buspar | -1.0000 | 0.0000 | 0.0000 |
| Klonopin | -0.8809 | 0.0204 | 0.2248 |
| White fish powder | -0.6325 | 0.1778 | 0.6946 |
| Borage oil | -0.6325 | 0.1778 | 0.6946 |
| Glutamine | -0.6325 | 0.1778 | 0.6946 |
| Intramax | -0.6325 | 0.1778 | 0.6946 |
| MegaRed | -0.5998 | 0.2082 | 0.6946 |
| Abilify | 0.4825 | 0.3324 | 0.6946 |

FIGURE 6
Integrating Longitudinal Cytokine Profiling with Health, Textual, and Medication Data in Relation to Health Improvement. **(A)** Number of blog posts written monthly from 2017 up until the end of January 2021. For the first two months of 2020, the patient had assistance with writing blog posts for the months of January and February (blue bars). From May 2020 and onwards, the patient was feeling well enough to start writing the blog posts on his own (green bars). **(B)** Topic analysis word cloud for blog posts written from January 2020 until the end of January 2021, offering a visual representation of the most frequently occurring words from blog posts in this time frame, all under the topic umbrella of "Living with CFS and health challenges". **(C)** Correlation analysis of the change in medication and health state over time. Changes in dosage for Skullcap, Buspar and Klonopin showed a strong correlation with improved health. **(D)** Medication usage over time is visualized for the 9 time points, which overlap with cytokine sample time points. To facilitate comparison, the dosage of each medication has been standardized over time using min-max scaling. This standardization is represented in a heatmap, gray squares represent no medication dosage recorded. List of medications are provided in bold to be distinguished from supplements. **(E)** Longitudinal monitoring of Clonazepam concentration in blood, which followed the reduction trend in his intake from 24 mg to 7 mg.

reduced activity in mast cell activation (activation z-score=-1.99; overlap p-value=1.44E-10) and mast cell differentiation (activation z-score=-2.23; overlap p-value= 9.01E-11) (Figure 5C). There was also a decrease in the attraction of eosinophils (activation z-score=-2; overlap p-value=6.20E-11) and chemotaxis of eosinophils (activation z-score=-1.5; overlap p-value=4.21E-20), as well as cellular infiltration by eosinophils (activation z-score=-1.5; overlap p-value=1.98E12).

## 3.6 Patient blog post sentiment analysis

For nuanced insights into subtle health changes, we employed natural language processing to gauge social media activity as a tool for assessing the patient's functional capacity in daily life activities and obtaining insights into temporal posting trends. Exploratory data analysis focused on post frequency and the average number of

words per post at monthly and yearly intervals, revealing no activity from June 2017 to December 2019 (Figure 6A). In January and February 2020, the patient received assistance to activate his personal blog and share one post every month (Figure 6A). From May 2020 onward, his sensorial intolerance improved to a degree that allowed him to use social media and post blogs without assistance (Figure 6A). Throughout the patient's blog posting journey in 2020 and 2021, there is an increase in the number of posts as well as the length of posts (Supplementary Figure S4B). To assess the emotional tone of blog posts (for the years 2020 and 2021), we conducted a sentiment analysis using a pre-trained BERT language model (Supplementary Figure S4C). Sentiments were visualized monthly and yearly as negative, neutral, and positive (Supplementary Figure S4C). Fisher exact tests revealed significant differences in sentiment distribution (Supplementary Table S7). In 2021, the odds ratio for negative vs. positive sentiments was substantially lower (0.13, p=0.03), indicating a significant decrease in negative sentiments. Similarly, neutral vs. positive comparison showed a significant decline in neutral sentiments in 2021 (0.18, p=0.04), emphasizing a notable shift toward a more positive emotional tone over time (Supplementary Figure S4C, Table S7).

To explore the nuances of linguistic patterns, we conducted a word cloud analysis, visually representing word frequencies across all posts in 2020 and 2021 (Supplementary Figure S4A). The most recurring words in 2020 posts include 'CFS,' 'people,' 'illness,' 'way,' 'I'm,' 'think,' 'see,' 'don't,' 'I've,' 'every,' 'life,' and 'help.' In 2021, the frequently used words are 'CFS,' 'dream,' 'sleep,' 'I'm,' 'love,' 'long,' 'new,' 'way,' 'day,' 'right,' 'adventure,' and 'people' (Supplementary Figure S4A). While there are overlaps, distinct words and themes emerge when comparing the most used words in 2020 versus 2021. Intrigued by the growing use of LLMs like chatGPT, we informally analyzed the frequently used words (23) identified by the word cloud. We prompted chatGPT to infer the overall message the patient conveyed in his blog posts between Jan 2020 to Jan 2021 (Figure 5S).

ChatGPT analysis revealed that the patient reflects on his struggles with ME/CFS, its severity and profound impact on individuals' lives. Additionally, it suggests the patient's strong interest in disseminating information and sharing personal experiences related to ME/CFS, thereby contributing to ongoing research efforts (Supplementary Figure S5). Promoted for a comparison between 2020 and 2021, chatGPT identifies that although there is still some mix of challenging emotions and experiences, it does note a change in emotional state—a positive outlook in 2021 (Supplementary Figure S6).

For a more formal analysis aimed at identifying specific themes across blog posts in 2020 and 2021, we conducted a topic modeling analysis using a latent Dirichlet allocation (LDA) model. Across all posts, the first prominent topic involves words discussing living with CFS and the health challenges the patient faces. Three other main topics identified include personal growth and lifestyle changes, research funding and scientific review, and health strategies and supplements (Figure 6B; Supplementary Figure S4D). Utilizing natural language processing techniques for textual data analysis saves time and resources compared to manually going through each blog post to identify a patient's current journey and health state. Furthermore, this reduces bias and interpretation of content, particularly crucial in ME/CFS, where subjective experiences vary. Extracting valuable information from written expressions can provide a means for non-verbal patients to contribute to research and connect with the ME/CFS community. To this end, we developed LexiTime, an application for textual data processing including sentiment analysis and topic modeling. The application is accessible at https://github.com/singjc/lexitime.

Additionally, we explored the relationship between medication changes and the patient's health status over time (Figure 6C; Supplementary Table S8). Working closely with caregivers, we gathered a comprehensive medication list spanning the dates of the 9 longitudinal blood samples, including three days before and after each time point. To facilitate comparison, we standardized medication dosages using min-max scaling and presented the patterns in a heatmap, showcasing both individual time points and 7-day windows surrounding each blood draw date (Figure 6D; Supplementary Figure S7). Our correlation analysis focused on comparing the doses of all medications on the day of blood draw (Figure 6D). Significantly, changes in dosage and reduction of intake for Skullcap, Buspar, and Klonopin exhibited a strong correlation with improved health (Figure 6C). We also noted a positive correlation between the increase in low-dose Abilify and health improvement, although the latter did not achieve standard significance (Figure 6C). The integration of clinical data unveiled a reduction in blood Klonopin levels in response to lowering the medication dose (Figure 6E).

# 4 Discussion

In the ME/CFS research landscape, the focus has traditionally been on comparing patients with healthy controls, with limited attention to longitudinal aspects and periods of improvement (58, 59). Our study addresses this gap by taking a single patient-centered approach (60, 61) exploring molecular and phenotypic differences underlying severity improvements in ME/CFS. While acknowledging the N-of-1 nature of our study and the necessity for larger cohort studies, our integrative longitudinal strategy, incorporating health, clinical, cytokine profiling, and textual data over more than 4 years period offers invaluable insights. These findings enhance our comprehension of factors influencing ME/CFS development and severity, providing personalized insights into medical interventions (Figure 7).

We refined the severity framework by introducing the "extremely severe" category, subdivided into A, B, C, D, and E, to capture the complete spectrum of ME/CFS severity and its true debilitating nature at maximum severity (9). While the current very severe category, such as those offered by ICC, includes individuals who are bedridden and require assistance with basic functions (5, 9), some ME/CFS patients may experience extreme sensory sensitivities and post-exertional malaise (PEM) that dangerously affect their ability to receive life necessities such as food and medication. In extreme cases, patients become fully isolated from others, resembling conditions of solitary confinement (18). Recognizing the existence of such a level of severe

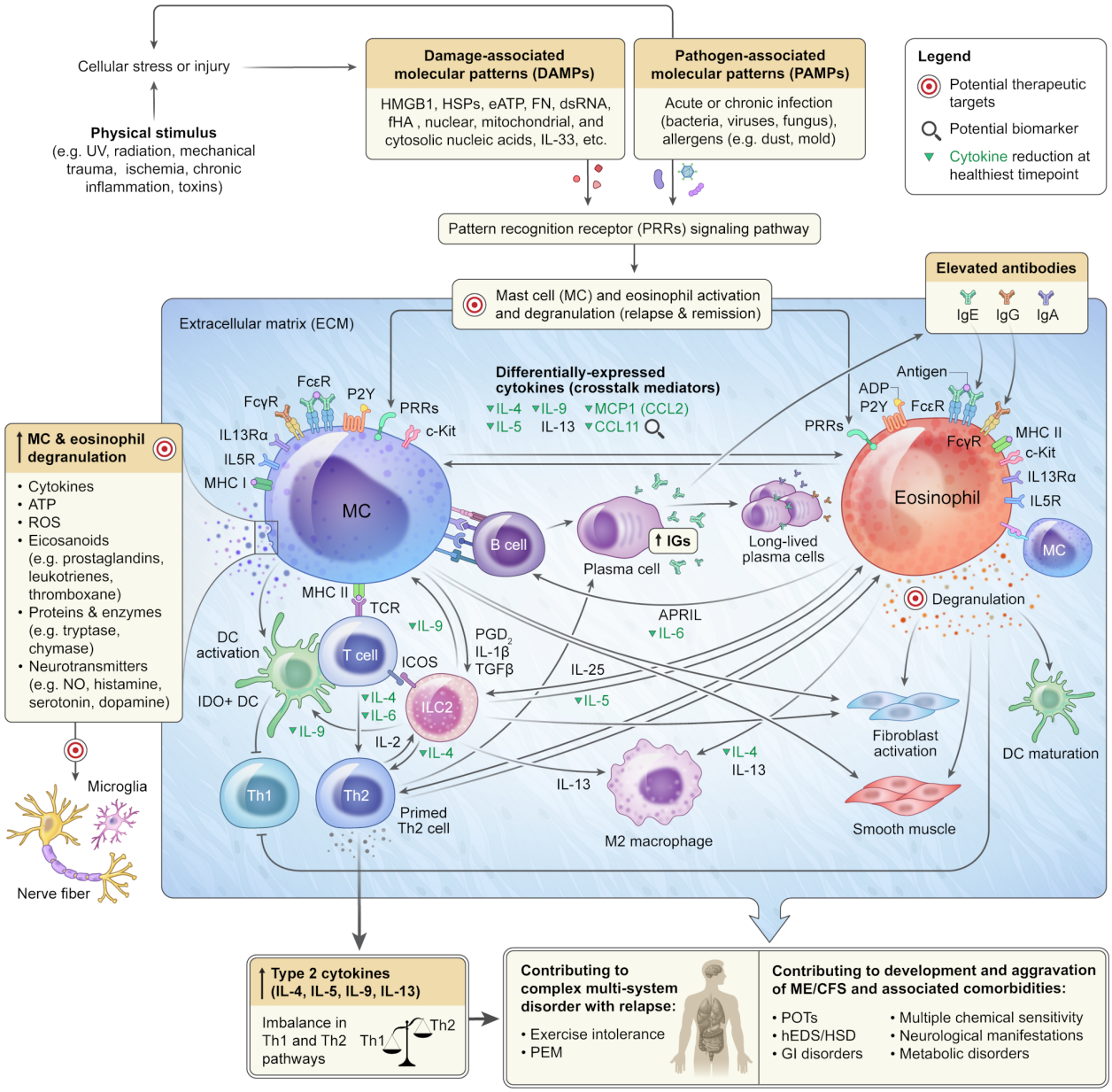



FIGURE 7
A Potential Mechanism Underlying ME/CFS Development, Aggravation and Comorbidities. Mast cells, present in nearly all human tissues, and eosinophils, found in the gastrointestinal tract, secondary lymphoid tissues, adipose tissue, thymus, mammary gland, and uterus, are tissue-resident cells. Aberrant DAMPs and PAMPs signaling cascades can lead to systemic overactivation and degranulation of mast cells and eosinophils, resulting in the release of over a hundred molecules, including potent inflammatory mediators, into the extracellular matrix of connective tissue. The synergistic activity of mast cells and eosinophils upon systemic activation can skew Th1/Th2 to Th2-immune responses, leading to tissue injuries, autoimmunity, impairment of multiple organs and biological systems as well as causing exercise intolerance and post-exertional malaise in predisposed individuals. Unresolved systemic mast cell and eosinophil overactivation could contribute to the development and aggravation of ME/CFS and related multisystem disorders and comorbidities. The schematic also depicts potential therapeutic targets and biomarkers.

hypersensitivity and PEM is crucial for advancing care for patients at the highest level of the severity spectrum.

The "extremely severe" category, as outlined in our manuscript, pertains to individuals whose lives are impacted to an extent of 80-100%, profoundly restricting their basic movements, self-care, occupation, communication, and access to social media. It is noteworthy that the integration of the internet and social media into daily life activities over recent decades has been significant; hence, the burden of ME/CFS on those whose severity affects basic access to these platforms may profoundly impact their quality of life and contribute to the worsening of their condition. We believe severity based on a patient's ability to receive life support and their most basic interaction with the outside world via social media warrants explicit recognition to underscore the significant burden faced by these patients and to delineate appropriate medical interventions and support measures.

While current severity assessment platforms offer a solid foundation for recognizing disease severity and patient

classification, integrating this aspect into patients' diagnosis and severity assessment criteria can provide a more refined delineation of the condition's severity spectrum (62). This addition facilitates the assessment of even minor improvements in response to treatment. Furthermore, delving into potential shared mechanisms between ME/CFS and Hypermobility Spectrum Disorder addresses significant facets of ME/CFS.

Our ME-CFSTrackerApp supports real-time tracking of symptoms, medications, and life events, benefiting physicians and researchers in more precise single-symptom assessment, treatment optimization, triggers and patterns identification, enhanced patient-doctor communication, longitudinal research data, and efficient data sharing. Crucially, the app enables remote real-time monitoring, facilitating proactive interventions, particularly benefiting severe cases (63). The data can be used for careful subject selection and eligibility criteria for clinical trials, targeted therapy and research studies. Additionally, employing natural language processing and open AI tools like ChatGPT, as well as the development of LexiTime application for textual data processing, including sentiment analysis and topic modeling, holds significant implications for ME/CFS research, particularly for patients with extreme severity who may face challenges in verbal communication (64, 65).

The deliberate inclusion of an extremely severe ME/CFS patient in our analysis offers a unique perspective on immune dynamics at critical disease stages, crucial for understanding the full spectrum of ME/CFS and tailoring interventions (18, 66). The identification of two leukocytosis episodes preceding health issues, particularly linked to infectious mononucleosis, aligns with the widely accepted understanding of ME/CFS etiology. This observation supports the notion that specific infections, such as herpes viruses, can act as catalysts for ME/CFS development (67–70). Additionally, recognizing environmental risk factors such as infection, overexertion, toxin exposure and medication side effects as crucial contributors to ME/CFS progression from mild to extremely severe adds significant value. This acknowledgment not only improves our understanding of the disease's etiology but also directs focused research efforts to explore underlying mechanisms and develop strategies to mitigate illness severity.

The integration of cytokine analysis from nine longitudinal samples, with health, clinical, and textual data provided deeper insights into the immune signature of ME/CFS during transitions in health severity. At the extremely severe A stage, the patient, while remaining fully bedbound and reliant on caregivers for most aspects of personal life, experienced a reduction in cognitive impairment and sensorial intolerance. This improvement allowed the patient to tolerate sounds, engage with music, access the internet, communicate in writing, and be comfortable with people's presence in the room. The noteworthy decrease in CCL11 during the healthiest time point aligns with previous ME/CFS cytokine studies, indicating a positive correlation between CCL11 and ME/CFS severity or duration (43, 71). CCL11 has been implicated in various diseases, including fibromyalgia (72), osteoporosis (73), metabolic conditions like non-alcoholic fatty liver disease (NAFLD) (74), accelerated aging, and neurodegenerative disorders such as chronic traumatic encephalopathy (75), multiple sclerosis (76), and the chemotherapy and long COVID-related brain fog (77). The consistent research findings revealing a positive correlation between elevated CCL11 levels, and the severity of sensorial intolerance and cognitive impairment underscore the need for further investigation into the significance of this cytokine in the context of ME/CFS and its potential value as a diagnostic and therapeutic biomarker (Figure 7).

Additionally, CCL11 plays a crucial role in recruiting eosinophils, implicating it in allergic responses and a shift toward a Th2 immune response and hypersensitivity. Interestingly, most significantly reduced cytokines at the healthiest time point have also been associated with eosinophils and mast cell activation, Th2 immune response and IgE signaling (Figure 7). These cytokines include IL5, MCP1, MIP1D, and CXCL9 (78–80). IL-5 is best known for its major roles in meditating eosinophil growth, activation, and survival and also differentiation of B-1 cells into Ig-secreting cells (78, 79, 81, 82). IL5 is expressed by many cell types including Th2 T-cell subsets, gamma delta T cells, basophils, group 2 innate lymphoid cells (ILC2s) and eosinophils (80, 81). Elevated IL5 has been reported in ME/CFS plasma (83) and many inflammatory conditions like eosinophilic gastroenteritis, eosinophilic dermatitis, and allergic reactions.

The observed reduction in MCP1 levels at the healthiest time point is also in line with a potential positive correlation between aberrant Th2 immune response and ME/CFS severity in this individual. MCP1, expressed by various cell types such as monocyte/macrophage, mast cells (84), dendritic cells, eosinophils (85), osteoclasts, osteoblasts, neurons, astrocytes, and microglia, plays a crucial role in recruiting immune cells like monocytes, eosinophils, and mast cells to inflammation sites resulting from tissue injury or infection (86, 87). This intricate involvement positions MCP1 as a key player in the pathogenesis of inflammatory diseases, including psoriasis, rheumatoid arthritis (88), and various neurological conditions such as brain ischemia (89), Alzheimer's (90), experimental autoimmune encephalomyelitis (EAE) (91), and traumatic brain injury (92, 93). MCP1 elevation was reported in fibromyalgia and linked to insulin signaling impairment in skeletal muscle cells of these patients (83). This alongside recent reports of increased MCP1 plasma levels in ME/CFS (83), suggests a reduction of MCP1 at healthiest time point might be linked to reduced neuroinflammation (94), improved blood-brain barrier permeability (95), diminished neuronal sensitization, and alleviated endothelial dysfunction (96). Adding another layer to its potential significance, MCP1's influence on the hypothalamus-pituitary-adrenal (HPA) axis (94), a critical regulator of stress responses and immune function, prompts further exploration into its diagnostic and therapeutic potential for ME/CFS.

Moreover, the reduction in CXCL9 (monokine induced by IFN-gamma) at the healthiest time point also underscores the potential involvement of eosinophils, mast cells, and an imbalance in Th1/Th2 immune responses in ME/CFS etiology in our patient (97–100). CXCL9, acting as a ligand for CXCR3 expressed in synovial mast cells and eosinophils, has been associated with inflammation in synovial tissues (100) and rheumatoid arthritis pathogenesis (99). Interestingly, elevated CXCL9 was reported in the cerebrospinal

fluid (CSF) of ME/CFS subjects, particularly those with a disease duration of less than 3 years (101), further emphasizing its potential relevance in ME/CFS etiology, in a subset of patients.

Furthermore, the decrease in IL28A, a type III interferon (102, 103), at the healthiest time point could also contribute to alleviating ME/CFS symptom severity by reducing systemic immune dysregulation, and interferon-associated fatigue, mitigating inflammatory response, and restoring Th1/Th2 balance (104), collectively enhancing cognitive function (105). Despite its physiological importance, aberrant IL28A activity has been linked to the promotion of inflammation and autoimmunity (106), and is associated with conditions such as lupus (107) and post-traumatic sepsis (108).

At the extremely severe stage A, elevation in plasma levels of Leptin, HGF, and MIF correlated positively with reduced disease severity, particularly in sensorial intolerance and cognitive function. It's essential to acknowledge that the observed cytokine elevation at the healthiest time point may be influenced by factors beyond health improvement, such as extended fasting hours, medication, infection, or trauma. However, considering the diverse multisystem biological functions of those cytokines in maintaining homeostasis, including the central and peripheral nervous system, energy regulation, immune system, and blood circulation, their elevation could contribute to overall health improvement.

Elevated leptin may positively impact ME/CFS by enhancing mental clarity, focus, mood, emotional well-being, metabolic regulation, energy production and utilization, neuroendocrine hormonal balance, motivation and immune function (109–114). Our current findings, indicating a negative correlation between plasma leptin and disease severity, differ from previous studies (42, 43), potentially attributed to the longitudinal nature of our research and variations in severity scales. Furthermore, the observed rise in leptin levels in the latest time point may be associated with slight changes in BMI (41, 115).

The varied physiological role of HGF (hepatocyte growth factor) suggests that an increase level may reduce ME/CFS symptom severity through tissue repair (116), anti-inflammatory effects, enhanced energy metabolism (117), neuroprotection (118, 119), improved blood circulation (120), immune modulation (121), and antioxidant properties (122–124). Further research into HGF's role in ME/CFS is warranted due to inconsistencies across studies (117–121).

MIF is a multifunctional molecule produced by various cell types, including activated macrophages. Beyond its proinflammatory roles, MIF is associated with many pathways such as inflammation, neural activities, and neuroplasticity (125, 126). It regulates catecholamine metabolism (127), protects dopaminergic neurons and has antidepressant effects at high concentrations. Additionally, MIF impacts the hypothalamic –pituitary–adrenal cortex axis (125, 126). Elevated MIF may correlate with improved ME/CFS symptoms, particularly in cognitive function and sensorial intolerance. However, elevated MIF at the healthiest point may stem from factors like infection (128), glucocorticoid use (129), and trauma (130). Further investigation is needed to understand MIF's role in ME/CFS pathophysiology, disease severity, and prognosis.

While specific cytokine changes, including the reduction in SFAS/FASLG, VEGF, CTACK/CCL27, IL9, IL6, MCP4, IL10, IL4, and increases in ENA78, GROA, IL2, TRACE, CCL21, FGF2, IL33, and TPO, did not achieve statistical significance individually, their collective alterations, as indicated by Z scores, may reveal a significant impact on the cytokine landscape in ME/CFS. Notably, IL4, IL6, IL9, IL10 (131), and IL33 play crucial roles in Th-2 immunity, the mast cell and eosinophil signaling network (132–138) (Figure 7).

Canonical pathway and upstream regulator analysis suggests potential mechanisms which could attenuate mast cells and eosinophil activities at the healthiest time point. This involves the predicted activation of Docosahexaenoic acid (DHA) and inhibition of KITLG and TLR4 signaling pathways (139). DHA and its metabolite, docosahexaenoyl ethanolamide (DHEA) show promise in preventing mast cell degranulation, IgE-mediated anaphylaxis reaction (140), eosinophil dysfunction (141) and also facilitates synaptogenesis and synaptic activity (similar to the endogenous cannabinoid receptor ligand anandamide) (142). Inhibition of KITLG and TLR4 could also decrease levels of various cytokines, including IL10, IL4, IL5, IL6, CCL2, and MCP1, thereby mitigating mast cell and eosinophil activation and aberrant Th2 immune responses (140, 143–149). Targeting TLR4 holds promise for reducing neuroinflammation (150–152).

Our study unveils novel insights into the potential roles of TP53 (tumor protein p53) and BCL6 (B-cell CLL/lymphoma 6) in ME/CFS pathogenesis (153, 154). Notably, both BCL6 and TP53 function as negative regulators in IgE-mediated mast cell activation (155, 156), exerting a dampening effect on both early and late-phase anaphylaxis. BCL6, a master regulator of humoral immunity, negatively modulates key molecules and cells associated with Th2-type inflammation (156–158). The implications of its involvement in preventing or attenuating allergic diseases suggest a potential link to ME/CFS in a subset of patients, especially considering its role in experimental autoimmune encephalomyelitis (EAE) (156). TP53, beyond its role as a tumor suppressor, plays a crucial part in various physiological processes, including cell metabolism, mitochondrial respiration, autophagy, and stress response. Balanced TP53 activation could reduce ME/CFS severity by promoting cellular repair (159), regulating metabolic pathways (160), and mitigating inflammation through the suppression of NF-κB transcriptional activity and mast cells and eosinophil-mediated Th2 dominant response (161). TP53's role in neurite outgrowth suggests potential benefits for cognitive function and overall neurological health (162, 163). These findings underscore the imperative for further exploration into the involvement of TP53 and BCL6 in ME/CFS pathophysiology.

The identification of a diminished Th2 immune response, coupled with reduced mast cell and eosinophil activation at the healthiest time point, unravels potential underlying pathological mechanisms in ME/CFS. This observation holds particular relevance to its association with major comorbidities such as EDS/hEDS/HSD. Mast cells and eosinophils, widely distributed in connective tissues (164), play crucial roles in immune regulation and extracellular matrix homeostasis (165, 166).

Notably, mast cell activation syndrome (MCAS) is highly prevalent in ME/CFS and connective tissue disorders, including

EDS/hEDS/HSD. Additionally, aberrant eosinophil function is commonly observed in connective tissue disorders (167, 168) and reported in the context of ME/CFS (169, 170). This underscores the necessity for further exploration into the dynamic interactions between mast cell and eosinophil immune responses and connective tissue function in ME/CFS (Figure 7).

Both mast cells and eosinophils exhibit widespread tissue distribution, with mast cells present in nearly all human tissues (171), and eosinophils mainly localized in the gastrointestinal tract, secondary lymphoid tissues, adipose tissue, thymus, mammary gland, and uterus (172). These cells play indispensable roles in both innate and adaptive immunity, particularly in tissues closely exposed to environmental factors like the skin and intestinal lining (173, 174), where they are engaged in bidirectional mast cell–eosinophil interactions known as the allergic effector unit (AEU) (175, 176). Infections, allergens (177), and exposure to environmental risk factors (e.g., UV, radiation, stress, mechanical trauma, and hypoxia) can activate a wide array of receptors, including PRRs (pattern recognition receptors) (e.g., TLRs, NLRs, RLRs), FC receptors, P2Y receptors (P2YR) (178, 179), MHC (major histocompatibility complex) class II (180, 181) and complement receptors (C3a and C5a) (182–184) on mast cells and eosinophils via binding to their cognate ligands. These factors could also lead to cell/tissue injury, resulting in the release of endogenous danger signals or DAMPs (damage-associated molecular patterns) (e.g., HMGB1, HSPs, eATP, FN, dsRNA, fHA, nuclear, mitochondrial, and cytosolic nucleic acids, cytokines) (185) into the extracellular space. Here, they can engage with the same PRRs to initiate mast cell (135) and eosinophil (186, 187) activation and intricate crosstalk between these cells and the rest of the immune and non-immune cells (137, 138, 180, 181, 188). Upon activation, both cells undergo degranulation, releasing various inflammatory mediators, including reactive oxygen species (ROS), cytokines, eicosanoids (e.g., prostaglandins, leukotrienes, thromboxane), proteins (cationic proteins) and enzymes (e.g., tryptase, chymase, peroxidase, β-hexosaminidase, β-glucuronidase, arylsulfatases) as well as neurotransmitters (e.g., nitric oxide, histamine, serotonin, dopamine, substance P) (188–190) (Figure 7).

Due to their widespread distribution, the overactivation of mast cells and eosinophils can impact multiple biological systems and organs, affecting cardiovascular, endothelial (191, 192), epithelial, mucosal, microvascular (193), metabolic (194), muscular, gastrointestinal, and connective tissues (193, 195–197) as well as peripheral, central and autonomic nervous system. This cascade of effects can contribute to the development of complex multi-system conditions, exemplified by ME/CFS, which manifests with a diverse range of comorbidities (198) such as connective tissue disorders, small fiber neuropathy, migraine (199–201), POTS (202, 203), immune system hypersensitivity (204, 205), and dermatological manifestations (e.g., dermatitis, tingling or numbness, sensitivity, and allodynia) (206), as well as neuroinflammation, GI disorders, leaky gut (207), and autoimmunity observed in many patients (82, 143, 208–213). The excessive response of mast cells and eosinophils, coupled with aberrant degranulation, not only has the potential to trigger or exacerbate congenital conditions but also contributes to the development of acquired forms (214). This aspect is particularly relevant in conditions like hEDS and HSD, where underlying genetic variations remain unidentified (215, 216).

While mast cells and eosinophils have been traditionally associated with type 2 immunity during allergies and helminth infections, they actively participate in immune responses against various pathogens, including bacteria, fungi, and viruses (174, 217–220). Their capacity to survey the environment through numerous receptors enables them to finely tune a balance between immune activation and suppression. This orchestration involves intricate crosstalk with a variety of cells, including dendritic (221), B, T, type 2 innate lymphoid cells (ILC2) (222), macrophage, monocyte, fibroblast, smooth muscle, neurons, microglia (223), as well as epithelial and endothelial cells. Recent revelations highlight the dual nature of mast cells and eosinophils (175, 182, 224, 224). While acting as potent agents against helminths, they also play a surprising role in fostering the coevolution of helminth parasites with their hosts through immunosuppressive activities (225). A noteworthy mechanism involves the reduction of Th1 immune cell proliferation and the promotion of apoptosis via the indoleamine 2,3-dioxygenase (IDO) gene (226). This leads to a decrease in Th1 cells and a tilting of the immune balance from Th1/Th2 towards Th2-dominated responses (227–233), potentiating systemic autoimmune inflammatory diseases (229).

Research indicates that overtraining can shift the Th1 to Th2 phenotype, resulting in diminished Th1 and NK cell function (234). Lower NK cell levels have been reported among ME/CFS patients (235). Furthermore, an overactive Th2 immune response has been implicated in individuals with exercise intolerance (234, 236). These findings, suggest an intricate crosstalk between dysregulated immune system, exercise intolerance, and post-exertional malaise in ME/CFS. Additionally, these findings might imply a primed Th2 immune system plays a role in the adverse reactions observed in ME/CFS patients to high-intensity aerobic exercise. Recent findings linking elevated Th2 immune response in long COVID patients with adverse reactions to aerobic exercise further highlight the importance of investigating the Th1/Th2 axis imbalance and post-exertional malaise in ME/CFS and related comorbidities for insights into etiology and lifestyle adjustments (236).

Adding to their significance, mast cells and eosinophils play pivotal roles in adaptive immunity, and guiding T (157, 237, 238) and B cells to transform into effector cells, such as antibody-producing plasmablasts and long-lived plasma cells (158, 189, 239–246). Their activated states may contribute to aberrant elevated antibody production (247) and T and B cell-dependent inflammatory and autoimmune diseases. The surplus IgEs, IgAs, and IgGs binding to mast cell and eosinophil FC receptors set off a vicious cycle, amplifying degranulation and escalating tissue damage and promoting autoimmunity (248–250). Uncontrolled Th2 activity may also mitigate pathogenic T-cell immunity. With elevated antibody levels observed in many ME/CFS patients (251–253), delving into the role of mast cell and eosinophil activation in triggering abnormal antibody responses could provide deeper insights into ME/CFS pathogenesis, severity, and guide diagnostic and therapeutic strategies (254).

In our study analyzing medication data from June 2017 to January 2021, a positive correlation was found between health

improvement in ME/CFS patients and a slight increase in low-dose Abilify (Aripiprazole), alongside the reduction and optimization of doses for Skullcap, buspar (buspirone), and klonopin (clonazepam). All immune cells, including mast cells and eosinophils, express receptors for various neurotransmitters and neuropeptides (255–258). Optimizing the dose of these medications, known for modulating neurotransmitters and neuropeptides, may contribute to health improvement by modulating the central, and peripheral nervous system and restoring Th1/Th2 balance, mitigating mast cells (259, 260) and eosinophils' overactivation (261, 262) along with other relevant biological players (255–258) (Figure 7).

Abilify's acts on dopamine D2 and serotonin 5-HT1A receptors, as a partial agonist and antagonist, respectively (263). As a partial agonist, Abilify could act as a D2 agonist, increasing dopamine activity in the presence of low levels of endogenous dopamine and exerting antagonistic activity in the presence of high levels (263). An in-depth investigation into aberrant dopaminergic signaling in ME/CFS and Abilify's use is warranted, given varying anecdotal reports, some indicating benefits and others worsening symptoms (264). Klonopin binds to GABA receptors in and outside the brain (265–269), enhancing GABA's inhibitory effect and regulating serotonin utilization (270, 271). Buspirone, an anxiolytic drug, acts as a partial agonist of serotonin and dopamine receptors (272). Despite distinct targets, both klonopin and buspar have been used to manage pain and improve cognition (273–277). However, higher doses may result in cognitive issues (277). Skullcap, a native American medicinal plant has been used for treating menstrual disorders, nervousness, and kidney problems (278). However, at higher doses it can cause giddiness, stupor, mental confusion, twitching, irregular heartbeat, and seizures (279). Notably, baicalin, a component of Skullcap, binds to GABA A receptor. Optimizing the doses of these medications could potentially enhance cognitive function and minimize side effects due to drug interactions (280–283). Our analysis of medication correlations with severity underscores challenges faced by ME/CFS patients in navigating their path to recovery. The intricate and diverse nature of ME/CFS, coupled with the absence of FDA-approved treatments, often prompts patients to adopt a trial-and-error approach, experimenting with various medications and interventions to address their health needs (284, 285).

Potential interactions among these interventions are frequently overlooked due to the absence of proper diagnostic assessments and objective evaluations of disease severity. Developing tools to monitor and assess potential adverse effects will enhance patient safety, inform personalized treatment plans, and contribute to the advancement of ME/CFS care (170). The ME/CFSTracker app serves as a valuable tool for patients, caregivers, and medical teams, enabling the easy collection of longitudinal health changes and a more precise assessment of severity in response to therapeutics and nutraceutical interventions.

Our study has limitations, such as a small sample size and the heterogeneous nature of ME/CFS, which may limit the generalizability of our findings. The observed aberrant Th2-cytokine expression and dysregulated mast cells and eosinophil function, causing a shift from Th1 to Th2 immune response, may apply to a specific subset of patients rather than the entire spectrum (286–290). Further longitudinal studies are needed to validate and extend the scope of our results.

## 5 Conclusion

Our study underscores the values of integrating longitudinal health, clinical, pharmaceutical, nutraceutical, and multi-omics data, and the use AI to advance our understanding of factors and mechanisms underlying ME/CFS development, progression, and its associated comorbidities, guiding personalized data-driven therapies (279). We introduced an updated platform for objective severity assessment and created two applications, the ME-CFSTrackerApp, and LexiTime, aiming to facilitate real-time symptom tracking and text mining to optimize treatment strategies and communication. Our longitudinal cytokine profiling suggests the need for further research into the role of aberrant Th2-type cytokines and the synergistic activities between mast cells and eosinophils in the pathogenesis and severity of ME/CFS, particularly in cognitive impairment and sensorial intolerance. Our results also highlight a potential shared underlying mechanism between ME/CFS and its major comorbidities such as hEDS/HSD, POTS, MCAS, multiple chemical sensitivity, peripheral neuropathy, and the neuro-immune and brain-gut interaction axis.

Our findings align with previous research, supporting the potential of CCL11, IL5, and MCP1 as biomarkers for ME/CFS diagnostics and therapeutics. Identification of master regulators like BCL6, TP53, KTLG offers a mechanistic model linking chronic systemic activation of mast cells and eosinophils to the development and aggravation of multi-system conditions such as ME/CFS (30, 160, 196, 202, 280–282). Our results underscore the need for further exploration into mast cell- and eosinophil-directed biologic therapies, and the significance of low-dose drugs with partial agonists activity toward neurotransmitters in ME/CFS treatment (Figure 7).

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving humans were approved by Stanford Research Compliance Office. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

FJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JS: Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. RM: Data curation, Methodology, Visualization, Writing – review & editing. SJ: Data curation, Writing – review & editing. JD: Data curation, Writing – review & editing. WD: Data curation, Writing – review & editing. NJ: Methodology, Software, Writing – review & editing. KW: Methodology, Software, Writing – review & editing. AR: Visualization, Writing – review & editing. HR: Writing – review & editing. HM: Writing – review & editing. MS: Funding acquisition, Resources, Writing – review & editing. RD: Funding acquisition, Resources, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1369295/full#supplementary-material

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# Kikuchi-Fujimoto disease evolves into lupus encephalopathy characterized by venous sinus thrombosis: a case report

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Kikuchi-Fujimoto disease (KFD) is a benign, self-limiting illness that can progress to systemic lupus erythematosus (SLE) in approximately 30% of cases. Neurological injuries can occur in both diseases, albeit with distinct presentations. Venous sinus thrombosis is a serious cerebrovascular complication in patients with neuropsychiatric SLE but is rarely observed in patients with KFD. The involvement of various antibodies, particularly antiphospholipid antibodies, can cause vascular endothelial cell injury, resulting in focal cerebral ischemia and intracranial vascular embolism in SLE. However, there are cases in which thrombotic pathology occurs without antiphospholipid antibody positivity, attributed to vascular lesions. In this report, we present a case of KFD and lupus encephalopathy featuring cerebral venous sinus thrombosis, despite the patient being negative for antiphospholipid antibody. We also conducted a comparative analysis of C3 and C4 levels in cerebrospinal fluid (CSF) and peripheral blood, along with the protein ratio in CSF and serum, to elucidate the pathological changes and characteristics of lupus encephalopathy.

KEYWORDS

**neuropsychiatric lupus, venous sinus thrombotic, Kikuchi-Fujimoto disease, necrotizing lymphadenitis, cerebrovascular disease**

**Abbreviations:** Kikuchi-Fujimoto disease, KFD; systemic lupus erythematosus, SLE; Neuropsychiatric systemic lupus erythematosus, NPSLE; central nervous system, CNS; Cerebral venous sinus thrombosis, CVST; magnetic resonance venography, MRV; computed tomography venography, CTV; blood–brain barrier, BBB; hydroxychloroquine sulfate, HCQ; antiphospholipid, aPL; deep vein thrombosis, DVT; disseminated intravascular coagulation, DIC; electroencephalogram, EEG.

# 1 Introduction

Kikuchi-Fujimoto disease (KFD) is characterized by lymph node enlargement, featuring subacute necrotizing lymphadenopathy with symptoms such as swollen lymph nodes, pain, and fever. The lymph node biopsy reveals a proliferative and necrotizing process centered in the paracortex, characterized by patchy circumscribed or confluent areas of necrosis associated with karyorrhexis and marked by the absence of granulocytes and the paucity of plasma cells (1). These distinctive features could differentiate KFD from nearly all other forms of nodal hyperplasia. Biopsy is crucial for KFD diagnosis, which is linked to various infectious and autoimmune diseases, including systemic lupus erythematosus (SLE) (2). While KFD is sometimes seen as a precursor to SLE (3, 4), its direct impact on SLE activity or prognosis remains unclear. Even in severe cases involving neurological damage, distinguishing KFD-related damage from SLE-induced lupus encephalopathy requires serum immunology and imaging examinations.

Neuropsychiatric SLE (NPSLE) is a severe complication involving the nervous system (5), displaying diverse manifestations ranging in severity with prognostic implications. NPSLE includes various neurological and psychiatric symptoms, often challenging to differentiate from unrelated events. Common complaints in SLE patients encompass headaches, mood disorders, anxiety, and mild cognitive dysfunction, which may not reflect disease activity in the central nervous system (CNS) and can be misdiagnosed or overlooked (6). Cerebral venous sinus thrombosis (CVST) is a rare vascular lesion within NPSLE, occurring even in patients without antiphospholipid antibodies, typically presenting with intracranial hypertension and headaches (7). Diagnostic tools such as cerebral magnetic resonance venography (MRV) or computed tomography venography (CTV) are crucial for diagnosing NPSLE with CVST. Active SLE control coupled with anticoagulant therapy improves NPSLE prognosis, and identifying assessment methods and biomarkers for NPSLE is vital to avoid misdiagnosis.

This report presents a unique case of a patient with SLE initially diagnosed with KFD, later developing CVST during immunosuppressive treatment. Headache and anxiety masked the true condition, and thorough serum immunological tests and imaging exams were crucial for diagnosis and treatment, leading to positive therapeutic outcomes. This case contributes to a deeper understanding of the characteristics and mechanisms of NPSLE.

# 2 Case presentation

A 25-year-old woman was admitted to our hospital on November 11, 2023, with a high fever (peaking at 39°C) and lymph node pain persisting for 1 month. We performed a lymph node pathological biopsy (Figures 1A, B), which led to the diagnosis of KFD (necrotic lymphadenitis). Treatment with anti-inflammatory medication (40 mg methylprednisolone PO qd) led to normalization of her body temperature and significant alleviation of neck lymph node pain. However, during the course of her illness, she developed increased anxiety and headaches, likely due to work stress. After consultation with a psychiatrist, she was diagnosed with a mild anxiety state, but treatment with alprazolam did not significantly improve her symptoms. Due to concerns about potential neurological complications from KFD, a cerebral MRI scan was conducted, which raised suspicion of subarachnoid hemorrhage or infectious lesions. Subsequently, a lumbar puncture and CSF examination were performed, revealing normal results (routine, biochemical, and smear), with $Cl^-$ at 121 (120–132mmol/L), Glu at 3.1 (2.2–3.9mmol/L), Pro at 0.23 (0.12–0.60g/L), and negative findings for acid bacteria, *Cryptococcus* fungi, and bacteria, with slightly elevated CSF pressure (230 mm$H_2O$; normal: 80–180 mm$H_2O$).

The frequent headaches and anxiety symptoms observed did not align with the typical manifestations of KFD, such as aseptic meningitis (7). Considering the comprehensive clinical manifestations, sex, age, and other factors, we suspected an alternative diagnosis despite the initial KFD diagnosis. An immunological examination was conducted (Table 1), revealing a definitive diagnosis of SLE. Both the headache and anxiety were attributed to SLE, leading to the initiation of treatment with methylprednisolone (80 mg IVGTT D1-D7), mycophenolate mofetil (750 mg bid PO), and hydroxychloroquine sulfate (200 mg bid PO). However, after 7 days of therapy, there was no significant improvement in her headache and anxiety symptoms, prompting

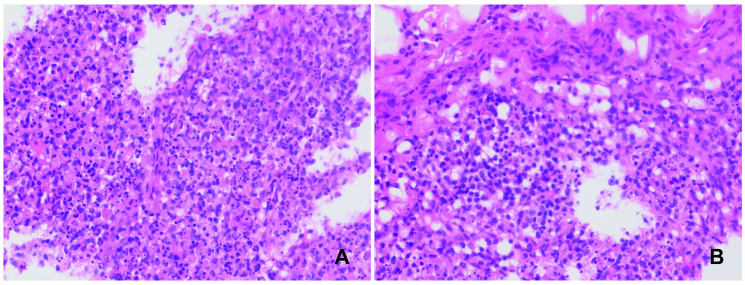



FIGURE 1
Left subclavian lymph node biopsy. Conventional hematoxylin and eosin staining (H&E), 400X. Multiple lesions containing a significant number of histiocytes and nuclear debris are observed in the lymph nodes. No neutrophils or plasma cells are seen **(A, B)**.

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TABLE 1 Antibodies, immunological test results, and reference interval.

| Antibodies | Results | Reference interval |
|---|---|---|
| ANA | **1:1000 granular type** | Negative |
| Anti-U1-nRNP | Negative | Negative |
| Anti-Smith | Negative | Negative |
| Anti-SSA | **Positive** | Negative |
| Anti-Ro52 | **Positive** | Negative |
| Anti-dsDNA | Negative | Negative |
| Ribosomal P protein | Negative | Negative |
| Complement 3 | **0.60** | 0.79–1.52g/L |
| Complement 4 | 0.16 | 0.16–0.38g/L |
| IgG | **17.80** | 7.51–15.60 g/L |
| IgM | 0.71 | 0.46–3.04 g/L |
| IgA | 1.99 | 0.82–4.53 g/L |
| Anti-β2 GP1 | Negative | Negative |
| Antiphospholipid | Negative | Negative |
| LA1/LA2 | 1.09 | <1.20 |
| Anti-dsDNA | 9.9 | 0–100 IU/mL |
| ANCA | Negative | Negative |

ANA, Antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-β2-GP1, anti-beta-2 glycoprotein 1; dsDNA, double-stranded DNA; Ig, immunoglobulin; LA, lupus anticoagulant; RNP, ribonucleoprotein.
Bold font prompted abnormal results.

further investigation. Cerebral MRA+MRV (Figures 2A–D) and CTV (Figure 2E) scans revealed superior sagittal sinus thrombosis as the cause of her headache. An electroencephalogram also indicated mild abnormalities, confirming the presence of NPSLE.

The final diagnosis for the patient was identified as NPSLE secondary to KFD, characterized by CVST. To assess blood–brain barrier (BBB) permeability and understand the pathological mechanism of NPSLE, the albumin CSF-to-serum ratio was calculated, revealing an albumin CSF concentration of 0.23 g/L, albumin serum concentration of 42 g/L (normal: 40–55g/L), and albumin CSF/serum ratio exceeding $5.48\times10^{-3}$.

Treatment adjustments included transitioning to intravenous infusion of cyclophosphamide at a dosage of 600 mg over 2 days, tapering methylprednisolone dosage to 50 mg per day orally, and administering hydroxychloroquine sulfate (HCQ) at 200 mg twice daily orally. Importantly, low-molecular-weight heparin was administered for its antithrombotic effects. After 4 weeks of treatment, significant alleviation of headache and anxiety was observed, along with significant improvement in the patient's overall well-being. A repeat cerebral CTV was scheduled to reassess the status of CVST, which revealed marked reduction in venous sinus thrombosis and recanalization of the thrombus (Figure 2F), along with significantly increased activity markers of C3 and C4 (Table 1, Figure 3). The patient is currently under close monitoring with regular follow-up appointments.

# 3 Discussion

NPSLE is a severe complication of SLE that affects the nervous system, manifesting as neurological or psychiatric symptoms. The underlying mechanisms of NPSLE are complex and may involve genetic factors, dysfunction of the BBB, vascular lesions, autoimmune antibodies, cytokines, and neuronal cell death, all potentially contributing to NPSLE development (5, 8). Autopsy findings in patients with NPSLE suggest that damage to the CNS is linked to cerebrovascular lesions, with common pathological manifestations including cerebral microvascular ischemia and thrombosis, small vessel non-inflammatory lesions, focal vascular occlusion, and microhemorrhage. Several studies have indicated that antiphospholipid (aPL) antibodies are associated with diffuse NPSLE syndromes, indicating a broader pathogenic role beyond their prothrombotic effects (9).

CVST is rare in patients with SLE, with a low incidence of approximately 0.36% (10). However, in this case, the patient experienced multiple CVST without positive aPL antibodies. We hypothesize that cerebrovascular disease in such patients is primarily related to immune inflammation, immune complex deposition, and activation of the complement pathway. Factors such as defective fibrinolysis, altered antithrombin III function, hyperfibrinogenemia, or coagulation changes may also play a role (11, 12). The presence of multiple thromboses in the cerebral venous system suggests a hypercoagulable state in the patient's body. Despite the absence of aPL antibodies, the high SLE activity and severity of the injury were evident from the neurological damage and SLEDAI score. Treatment with immunosuppressants and anticoagulants proved effective, indicating that immune complex-induced vasculitis may play a significant role in CVST pathogenesis.

Additionally, this case initially diagnosed as KFD due to neurological symptoms and positive auto-antibodies highlights the importance of distinguishing between neurological damage caused by KFD and NPSLE. As KFD shares some clinical and histological features with SLE, it has been proposed that KFD may represent a self-limiting SLE-like autoimmune disorder (13, 14). CNS involvement, such as aseptic meningitis, meningoencephalitis, acute cerebellar symptoms with tremors and ataxia, and optic neuritis, has been reported in KFD (15, 16), with aseptic meningitis being a common complication. However, the mechanisms of deep vein thrombosis and disseminated intravascular coagulation occurring within KFD are rarely reported. For this case, CVST without positive aPL antibodies may involve endothelial damage, enhanced expression and release of procoagulant substances by granulocytes and macrophages, and activation of the coagulation cascade (17, 18). If symptoms persist or new ones arise after treatment, other diseases should be considered. Severe headache and anxiety should alert clinicians to identify the actual causative factor. For young women with underlying KFD, the possibility of autoimmune diseases such as SLE should be considered if presenting symptoms persist despite standard treatment. Auto-antibody testing can aid in diagnosis. Atypical symptoms such as autoimmune hemolytic anemia and the

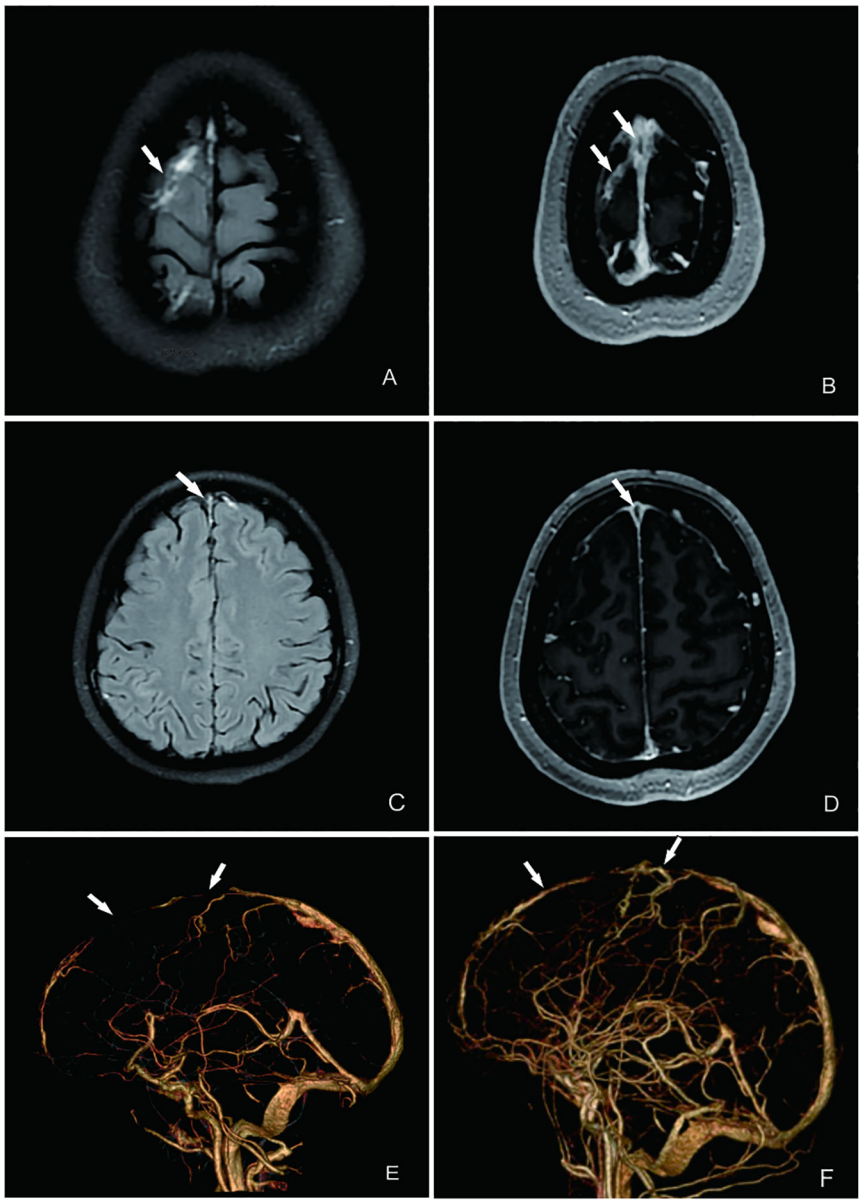



FIGURE 2
MRI and CTV of the patient's brain showing multiple intracranial thrombosis in the venous sinus. **(A)** T2 imaging suggests multiple superficial venous thrombosis (indicated by the arrow). **(B)** T1-enhanced imaging showing the same results as those shown in **(A)**. **(C)** T2 flare imaging indicating superior sagittal sinus thrombosis (indicated by the arrow). **(D)** T2-enhanced imaging showing the same results as those shown in **(C)**. **(E)** CTV showing a filling defect in the superior sagittal sinus on CTV, indicating thrombosis formation. **(F)** After treatment of CTV, partial resolution of the superior sagittal sinus thrombus and improvement in thrombus severity are seen, compared with before treatment.

need for rheumatology referral and follow-up for possible development of SLE are crucial aspects to consider (19). Moreover, investigating the cytokines and inflammatory markers associated with KFD could elucidate the thrombotic mechanisms.

The overactivation of the complement pathway can lead to neuronal damage in various neurological diseases (20). We assessed C3 and C4 levels in peripheral blood and CSF to elucidate the function of the BBB in NPSLE. Several studies on immune-mediated diseases have measured CSF concentrations of C3 and C4 to evaluate the role of the complement system. However, measuring C3 and C4 concentrations in CSF alone is insufficient for detecting intrathecal complement production in the CNS. Despite complement components being locally produced by resident brain cells (21), their synthesis in the brain is low or undetectable under healthy conditions (22). Consequently, BBB damage permits complement entry from the systemic circulation, resulting in elevated complement concentrations in CSF. Our case results revealed negative detection of C3 and C4 levels in CSF, which significantly differed from those in peripheral blood, although they were markedly decreased in serum. Comparing complement C3 and C4 levels in the CSF of patients with lupus encephalopathy and non-SLE patients showed no marked

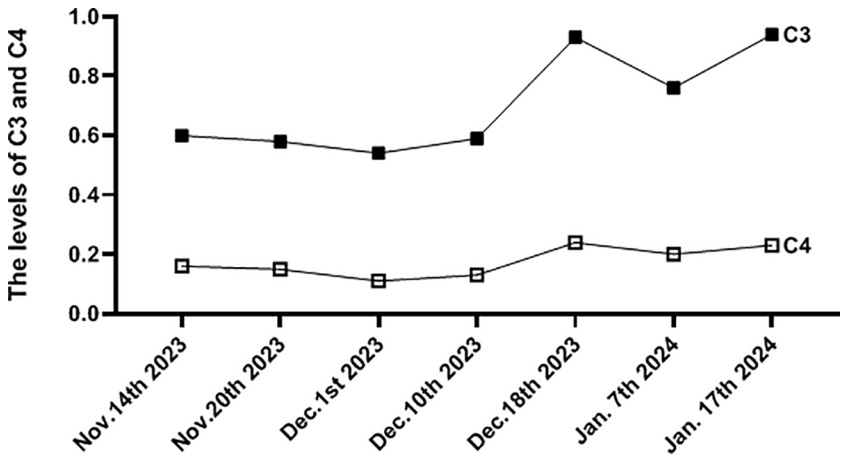



FIGURE 3
The picture showed the levels change of C3 and C4 during the process of treatment. (g/L, reference value C3,0.79-1.52; C4, 0.16-0.38).

differences, indicating that diagnosing and assessing NPSLE based on CSF and serum C3 and C4 levels alone is inadequate. Several reports provide methods to evaluate the function of the BBB and NPSLE activity. The albumin CSF-to-serum ratio serves as a surrogate marker for BBB permeability (23) and can help assess CNS inflammation. In this case, the elevated albumin CSF-to-serum ratio of $5.48\times10^{-3}$, exceeding the normal value of $5.0\times10^{-3}$, indicated BBB injury in the patient, highlighting the role of immune inflammation in BBB permeability.

## 4 Conclusion

This case report emphasizes the differences between KFD anNPSLE in terms of neurological injury and management. CVST in NPSLE can occur without positive aPL antibodies and requires distinct treatments compared to KFD. NPSLE treatment depends on disease activity and organ damage severity. Anticoagulation and antiplatelet therapies are essential for CVST cases. Additionally, assessing changes in C3 and C4 levels in CSF alone is inadequate for evaluating NPSLE activity, but the CSF-to-serum protein ratio can effectively demonstrate BBB injury. Further research is needed to understand the pathological mechanisms of NPSLE.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Biomedical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

WQ: Writing – original draft, Writing – review & editing. SY: Writing – review & editing. LZ: Writing – review & editing. ML: Writing – review & editing, Resources. FL: Writing – review & editing. JT: Methodology, Writing – original draft. JY: Investigation, Writing – original draft. GZ: Conceptualization, Writing – review & editing. XR: Conceptualization, Methodology, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1389993/full#supplementary-material

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# Sulfasalazine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) coinfected with COVID-19 complicated by hemophagocytic lymphohistiocytosis: a case report

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is characterized by a widespread maculopapular rash, lymphadenopathy, fever, and multisystem involvement. Conversely, hemophagocytic lymphohistiocytosis (HLH) is an infrequent yet critical condition presenting with fever, hepatosplenomegaly, cytopenias, coagulation abnormalities, and elevated inflammatory markers. The overlapping clinical and laboratory features between DRESS and HLH poses a significant diagnostic challenge. Secondary HLH (sHLH) typically occurs in adults triggered by viral infections, malignancies, rheumatologic diseases, or immune deficiencies. Recently, COVID-19 has also been identified as one of the triggers for sHLH. Herein, we present a case of Sulfasalazine-induced DRESS coinfected with COVID-19 that subsequently progressed into HLH. Our patient exhibited common hepatorenal and splenic involvement along with rare cholecystitis and appendicitis. However, a significant improvement was observed upon the addition of etoposide and azathioprine. We hypothesize that excessive activation of the immune system and cytokine storm due to DRESS combined with COVID-19 infection led to more extensive systemic damage resulting in HLH development. This highlights the potential for severe consequences when DRESS coincides with HLH during a COVID-19 infection.

KEYWORDS

**drug reaction with eosinophilia and systemic symptoms, COVID-19, hemophagocytic lymphohistiocytosis, ebv, CMV**

## Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe condition that typically manifests 1-6 weeks after exposure to certain medications or their metabolites. It is characterized by extensive maculopapular eruptions, lymphadenopathy, fever, and involvement of multiple organs (1). The mortality rate of DRESS ranges from 1.7% to 8.8%, with recurrence in affected individuals increasing the mortality rate to as much as 29% (2, 3). Hemophagocytic lymphohistiocytosis (HLH) is an uncommon yet fatal syndrome marked by fever, hepatosplenomegaly, cytopenias, coagulopathy, and elevated inflammatory markers among other symptoms (4). In adults, studies have estimated the overall mortality rates to be approximately 40-50%, with early mortality being around 20% despite treatment (5, 6).

The pathogenesis of DRESS and HLH remains incompletely understood. DRESS is characterized by a drug-induced Type IV hypersensitivity reaction, involving the activation of drug-specific CD4 and CD8 T cells as well as dysfunction of regulatory T cells. Immune dysregulations in DRESS are manifested by elevated levels of certain human leukocyte antigens (HLA), reactivation of herpesviruses (HHV-6, Epstein-Barr virus (EBV), cytomegalovirus (CMV)), and autoimmune sequelae. HLH, also known as macrophage activation syndrome (MAS) in the context of rheumatologic disease, is a hyperinflammatory condition resulting from excessive phagocytic activity of macrophages on hematopoietic cells. It can be classified into primary or secondary HLH based on its etiology: primary HLH predominantly affects infants and children due to genotypic defects, while sHLH typically occurs in adults triggered by viral infections, malignancies, rheumatologic diseases, or immune deficiencies. Recently, COVID-19 has also been identified as one of the triggers for sHLH (7).

While there is some overlap in pathogenesis, clinical features, and laboratory abnormalities between DRESS and HLH associated with fever, lymphadenopathy, multisystem organ failure, viral infection/reactivation, and abnormal T cell activation, the coexistence of DRESS and HLH is a rare and potentially fatal condition. The most frequently reported drugs implicated in DRESS complicated by HLH include allopurinol, β-lactam antibiotics, and phenobarbital (8). In this case report, we present a patient who developed Sulfasalazine-induced DRESS coinfected with COVID-19 that subsequently evolved into HLH. This case highlights the intricate interplay between drug reactions, viral infection, and immunological responses.

## Case report

A 36-year-old Chinese man was diagnosed with ankylosing spondylitis due to low back pain and initiated sulfasalazine therapy one month ago. Two weeks after starting sulfasalazine, the patient developed high fever (up to 40°C), facial swelling and generalized erythema, and subsequent cervical lymphadenopathy. Despite receiving antibiotic treatment (ceftriaxone, amoxicillin, and levofloxacin) at a local hospital, there was no improvement in his condition. Laboratory examination revealed leukocytosis ($228.9\times10^9$/L) and abnormal liver function tests characterized by elevated aspartate aminotransferase (324 U/L; Normal value <50 U/L) and alanine aminotransferase (114 U/L; reference range < 40). Additionally, elevated B-type natriuretic peptide (BNP) levels (1411 pg/ml; normal range: 0-88) were detected along with positive COVID-19 PCR results. The patient was diagnosed with drug hypersensitivity syndrome, drug-induced liver injury, and COVID-19 infection. Subsequently, administration of methylprednisolone (160 mg/day), intravenous immunoglobulin (32.5g/day), and Paxlovid for five days led to relief of high fever and significant subsidence of the rash. Following this initial treatment phase, the patient was transferred to our department for further management. Physical examination showed diffuse exanthematous eruption on the trunk (Figure 1). The methylprednisolone dosage was gradually reduced every 3–5 days, during which time most of the skin lesions resolved and the levels of leukocytosis, aspartate aminotransferase, alanine aminotransferase and BNP approached normal ranges. However, after 5 days, the patient experienced an abrupt onset of high fever (up to 40°C) accompanied by abdominal pain. Laboratory evaluation revealed multiple abnormalities, including elevated serum ferritin levels of 11895.00 ng/ml (reference range: 24-336), decreased fibrinogen levels of 1.02 g/L (reference range: 2-4), increased procalcitonin(PCT) levels of 0.61 ng/ml(reference range <0.048), significantly elevated alanine aminotransferase levels of 2462 IU/L (reference range < 50), markedly elevated aspartate aminotransferase levels of 1191 IU/L (reference range < 40), highly increased erythrocyte sedimentation rate (ESR) 109 mm/h (reference range <21), substantially raised CRP level at 145mg/L (reference range <5), extremely high triglycerides concentration at 9.79 mmol/L(reference range: 0.29-1.83). Additionally, the absolute count of NK cells was found to be 32 cells/ul (reference range:154-768). Multiple cytokines were observed to be elevated including interleukin (IL)-2, IL-2R, IL-6, IL-8, IL-10, IFN-gamma(IFN-γ).Tests for antineutrophil cytoplasmic antibody and rheumatoid factor yielded negative results, as did serological tests for hepatitis viruses and human immunodeficiency virus(HIV). EBV DNA was detected at a concentration of 4.11E+05 copies/mL and human CMV was detected at 3.73E+03 copies/mL. Antinuclear antibodies were positive with a titer of 1:1000 speckled pattern. Extractable nuclear antigen antibodies tests showed positive for anti-U1-snRNP antibodies (23.9 AI) and anti-SS-A antibodies (22.7 AI). Thyroid function tests revealed a higher level of reverse triiodothyronine (rT3) at 1.78 nmol/L (normal range: 0.78-1.38), along with a comprehensive thyroid panel including lower levels of triiodothyronine (T3) at 0.64 nmol/L(reference range: 1.3-3.1), free T3 at 1.96 pmol/L(reference range: 3.6-7.5), thyroxine (T4) at 48.60 nmol/L(normal range: 62-164), free thyroxine (fT4) at 11.20 pmol/L (normal range: 12-22), thyroglobulin at a reduced level of only 0.10 ug/L(reference range: 3.5-77), elevated anti-thyroglobulin antibodies at the concentration of 250.00 IU/ml(reference range,<115), and increased anti-thyroid peroxidase antibodies at 44.50 IU/ml (reference range, <34). The abdominal CT scan revealed heterogeneous liver densities, suggestive of intrahepatic lymphatic




FIGURE 1
**(A–C)** Diffuse erythema and scale over face and the trunk, on admission; **(a–c)** Post-treatment improvement showing only scattered erythema on the face and almost complete improvement over the trunk.

congestion and a potential liver cyst, as well as an enlarged gallbladder exhibiting edema and splenomegaly (Figure 2A). The kidneys displayed irregular borders, accompanied by thickened bilateral renal fascia and parietal peritoneum, as well as a slightly hazy appearance of the surrounding adipose tissue. Additionally, the scan identified an 11 mm dilated appendix that was non-compressible, surrounded by a hazy fat space and several striated shadows in close proximity (see Figure 2B). A small amount of pelvic fluid was present. The PET-CT scans did not reveal any definitive evidence of malignancy (Figure 2C). Ultrasonographic evaluation of the axillary lymph nodes showed several nodes without significant increase in internal blood flow signal. Furthermore, bone marrow biopsy findings were negative for malignancy and hemophagocytosis indications were absent (Figure 3).

The RegiSCAR score was determined to be 7, supporting the diagnosis of DRESS (Table 1).[9] According to the Naranjo adverse drug reaction probability scale, it was probably that sulfasalazine induced this condition. At the same time, our patient fulfilled seven out of the eight required criteria for HLH (Table 2).[10] Ultimately, the patient was diagnosed with sulfasalazine-induced DRES triggering sHLH. Concurrent diagnoses of undifferentiated connective tissue disease and low T3 syndrome were also made. The patient was promptly transferred to the hematology department and initiated on treatment regimen based on the revised diagnostic guidelines for HLH-2004, which included dexamethasone (15 mg/day for 3 days), followed by etoposide (80 mg/day once), and azathioprine (50 mg twice a day). By the third day of therapy, fever subsided while some biochemical parameters normalized. Systemic steroid tapering occurred gradually without any relapse during the two-month follow-up period.

## Discussion

In this report, we present a comprehensive case of DRESS syndrome induced by sulfasalazine, which was further complicated

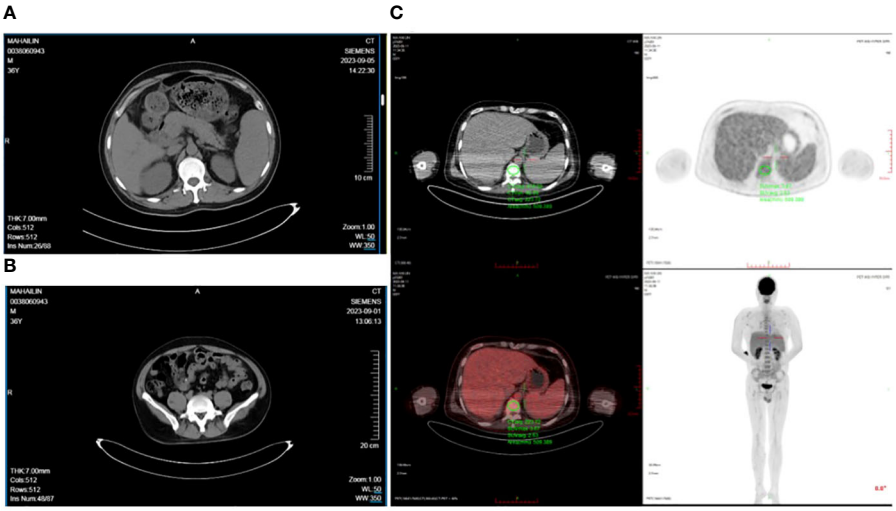



FIGURE 2
**(A)** The gallbladder wall was edematous, thickened, and rough with a slightly blurred surrounding fat space suggesting acute cholecystitis, **(B)** The appendix was slightly thickened, about 1.2 cm at its thickest, with a blurred surrounding fat space and multiple striated shadows, **(C)** PET-CT scans did not reveal any definitive signs of malignancy.

by COVID-19 coinfection and concurrent reactivation of EBV and CMV, resulting in sHLH. The diagnosis of DRESS was confirmed based on clinical manifestations including fever, rash, cervical lymphadenopathy, atypical lymphocytes, and involvement of internal organs, such as liver and spleen. The patient's RegiSCAR score, an important diagnostic tool for DRESS, was calculated to be 7 indicating a high probability of this syndrome (9). We employed the HLH-2004 criteria to diagnose and score HLH (10) in our patient who ffulfilled 7 out of the required 8 criteria. Secondary HLH is a critical condition that can be triggered by various factors. In this case, potential contributors include drug reaction, viral reactivations (EBV and CMV), as well as the patient's rheumatologic condition and COVID-19 infection. While virus reactivations are observed in over 70% of DRESS cases, not all progress to HLH. Therefore, some researchers have postulated that viruses may not be the primary factor inducing HLH but could contribute to the final prognosis (11). However, limited testing for human herpesvirus 6 (HHV-6) reactivation at our facility hindered a comprehensive understanding of its role in the etiology of this case. Furthermore, the absence of malignancy or evidence suggesting other common triggers complicates our understanding regarding the etiology behind HLH in this particular patient. Since the onset of the COVID-19 pandemic, HLH has been increasingly identified among patients during both acute phase or recovery phase from COVID-19 infection. Similarly, both HLH and Covid-19 are hyperinflammatory syndromes characterized by hypercytokinemia, and share similar pathophysiological mechanisms (12). Therefore, COVID-19 infection played an important role in contributing to the complex condition observed in this patient.

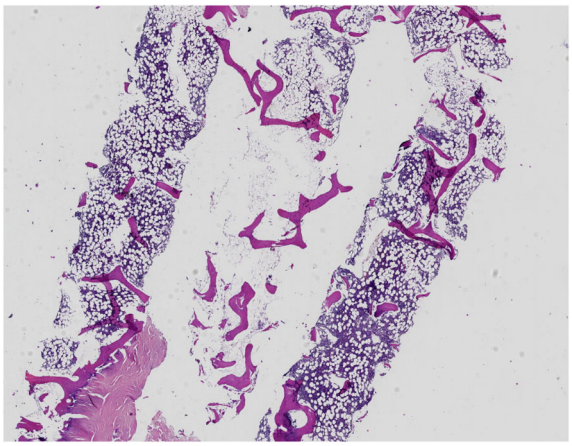


FIGURE 3
A bone marrow biopsy was negative for malignancy and did not show evidence of hemophagocytosis.

Although the development of DRESS syndrome has been associated with over 50 drugs, reports implicating sulfasalazine as a causative agent are rare, with only a few documented instances (13, 14). It is noteworthy that patients with sulfonamide-induced DRESS often exhibit deficient N-acetyltransferase activity, which may contribute to hypersensitivity reactions (15). Sulfasalazine-induced DRESS complicated by viral activation and subsequent HLH has been infrequently reported in the literature. The first case was documented by Komatsuda et al. in 2008, followed by reports from Liang et al., involving two female patients (8, 16). These cases primarily involved HLH triggered by EBV reactivation. To our knowledge, this is the first reported case of sulfasalazine-induced DRESS coinfected with COVID-19 leading to HLH (17). This highlights the importance for clinicians to be aware of this rare but potentially fatal complication. The complex and multifaceted nature of DRESS syndrome is underscored by its intricate interplay between drug hypersensitivity, viral reactivation, and immune dysregulation.

TABLE 1 RegiSCAR scoring system in DRESS for the patient (9).

| Criteria | Score | | | | patient score |
|---|---|---|---|---|---|
| | –1 | 0 | 1 | 2 | |
| Fever ≥38.5°C | No/ unknown | Yes | | | 0 |
| Enlarged lymph nodes | | No/ unknown | Yes | | 1 |
| Eosinophilia(× $10^9$/L) | | No/ unknown | ≥ 0.7 × $10^9$/L or ≥ 10% if WBC < 4.0 × $10^9$/L | ≥ 1.5 × $10^9$/L or ≥ 20% if WBC < 4.0 × $10^9$/L | |
| Atypical lymphocytosis | | No/ unknown | Yes | | 1 |
| Skin rash extent (% body surface area) | | No/ unknown | >50% Yes | | 1 |
| Skin rash suggesting DRESS[a] | | No/ unknown | Yes | | 1 |
| Skin biopsy suggesting DRESS | No | Yes/ unknown | | | |
| Organ involvement<br>Liver<br>Kidney<br>Lung<br>Muscle/heart<br>Pancreas<br>Other organ | | No | 1 organ | ≥ 2 organs | 2 |
| Rash resolution ≥ 15 d | No/ unknown | Yes | | | |
| Excluding other causes[b] | | No/ unknown | Yes | | 1 |
| Total score(maximum =9) | | | | | 7 |

DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; WBC, white blood cell. Diagnosis made based on total score: < 2 points: not DIHS; 2–3 points: possible DIHS; 4–5 points: probable DIHS; > 5 points: definitive case. Our patient received a score of 7, corresponding to a definite DIHS case.[a] Suggests DRESS if ≥ 2 purpuric lesions, infiltration, facial edema, psoriasiform desquamation.[b]If ≥ 3 negative: antinuclear antibody, blood culture, hepatitis A virus, hepatitis B virus, hepatitis C virus, chlamydia, mycoplasma.

While the complication of HLH in DRESS syndrome is not uncommon, its pathogenesis is not well understood. Although numerous cases of DRESS and HLH have been reported, most have associated HLH with concurrent infections, providing limited information on the immunologic features or establishing an unclear link between the two diseases. An analysis of 23 cases from the PubMed/MEDLINE database suggested that untreated or persistent DRESS may lead onset of HLH (18). Furthermore, it hypothesized that DRESS and HLH may share a same spectrum of immune dysfunction based on their overlapping characteristics (19). Despite similarities such as activated lymphocytes and hypercytokinemia, the marked and predominant CD8+ T-cell activation observed in HLH is not consistently seen in DRESS (20, 21), which could explain why only certain patients with DRESS develop HLH. Additionally, there may be a lack of recognition of HLH within dermatology practice leading to potential missed diagnoses and an underestimation of the coexistence between these conditions. Timely diagnosis and management are crucial for improving outcomes in patients with both DRESS and associated HLH. Moreover, the exact nature of the relationship between DRESS and HLH remains unclear; further exploration through dedicated disease cohort establishment is required to determine whether DRESS causes or manifests of a shared pathogenic process.

Both DRESS and HLH can result in significant visceral damage, with the liver being the most commonly affected internal organ. However, these diseases can also affect other internal organs such as

TABLE 2 Hemophagocytic lymphohistiocytosis diagnostic criteria (10).

| HLH-2004 criteria | patient |
|---|---|
| Fever | yes |
| Splenomegaly | yes |
| Cytopenias (affecting 2 of 3 lineages in the peripheral blood): hemoglobin, <9 g/dL; platelets, <100 109/L; neutrophils, <1 109/L | yes |
| Hypofibrinogenemia (<150 mg/dL) and/or hypertriglyceridemia (fasting >265 mg/dL) | yes |
| Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver | |
| Low or absent NK-cell activity | yes |
| Ferritin >500 ng/mL | yes |
| Elevated soluble CD25 (soluble IL-2 receptor-a) | yes |

Diagnosis of hemophagocytic lymphohistiocytosis is made when at least 5 of the 8 criteria are fulfilled.

the heart, lungs, kidneys, and other gastrointestinal tract. Although cholecystitis has been rarely reported in both DRESS and HLH cases (22), appendicitis has not been documented in existing literature. COVID-19 may present gastrointestinal symptoms and has been observed to involve the gallbladder and appendix in a limited number of cases. Acute acalculous cholecystitis and appendicitis are infrequent but clinically significant gastroenterological associations of COVID-19 that can occur without accompanying pulmonary symptoms (23, 24). Our patient exhibited common hepatorenal and splenic involvement, along with rare occurrences of cholecystitis and appendicitis. We hypothesize that excessive immune system activation and cytokine storm resulting from combined DRESS syndrome, COVID-19 infection, and HLH contributed to more extensive systemic damage. This highlights the potential for more serious consequences when DRESS coexists with HLH during a COVID-19 infection.

Endocrine abnormalities in DRESS syndrome typically manifest as delayed sequelae rather than acute symptoms. Thyroid disorders can present in various forms such as thyroiditis or sick euthyroid syndrome (25). A retrospective analysis of 27 patients revealed that five developed anomalies in thyroid function, including sick euthyroid syndrome, thyroiditis, increased free T4 levels and decreased thyrotropin levels (26). Long-term thyroid complications following recovery from DRESS can range from hyperthyroidism to hypothyroidism; antithyroid antibodies often emerge several months after resolution of the condition (27). The presentation of abnormal thyroid function in our patient further underscores the importance of vigilant endocrine follow-up in these cases.

Furthermore, it is imperative to recognize that eosinophilia, which is commonly associated with DRESS syndrome, may not be present in around one-third of cases. This absence is particularly evident among individuals concurrently experiencing hemophagocytic disorders accompanied by leukopenia (28). Our patient's case exemplifies this observation and emphasizes the need for a thorough and sophisticated diagnostic approach due to the heterogeneous nature of DRESS syndrome presentations. These findings highlight the necessity for clinicians to remain aware of the varied manifestations associated with DRESS syndrome while emphasizing continuous monitoring for potential thyroid dysfunction as part of long-term care.

DRESS is a potentially life-threatening dermatological condition, and the presence of sHLH exacerbates its severity. Early intervention plays a pivotal role in achieving favorable patient outcomes and reducing mortality risk. Pathogenesis, clinical manifestations, and laboratory markers exhibit overlapping features between DRESS and HLH, leading to similarities in their treatment approaches. Whenever feasible, addressing the underlying trigger through appropriate agents targeting infection, malignancy or autoimmune disease should be prioritized as the initial management strategy for sHLH. High-dose corticosteroids are considered first-line therapy for both conditions. Additionally, immunoglobulins and immunosuppressive agents such as methotrexate, azathioprine, and cyclosporine can be used in combination. In severe cases of HLH, etoposide may be employed as a therapeutic option. Furthermore, interleukin-1 inhibitors like anakinra, rilonacept or canakinumab can also be utilized for treating HLH (29). Tocilizumab and JAK inhibitors such as Baricitinib have shown promise in managing macrophage activation syndrome (MAS) associated with COVID-19 infection (30). In this case, initial treatment with high-dose steroids and immunoglobulins failed to yield satisfactory outcomes; however, a significant improvement was observed upon the addition of etoposide and azathioprine.

This case highlights the crucial need for a comprehensive and vigilant differential diagnosis when patients present symptoms suggestive of severe drug hypersensitivity. The correlation between DRESS syndrome and hemophagocytic lymphohistiocytosis (HLH) necessitates heightened awareness and early recognition among clinicians to facilitate timely intervention. In the management of DRESS syndrome, it is advisable to regularly monitor eosinophil levels and conduct serial complete blood counts (CBC), particularly in patients with underlying autoimmune diseases or concurrent COVID-19 infections. These specific conditions can exacerbate the severity or modify the progression of DRESS syndrome and its complications; hence close monitoring and prompt treatment are imperative.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

ML: Data curation, Writing – original draft. FL: Data curation, Writing – original draft. YD: Data curation, Writing – original draft. YZ: Data curation, Writing – original draft. XC: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Challenges in autoimmune polyendocrine syndrome type 2 with the full triad induced by anti-programmed cell death 1: a case report and review of the literature

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**Background:** Immune checkpoint inhibitors (ICPis) induce autoimmune diseases, including autoimmune polyendocrine syndrome type 2 (APS-2), which is defined as a combination of at least two of the following endocrinopathies: autoimmune thyroid disease, type 1 diabetes, and Addison's disease. Cases with the full triad are rare. We present a case of an elderly woman who developed APS-2 with the complete triad shortly after starting anti-programmed cell death 1 (anti-PD1) treatment and review the related literature.

**Case:** A 60-year-old woman, without any personal or family history of autoimmune and endocrine diseases, started the immunotherapy of anti-PD1 (camrelizumab) for squamous cell carcinoma of the urethral meatus. She developed primary hypothyroidism with elevated antibodies to thyroid peroxidase and thyroglobulin after 25 weeks of treatment, and developed primary adrenal insufficiency with adrenal crisis and fulminant type 1 diabetes with ketoacidosis after 45 weeks. Therefore, this patient met the diagnosis of APS-2 and was given multiple hormone replacement including glucocorticoid, levothyroxine and insulin therapy. Continuous improvement was achieved through regular monitoring and titration of the dosage.

**Conclusions:** Different components of APS-2 may appear at different time points after anti-PD1 administration, and can be acute and life-threatening. A good prognosis can be obtained by appropriate replacement with multiple hormones.

**Insights:** With the clinical application of ICPis to APS-2, the complexity of its treatment should be paid enough attention.

KEYWORDS

**anti-programmed cell death protein 1, autoimmune polyendocrine syndrome type 2, adrenal insufficiency, adrenal crisis, hypothyroidism, type 1 diabetes mellitus**

## Introduction

Immune checkpoint inhibitors (ICPis) are novel antitumor agents. Over-activated immune cells may also lead to clinical manifestations of autoimmune abnormalities in multiple systems of the body, namely immune-related adverse events (irAEs) (1). Endocrine glands are common targets of irAEs, particularly the thyroid and pituitary. A meta-analysis has shown that patients treated with anti-programmed cell death protein 1 (c) combined with anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) had the highest incidence of hypothyroidism and hyperthyroidism, patients treated with anti-PD1 alone were at even higher risk of hypothyroidism, and patients treated with anti-CTLA-4 alone were at even higher risk of developing pituitary inflammation (2). With the gradual increase in clinical use of ICPis, reports on the involvement of two or more glands are becoming more common. ICPis therapy can usually be continued with close monitoring. However, moderate to severe irAEs may cause severe organ dysfunction, a reduced quality of life, and even death, requiring early recognition and appropriate management (3).

Here, we present a case of autoimmune polyendocrine syndrome type 2 (APS-2) after anti-PD1 treatment in a patient with squamous carcinoma of the urethral meatus. APS-2 is defined as the occurrence of any type 1 diabetes mellitus (T1DM), autoimmune thyroiditis, and primary adrenal insufficiency (Addison's disease). In this case, the patient presented with primary hypothyroidism and T1DM with ketoacidosis and primary adrenal insufficiency with adrenal crisis, i.e., all components of APS-2 were present. In this paper, we will present the clinical manifestations and treatment of this special case and also review the reported cases of anti-PD1-induced APS-2 in the literature, to help clinicians improve their awareness and understanding of this disease when anti-PD1 is widely used today.

## Case description

1. The baseline situation: A 60-year-old female, without any personal or family history of autoimmune and endocrine diseases, was diagnosed with squamous cell carcinoma of the urethral meatus with inguinal lymph node metastasis and was treated with camrelizumab (anti-PD1, 200mg every 3 weeks) 14 times combined with anlotinib hydrochloride capsules (12mg/day) at regular intervals from February to December 2020. Before anti-PD1 administration, blood glucose level and thyroid function was normal except for a mild increase in thyroglobulin antibody (TgAb). However, the baseline adrenal function and islet function were not examined. The first application of anti-PD1 was on February 12, 2020. After the initial use of anti-PD1, the oncologist regularly monitored the patient's thyroid function, adrenal function and blood glucose and found them to be within the normal range.

2. The progress of APS-2:

(1) The first occurrence of hypothyroidism: At the 25$^{th}$ week after anti-PD1 administration, a significant increase in thyroid autoimmune antibodies (ARCHITECT Anti-Tg/Anti-TPO Reagent Kit, Chemiluminescent Micro-Particle Immunoassay) combined with hypothyroidism was found, while adrenal function remained normal during the same period, and growth hormone (GH) and sex hormone were not tested. The patient started on levothyroxine sodium tablets (L-T4) 12.5ug/d and gradually increased to 75ug/d., When tested one month after taking L-T4, thyroid function returned to normal, so 75ug/d was continued.

(2) The simultaneous occurrence of T1DM and Addison's disease: At the 45$^{th}$ week after anti-PD1 administration, the patient developed fatigue, nausea, epigastric discomfort, and vomiting, accompanied by weight loss (5 kg in 1 week). Physical examination was as follows: height 165 cm, weight 45 kg, body mass index 16.5 kg/m, body temperature 36.3°C, pulse 120 beats/min, respiration 30 breaths/min, blood pressure 127/92 mmHg, Although mentally lethargic, the patient can answer the doctor's question correctly. No alopecia, pigmentation, vitiligo, oedema or bleeding spots on the skin and mucous membranes. No abnormalities on thyroid inspection and palpation. Heart rate 120 beats/min with normal rhythm. Mild tenderness appeared in the upper abdomen without rebound pain or muscle tension. No muscle weakness or other nervous system abnormalities were found in physical examinations.

The patient had significantly elevated blood glucose, with fasting glucose of 21.06 mmol/L, reduced fasting C-peptide and insulin, urinary ketone bodies 4+, and significantly lower PH indicating diabetic ketoacidosis (DKA), and then admitted to the hospital. Other laboratory and imaging findings included negative autoimmune antibodies for type 1 diabetes (Line Immuno Assay for the Detection of Antibodies in Autoimmune Diabetes, Western blotting), normal levels of sex hormone, human growth hormone (GH), insulin growth factor-1 (IGF-1), parathyroid hormone (PTH), serum transaminase and creatinine (Table 1). The ultrasound indicated that the echo of thyroid tissue was rough without other obvious abnormality in the thyroid or parathyroid area (Figure 1). Also, the ultrasound indicated no obvious lesions in bilateral adrenals (Figure 2). Contrast-enhanced magnetic resonance imaging (MRI) of pituitary indicated no definite abnormalities (Figure 3).

(3) Diagnosis: Considering the patient had no previous history of diabetes, the sudden onset of T1DM and DKA were speculated to be drug-induced. The patient had an acute onset of DKA, fasting blood glucose > 16mmol/L, HbA1c < 8.5% and serum fasting C-peptide < 0.3ng/mL, which met the diagnostic criteria of fulminant type 1 diabetes. Decreased blood cortisol and significantly increased ACTH was found accompanied by low sodium, which supported the appearance of primary adrenal insufficiency (Addison's disease). Considering the patient's concurrent severe symptoms of nausea, vomiting, and lethargy, we diagnosed adrenal crisis. The patient had T1DM, primary hypothyroidism together with Addison's disease, therefore, she can be diagnosed as APS-2 secondary to anti PD-1 administration.

(4) Treatment: The treatment of DKA included sufficient liquid supplementation, insulin therapy, and immediate correction of ionic disturbances. Finally, due to economic reasons, the patient did not choose insulin pump, but chose subcutaneous injection of short-acting insulin three times a day and long-acting insulin once a

TABLE 1 Laboratory and hormonal test results.

| Test | Baseline [a] | Week 12 | Onset of primary hypothyroidism (week 25) | Onset of TIDM and Addison's disease (week 45) | Week 79 | Reference Range |
|---|---|---|---|---|---|---|
| FT3 (pmol/L)[b] | 5.36↑ | 15.49↑ | <1.64↓ | 5.79↑ | 2.87 | 2.63–5.71 |
| FT4 (pmol/L)[b] | 14.82 | 4.96↓ | 5.27↓ | 15.5 | 14.24 | 9.01–19.05 |
| TSH (uIU/mL)[b] | 2.23 | 0.8792 | >100↑ | 1.3773 | 15.6720↑ | 0.3–4.8 |
| TPOAb (IU/mL) | 5.30 | 12.67↑ | 412.65↑ | 174.24↑ | 8.60↑ | 0–5.61 |
| TgAb (IU/mL) | 149.45↑ | >1000.00↑ | >1000.00↑ | >1000.00↑ | 37.92↑ | 0–4.11 |
| Cortisol (μg/dL) | – | 14.88 | – | 3.41↓ | 9.00 | 6.02–18.4 |
| ACTH (pg/mL) | – | 41.91 | – | 313.16↑ | 10.59 | 7.2–63.3 |
| Estradiol (pg/mL) | – | – | – | <15.0 | – | – |
| Testosterone (ng/mL) | – | – | – | 0.21 | – | – |
| LH (mIU/mL) | – | – | – | 54.70 | – | 10.87–58.64 |
| FSH (mIU/mL) | – | – | – | 96.83 | – | 16.74–113.59 |
| PRL (ng/mL) | – | – | – | 7.27 | – | 2.74–19.64 |
| Prog (ng/mL) | – | – | – | 0.29 | – | 0.01–0.78 |
| GH (ng/mL) | – | – | – | 1.274 | – | 0.014–5.219 |
| IGF-1 (ng/mL) | – | – | – | 43.29 | – | 60–350 |
| PTH(pg/mL) | – | – | – | 27.0 | – | 12–88 |
| FBG[b] | – | 6.1 mmol/L (109.8 mg/dL) | – | 25.72 mmol/L↑ (462.96 mg/dL) | – | 3.9-6.1 mmol/L (70.2–109.98 mg/dL) |
| FCP (ng/mL) | – | – | – | 0.15 | – | 0.78–5.19 |
| Fins (mU/L) | – | – | – | 0.3 | – | 2.3–11.8 |
| GA (%) [b] | – | – | – | 20.05 | – | – |
| HbA1c (%)[b] | – | – | – | 5.7 | 7.6 | – |
| K+ (mmol/L)[b] | 3.9 | 2.93 | – | 5.66 | 3.71 | 3.5–5.5 |
| Na+ (mmol/L)[b] | 141.5 | 139.7↑ | – | 126 | 128.3 | 136–145 |
| Cl−(mmol/L)[b] | 103.0 | 103.9 | – | 92.6 | 94.1 | 96–108 |
| GADA | – | – | – | negative | – | – |
| IA2A | – | – | – | negative | – | – |
| ICA | – | – | – | negative | – | – |
| IAA | – | – | – | negative | – | – |
| Amylase | | | | 145.6 | 47.4 | 35–135 |
| Lipase | – | – | – | 269.7 | 8.6 | 5.6–51.3 |

Baseline [a] referred to the time before the initial use of anti-PD1. [b], the measurement of electrolytes, FPG, GA, HbA1c and thyroid function were much more frequent than we can show, and we selected the values of the above several time points for display in this table. "-" means that the value was not measured. Abbreviations: FT4, free thyroxine; FT3, free triiodothyroxine; TSH, thyroid stimulating hormone; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; ACTH, adrenocorticotrophic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin; Prog, progesterone; GH, human growth hormone; IGF-1, insulin-like growth factor 1; PTH, parathyroid hormone; FBG, fasting blood glucose; FCP, fasting c-peptide; Fins. fasting insulin; HbA1c, glycated haemoglobin; GADA, glutamic acid decarboxylase antibody; IA2A, insulinoma-associated protein 2 antibody; ICA, islet cell antibody; IAA, insulin antibody; DKA, adrenal cortex antibody.
"↑" means higher than the reference range and "↓" means lower than the reference range.

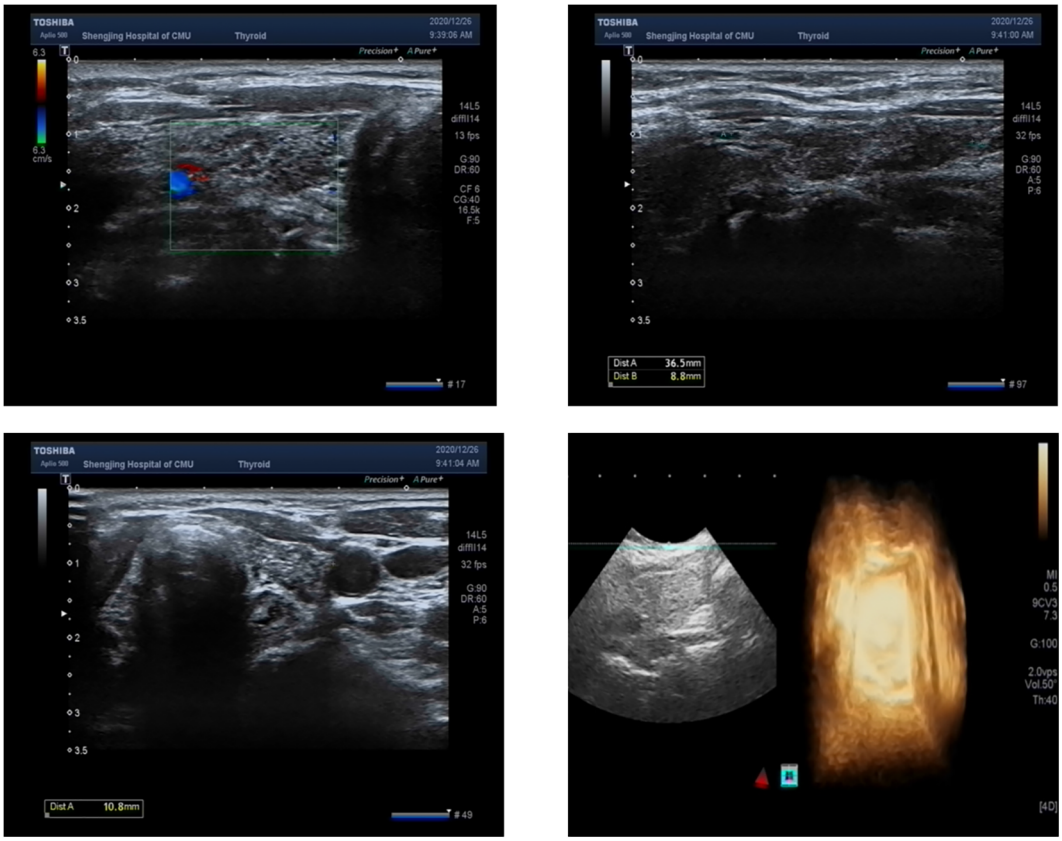



FIGURE 1
Ultrasound showing normal thyroid and parathyroid glands.

day for insulin replacement. The treatment of adrenal crisis involved sufficient liquid supplementation, glucocorticoid replacement including hydrocortisone intravenous infusion 200 mg/day and gradual reduction to oral dosage of 15mg/day. After pituitary crisis and ketoacidosis were corrected, the patient's condition was greatly improved and allowed to leave the hospital.

3. Follow-up: This patient was given multiple hormone replacement including: (1) glucocorticoid replacement: 10 mg hydrocortisone p.o. in the morning and 5 mg p.o. in the afternoon, and was suggested to increase the glucocorticoid dose by 3–5 times when under stress; (2) thyroid hormone supplementation: levothyroxine 75 μg p.o. in the morning; (3) insulin therapy of T1DM: insulin glargine 7 U subcutaneously before bedtime, insulin aspart 4 U before three meals, and the patient was taught and trained to titrate insulin dosage according to blood sugar levels. The patient's blood glucose fluctuated between 4 and 14 mmol/L (72-252mg/dL), with occasional appearance of hypoglycaemia. About six 6 months after discharge from the hospital, the patient measured HbA1c 7.6%, and the thyroid function and serum ion levels were in the normal range. Up to the last visit in our hospital, the hormone supplements remained the same dose.

As to the treatment of squamous cell carcinoma of the urethral meatus, the patient refused to continue using anti-PD1 because of the occurrence of APS-2. After full discussion with the doctor, the patient still chose to start chemotherapy (cisplatin combined with gemcitabine hydrochloride, which was adjusted to gemcitabine monotherapy due to poor tolerance). Six months later, local boost radiotherapy was performed, and the tumor was reduced after radiotherapy. Eleven months after discharge, the tumor progressed and the physical condition was not good. The patient was given Paclitaxel liposome for injection chemotherapy until January 27, 2022, when the last chemotherapy was performed. Since the last visit, the patient could not be contacted and was lost to follow-up.

## Discussion and conclusions

This is a case of APS-2 with the complete triad (type 1 diabetes, hypothyroidism, and adrenal insufficiency) following treatment with anti-PD1. In the first reported case (4), a patient in their 70s developed the full triad of APS-2 shortly after commencing anti-PD1 for unresectable melanoma in 2019. The primary manifestation of APS is the impaired function of multiple endocrine glands caused by autoimmune reactions. APS-2 is more frequent in women and usually develops in the 3rd to 4th decade of life. It is thought to be polygenic and is associated with

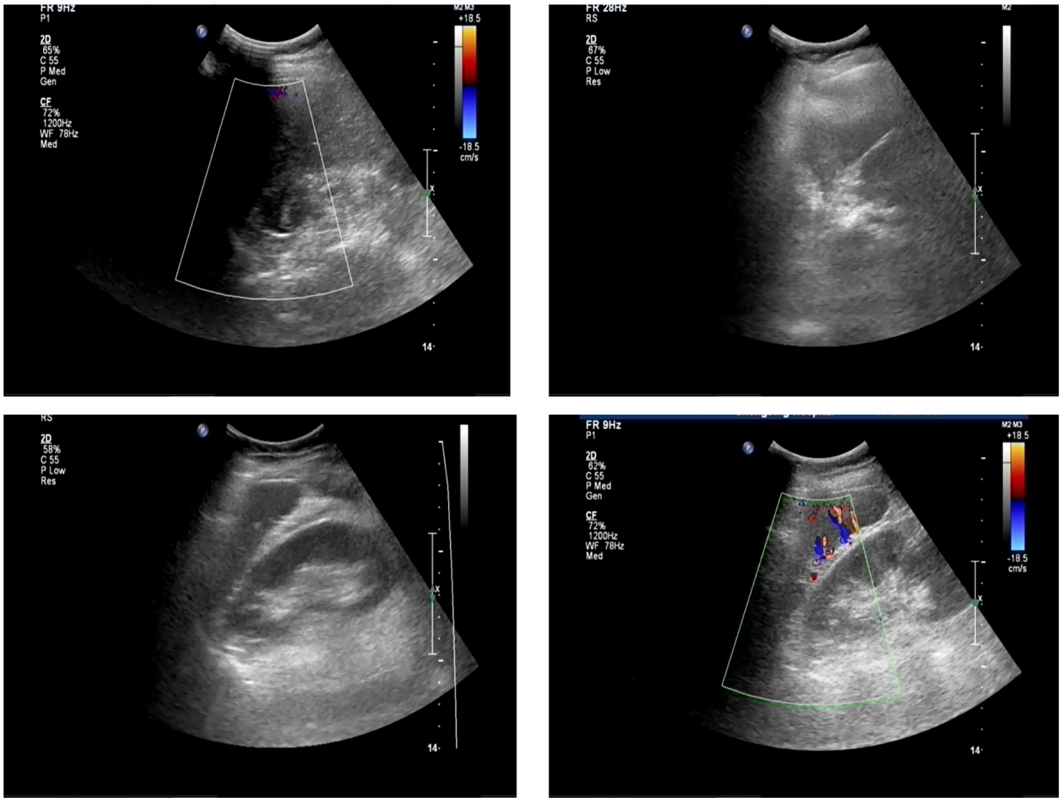


FIGURE 2
Ultrasound showing normal bilateral adrenal glands.

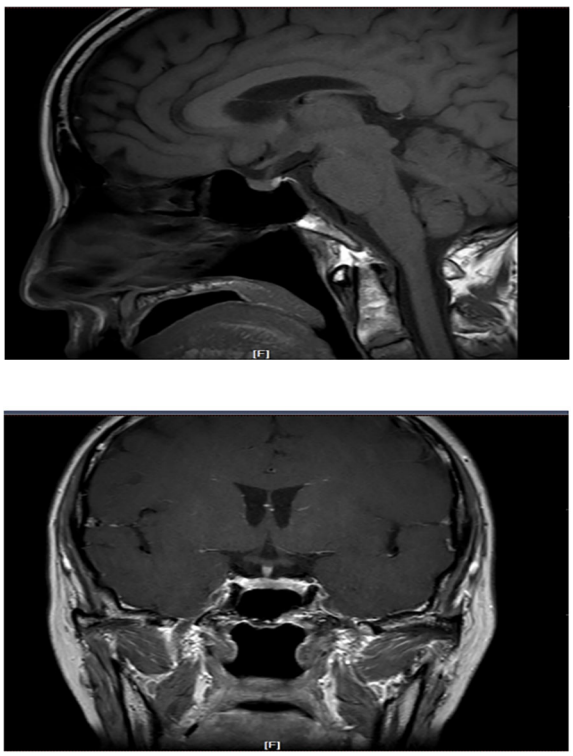


FIGURE 3
MRI with contrast showing a normal-sized pituitary and normal enhancement.

mutations in cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and human leukocyte antigen (HLA) DR3 and DR4 serotypes (5).

The initial endocrine gland injury in this patient involved the thyroid. The patient developed hypothyroidism 25 weeks after the first use of camrelizumab, presenting as significantly elevated TSH, TPOAb, and TgAb titres. The patient was diagnosed with primary hypothyroidism secondary to autoimmune destruction of the thyroid due to pharmacological factors rather than damage to the anterior pituitary. Six months after the onset of primary hypothyroidism, the patient developed fulminant type 1 diabetes with diabetic ketoacidosis as the first symptom. The patient met all three diagnostic criteria established in a 2007 Japanese study of fulminant type 1 diabetes (6): (1) Occurrence of diabetic ketosis or ketoacidosis soon (around 7 days) after the onset of hyperglycaemic symptoms (elevation of urinary and/or serum ketone bodies at first visit); (2)Plasma glucose level ≥16.0 mmol/l (>288 mg/dl) and glycated haemoglobin (HbA1c) level <8.5% at first visit; (3) Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/ml (<0.10 nmol/l) and <0.5 ng/ml (<0.17 nmol/l) after intravenous glucagon (or after meal) load at onset. Under the stress of diabetic ketoacidosis, the patient exhibited a potential latent adrenocortical insufficiency with an initial presentation of "adrenal crisis." We need to distinguish whether this adrenal insufficiency is primary or secondary. Common laboratory findings of primary adrenal insufficiency are a random or early-morning decrease in cortisol and an increase in ACTH, in

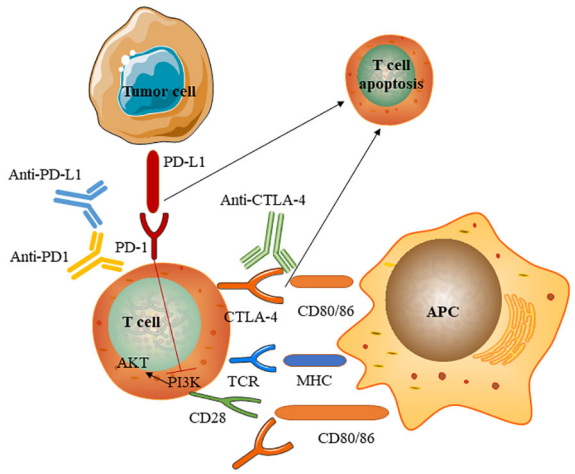



FIGURE 4
Mechanism of immune checkpoints and immune checkpoint inhibitors. Immune checkpoint inhibitors are monoclonal antibodies that target the CTLA-4 and PD-1 receptors and the PD-1 ligand PD-L1.T cell activation requires two signals: first, antigen recognition by the T cell receptor (TCR) following antigen presentation by major histocompatibility complex (MHC) class II molecules on the surface of antigen- presenting cells(APC); and, second, signal modulation by CD80 or CD86 binding to the CD28 receptor. CTLA-4 expressed on conventional T-cells interacts with its ligands CD80 and CD86 to initiate inhibitory signalling, enhance adhesion, and compete with CD28 to block interaction between CD28 and CD80/CD86.CTLA-4 inhibitors block CTLA-4 binding to CD80 or CD86 to promote T-cell activation PD-1 is a surface receptor that is expressed by T cells and promotes apoptosis of antigen- specific T cells and reduces apoptosis of regulatory T cells through its interaction with its ligand, PD- L1, which is expressed by tumour cells. Engagement of PD-1 with PD-L1 induces an intracellular inhibitory pathway to inhibit costimulatory CD28-activated PI3K pathways, leading to T-cell exhaustion. PD-1 and PD- L1 inhibitors block the PD-1–PD- L1 interaction, facilitating T cell activation.

some cases with the detection of 21-hydroxylase antibody (21-OH Ab) and adrenal cortex antibody (ACA) (7, 8). Imaging often indicates bilateral enlargement of the adrenal glands with clear margins. Secondary adrenal insufficiency presents with a random or early-morning decrease in cortisol without a substantial increase or even a decrease in ACTH and may be combined with a decrease in other endocrine hormones of the pituitary gland (e.g. TSH, LH, or FSH) (9). The reduced blood cortisol level and significantly elevated ACTH were consistent with primary adrenal insufficiency (Addison's disease). Moreover, although adrenal crisis was diagnosed at the same time as diabetes mellitus, it may have appeared earlier and presented only as mild hyponatremia or it may have appeared after the major stress of diabetic ketoacidosis.

Various difficulties were encountered during the treatment of this patient. (1) The lack of glucocorticoids reduced the ability to regulate blood glucose; accordingly, the patient was more prone to large fluctuations in blood glucose and was at higher risk of hypoglycaemia than that of other patients with type 1 diabetes. (2) Insufficient hydrocortisone supplementation induces adrenal crisis, whereas excessive supplementation is detrimental to glycaemic control. Therefore, every effort needed be made to maintain a balance between the doses of supplemental glucocorticoids and insulin.

Immune checkpoints are small molecules present on the cell surface of T-lymphocytes. They play critical roles in maintaining immune homeostasis and self-tolerance and modulating the duration and amplitude of physiological immune responses. Some immune checkpoints, such asCTLA-4 and PD-1, mediate inhibitory signals to blunt T-cell activity. ICPis serve to induce an anti-tumour immune response by blocking immune checkpoints. Normally, immune checkpoints downregulate T cell responses and act to protect the body from possibly damaging immune responses, such as autoimmune disease. However, tumours can evade the immune system through the activation of immune checkpoints and inhibition of the T cell response. Although the exact mechanism by which ICPis induce apoptosis remains unclear, We briefly summarise the mechanism of action of immune checkpoints and immune checkpoint inhibitors (Figure 4) (10, 11). The mechanisms underlying immune-related adverse events owing to ICPis depend on the type of ICPis therapy used (anti-PD1 or anti-PD-L1 versus anti-CTLA-4). anti-CTLA-4 can induce several cellular alterations, such as T cell activation and proliferation, impaired CD4+CD25+ regulatory T cell (Treg cell) survival and increased counts of type 17 T helper cells, in addition to the induction of cross-reactivity between anti-tumour T cells and antigens on healthy cells and autoantibody production. PD-1 and PD- L1 inhibitors reduce Treg cell survival and increase cytokine production (12).

A meta-analysis has revealed that endocrine disorders are among the most common irAEs in ICPis therapy (13). In particular, anti-CTLA-4 therapy was associated with pituitary inflammation, anti-PD1 therapy was associated with thyroid dysfunction, and the combination of anti-CTLA-4 and anti-PD1 therapy was associated with the highest incidence of ICPis-associated endocrine disorders. ICPis-associated endocrine disorders typically occur within 12 weeks after the start of ICPis treatment (13); however, they can occur months to years after ICPis are started. Some ICPis-related endocrine disorders may resolve spontaneously, but adrenal insufficiency and primary hypothyroidism are typically persistent (13). Similarly, in another meta-analysis, the most common endocrine disorders were hypothyroidism and hyperthyroidism, followed by hyperglycaemia, thyroiditis, and adrenal insufficiency. The risk ratios for adverse events were RR = 26.09% for adrenocortical insufficiency, RR = 26.67% for pituitary inflammation, and RR = 26.92% for hypopituitarism (14).

To review all published cases of APS-2 triggered by anti-PD1, PubMed was searched using the terms "autoimmune polyendocrine syndrome type 2" and "immune checkpoint inhibitors," revealing 34 relevant case reports since 2000 (Table 2). All 34 patients were treated with anti-PD1, of which five were treated with anti-PD1 in conjunction with anti-CTLA-4. The largest proportion of patients were in the United States (9/34, 26.4%), with other cases reported in various countries, including France, Australia, the United Kingdom, and Ireland. The median age at diagnosis of APS-2 was 61 years. Of the 34 patients, 15.7% (5/34) had a history of autoimmune thyroid disease. The tumour types were primarily melanoma (20/34, 58.8%) and lung cancer (7/34, 20.6%), with cases of renal cell carcinoma and cervical cancer. APS-2 includes type 1 diabetes, autoimmune thyroid disease, and Addison's disease. Among them, 88.2% (30/34)

TABLE 2 Summary of case reports of APS-2 induced by anti-PD1.

| First author | Year | Age (y) | Gender | Country | Tumour type | PD-1 inhibitors | Time[a] (weeks) | First onset disease | Conditions | Auto-Ab | HLA type | Response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hakami (15) | 2019 | 52 | Male | Ireland | melanoma | pembrolizumab | 21 | hypothyroidism | Primary hypothyroidism<br>T1DM | (-) | NR | CR |
| Sakurai (16) | 2018 | 68 | Female | Japan | RCC | nivolumab | 2 | Painless thyroiditis | Thyroiditis* (hypothyroidism)<br>T1DM (fulminant T1DM) | TPOAb(+)<br>TgAb(+) | DRB1*09: 01<br>DQB1*03: 03 | CR |
| Gauci (17) | 2017 | 73 | Male | France | melanoma | nivolumab | 6 | DKA | Graves' disease* (hyperthyroidism)<br>T1DM (fulminant T1DM) | GADA(+)<br>IA2A(+)<br>ZnT8A(+) | NR | CR |
| Paepegaey (8) | 2017 | 55 | Female | France | melanoma | pembrolizumab | 12 | thyroiditis | Thyroiditis (primary hypothyroidism)<br>autoimmune adrenalitis (adrenal crisis) | anti-21-OH (+)<br>ACA(+) | NR | PD |
| Li (18) | 2017 | 63 | Male | USA | NSCLC | nivolumab | 4 | DKA | T1DM<br>Thyroiditis<br>(Primary hypothyroidism) | GADA(+)<br>TPOAb(+) | NR | PD |
| Alhusseini (19) | 2017 | 65 | Male | USA | NSCLC | pembrolizumab + ipilimumab | 3 | DKA | T1DM<br>Thyroiditis<br>(hyperthyroidism/hypothyroidism) | GADA(+)<br>isletAb(+)<br>IAA(+)<br>TPOAb(+) | NR | PR |
| Lowe (20) | 2016 | 54 | Male | USA | melanoma | nivolumab + ipilimumab | 2 | Autoimmune thyroiditis | autoimmune thyroiditis (hyperthyroidism/hypothyroidism)<br>T1DM (fulminant T1DM)<br>hypophysitis (adrenal crisis) | GADA(+)<br>TRAb(+)<br>microsomalAb (+) | DQB1*0602 | CR |
| Kong (21) | 2016 | 68 | Male | Korea | NSCLC | pembrolizumab | 21 | DKA | T1DM (fulminant T1DM)<br>Subclinical hyperthyroidism | (-) | DRB1*09: 01<br>DQB1*03: 03 | PR |
| Hansen (22) | 2016 | 58 | Male | USA | melanoma | pembrolizumab | NR | hypothyroidism | hypothyroidism<br>T1DM | GADA(+) | NR | CR |
| Mellati (23) | 2015 | 66 | Female | USA | SCC jaw | PD-1 inhibitor | 7 | DKA | T1DM<br>hypothyroidism | TPOAg(+)<br>GADA(+) | DR3-DQ2<br>DR4-DQ8 | NR |
| Hughes (24) | 2015 | 55 | Female | USA | melanoma | nivolumab + ipilimumab | 20 | NR | autoimmune thyroid disease* (hypothyroidism)<br>T1DM | (-) | A2.1+<br>DR4+ | NR |
| Hughes (24) | 2015 | 64 | Female | USA | melanoma | pembrolizumab | < 4 | NR | autoimmune thyroid disease* (hypothyroidism)<br>T1DM | (-) | DR4+ | NR |

*(Continued)*





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TABLE 2 Continued

| First author | Year | Age (y) | Gender | Country | Tumour type | PD-1 inhibitors | Time[a] (weeks) | First onset disease | Conditions | Auto-Ab | HLA type | Response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gunjur (4) | 2019 | 78 | Female | Italy | melanoma | pembrolizumab | 3 | DKA | T1DM (fulminant T1DM)<br>AD (acute adrenal crisis)<br>Primary hypothyroidism | GADA(+)<br>IA-2A(+) | DRB1*04.16<br>DRB1*02.05<br>DRB1*01.03 | CR |
| Hofmann (25) | 2016 | 70 | Female | Germany | melanoma | nivolumab | NR | NR | T1DM<br>hyperthyroidism | (-) | NR | CR |
| Gaudy (26) | 2015 | 44 | Female | NR | melanoma | pembrolizumab | NR | DKA | T1DM (fulminant T1DM)<br>autoimmune thyroiditis* | (-) | NR | CR |
| Scott (27) | 2018 | 58 | Male | Australia | melanoma | pembrolizumab + ipilimumab | 2 | subclinical hyperthyroidism | T1DM<br>subclinical hyperthyroidism | (-) | NR | NR |
| Kurihara (28) | 2020 | 48 | Male | Japan | Parotid gland adenocarcinoma | nivolumab | 16 | thyrotoxicosis | T1DM<br>Graves' disease | TRAb(+) | DRB1*04:05 | PD |
| Filette (29) | 2019 | 61 | Male | Belgium | NSCLC | pembrolizumab | 8 | DKA | T1DM<br>Thyroiditis<br>(Subclinical hyperthyroidism) | GADA(+) | DRB1*04<br>DQA1*03:01<br>DQB1*03:02 | NR |
| Hong (30) | 2020 | 76 | Male | Korea | Lung cancer | pembrolizumab | 11 | DKA | T1DM<br>Addison's disease | (-) | NR | PR |
| Galligan (31) | 2018 | 82 | Male | Australia | SCC (oropharynx) | pembrolizumab | 9 | hyperglycaemia with ketosis | T1DM<br>hypothyroidism | (-) | DRB1*04 (DR4)<br>DQB1*03:02 (DQ8) | SD |
| Galligan (31) | 2018 | 23 | Male | Australia | melanoma | pembrolizumab | 8 | DKA | T1DM<br>Thyroiditis (hypothyroidism) | GADA(+)<br>TPOAg(+)<br>IAA (+) | DRB1*03 (DR3),<br>DRB1*04 (DR4),<br>DQB1*03:02 (DQ8) | PR |
| Marchand (32) | 2019 | 83 | Male | Belgium | melanoma | pembrolizumab | NR | NR | T1DM<br>Hashimoto's disease | TPOAg(+) | DRB1*01:01<br>DQA1*01<br>DQB1*05:01/<br>DRB1*16:01<br>DQA1*01PD<br>DQB1*05:02" | PR |
| Marchand (32) | 2019 | 65 | Male | Belgium | melanoma | pembrolizumab | NR | NR | T1DM (Fulminant T1DM)<br>Hashimoto's disease | TPOAg(+) | DRB1*04:01<br>DQA1*02<br>DQB1*02:02/<br>DRB1*07:01<br>DQA1*03<br>DQB1*03:01 | PD |

*(Continued)*





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TABLE 2 Continued

| First author | Year | Age (y) | Gender | Country | Tumour type | PD-1 inhibitors | Time[a] (weeks) | First onset disease | Conditions | Auto-Ab | HLA type | Response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hescot (33) | 2018 | 33 | Female | France | SCC (cervical) | pembrolizumab | 6 | autoimmune thyroiditis | AD (adrenal crisis)<br>Autoimmune thyroiditis (hypothyroidism) | TPOAg(+)<br>21-OHAb(+) | NR | PR |
| Humayun (34) | 2016 | 55 | Male | UK | melanoma | Ipilimumab/ pembrolizumab | 2 | pan-hypopituitarism | hypophysitis (adrenal insufficiency)<br>T1DM | – | NR | SD |
| Kuru (35) | 2017 | 83 | Female | USA | melanoma | Nivomulab | 20 | thyroiditis | autoimmune thyroiditis<br>hypophysitis (acute adrenal crisis) | TPOAg(+) | NR | PR |
| Marchand (36) | 2017 | 55 | Male | NR | pulmonary pleomorphic carcinoma | Nivolumab | 19 | DKA | T1DM<br>hypophysitis<br>(adrenal insufficiency) | – | NR | PR |
| Sum (37) | 2018 | 75 | Male | USA | melanoma | Nivolumab + ipilimumab | NR | T1DM | T1DM<br>hypophysitis (adrenal insufficiency)<br>subclinical hypothyroidism | GADA(+) | NR | CR |
| Tzouli (38) | 2018 | 56 | Female | UK | NSCLC | Nivolumab | NR | DKA | T1DM (fulminant T1DM)<br>hypothyroidism | GADA(+) | NR | PR |
| Okahata (39) | 2019 | 52 | Female | Japan | Breast cancer | Nivolumab | 28 | adrenal insufficiency | secondary adrenal insufficiency<br>T1DM (fulminant T1DM) | – | DRB1*14:05, 14:06 | NR |
| Lupi (40) | 2019 | 80 | Male | Italy | melanoma | Nivolumab | 6 | thyrotoxicosis | autoimmune hypothyroidism<br>hypophysitis (acute adrenal crisis) | TgAb(+)<br>TPO(+) | NR | SD |
| Lupi (40) | 2019 | 43 | Female | Italy | melanoma | Pembrolizumab | 4 | thyrotoxicosis | Autoimmune hypothyroidism<br>T1DM<br>hypophysitis (acute adrenal crisis) | TPOAb(+)<br>APA(+) | DQB1*02<br>DQB1*0602<br>DQA1*0102 | SD |
| Machado (41) | 2019 | 55 | Male | Portugal | NSCLC | Nivolumab | 14 | thyroiditis | painless thyroiditis<br>hypophysitis (secondary adrenal insufficiency) | (-) | NR | PR |
| Mayumi (42) | 2021 | 59 | Male | Japan | oral mucosal malignant melanoma | nivolumab | 4 | hypothyroidism | hypothyroidism<br>secondary adrenal insufficiency<br>T1DM | NR | NR | NR |

auto-Ab, auto-antibody; IAA, insulin antibody; IA–2A, insulinoma-associated protein 2 antibody; GADA, glutamic acid decarboxylase antibody; ZnT8A, zinc transporter 8 antibodies; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TRAb, thyroid-stimulating hormone receptor antibody; 21-OHAb,21-hydroxylase antibody; ACA, adrenal cortex antibody; APA, anti-pituitary antibody; DKA, diabetes ketoacidosis; T1DM, type 1 diabetes mellitus; AD, Addison's disease; APS-2, autoimmune polyendocrine syndrome type II; HLA, human leukocyte antigen; SCC jaw, sarcomatoid squamous cell carcinoma of the jaw; NSCLC, non-small-cell lung carcinoma; CR, complete response; PR, partial response; NR, not reported, PD, progressive disease; SD, stable disease
Time[a] (weeks): weeks ever since the start of anti-PD1 therapy to onset of APS-2. *auto-immune condition preceded treatment with anti-PD1 axis therapy.





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developed autoimmune thyroid disease, 85.3% (29/34) developed type 1 diabetes, 35.3% (12/34) developed Addison's disease, and related autoantibodies were detected in 58.8% (20/34) of cases.

There is no specific differential diagnosis for patients with APS-2. Autoantibodies such as thyroid peroxidase antibodies in AITD, GADA in type 1 diabetes mellitus(T1DM), and 21-OH Ab in Addison's disease contribute to the diagnosis and follow-up (43). The relationship between ICPis-related T1DM and islet autoantibodies remains unclear, and islet autoantibodies are present in about half of cases according to a review (44). Compared to islet autoantibody-negative individuals, islet autoantibody-positive individuals have a shorter onset and a higher rate of diabetic ketoacidosis (45). However, some patients treated with ICPis are antibody-positive but do not develop diabetes (46). A Japanese study also reported no correlation between thyroid autoantibodies and ICPis-related thyroid dysfunction (47). Therefore, the relationship between endocrine gland damage caused by ICPis and autoantibodies remains unclear, and threshold values for treatment and outcome prediction warrant further study.

The present case emphasises that immunosuppression-induced endocrine adverse reactions may involve multiple glands, especially the coexistence of life-threatening diabetic ketoacidosis and adrenal crisis, making early recognition, rapid diagnosis, and timely treatment especially important. In particular, the following points are noted. (1) When ICPis damage one gland, it is important to consider whether there is concomitant autoimmune damage to other glands. (2) It is recommended that all patients with hypothyroidism be evaluated for adrenal function prior to treatment. Special attention should be paid to clinical manifestations after treatment with levothyroxine, and the combination of adrenal insufficiency should be considered if fatigue worsens or if nausea, vomiting, or other discomfort develops. If both hypothyroidism and hypoadrenalism are present, levothyroxine alone may induce adrenal crisis. (3) Physicians should be aware of concomitant adrenal insufficiency in patients with T1DM when the dose of insulin required is lower than before, and blood glucose monitoring should be enhanced when glucocorticoids are given to patients with hypoadrenalism.

With the increased use of ICPis in clinical practice, several guidelines/consensus statements recommend the management of immune-related adverse events caused by ICPis (3, 48). Detailed medical history (especially the history of endocrine and autoimmune diseases), rational baseline screening (including adrenal function, thyroid function, and blood glucose tests), and regular follow-up (monitoring changes in endocrine indexes and the development of symptoms and signs) are needed to detect endocrine gland damage in a timely manner and avoid life-threatening diabetic ketoacidosis, adrenal crisis, thyroid crisis, and other serious events.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the studies involving humans because the study did not identify data. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

QP: Writing – original draft. PL: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Glossary

| | |
|---|---|
| APS-2 | autoimmune polyendocrine syndrome type 2 |
| ICPis | immune checkpoint inhibitors |
| irAEs | immune-related adverse events |
| anti-PD1 | anti-programmed cell death protein 1 |
| anti-PD-L1 | anti-programmed cell death ligand 1 |
| anti-CTLA-4 | anti-cytotoxic T-lymphocyte antigen 4 |
| T1DM | type 1 diabetes mellitus |
| TgAb | thyroglobulin antibody |
| ACTH | adrenocorticotrophic hormone |
| FT3 | free triiodothyroxine |
| FT4 | free thyroxine |
| TSH | thyroid stimulating hormone |
| TPOAb | thyroid peroxidase antibody |
| LH | luteinising hormone |
| FSH | follicle-stimulating hormone |
| GH | human growth hormone |
| GADA | glutamic acid decarboxylase antibody |
| IA2A | insulinoma-associated protein 2 antibody |
| ZnT8A | zinc transporter 8 antibody |
| ICA | islet cell antibody |
| IAA | insulin antibody |
| DKA | diabetes ketoacidosis |
| 21-OH Ab | 21-hydroxylase antibody |
| CA | adrenal cortex antibody |

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# Antiphospholipid antibody-related hepatic vasculitis in a juvenile after non-severe COVID-19: a case report and literature review

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Antiphospholipid antibodies (aPL) are both laboratory evidence and causative factors for a broad spectrum of clinical manifestations of antiphospholipid syndrome (APS), with thrombotic and obstetric events being the most prevalent. Despite the aPL-triggered vasculopathy nature of APS, vasculitic-like manifestations rarely exist in APS and mainly appear associated with other concurrent connective tissue diseases like systemic lupus erythematous. Several studies have characterized pulmonary capillaritis related to pathogenic aPL, suggesting vasculitis as a potential associated non-thrombotic manifestation. Here, we describe a 15-year-old girl who develops hepatic infarction in the presence of highly positive aPL, temporally related to prior non-severe COVID-19 infection. aPL-related hepatic vasculitis, which has not been reported before, contributes to liver ischemic necrosis. Immunosuppression therapy brings about favorable outcomes. Our case together with retrieved literature provides supportive evidence for aPL-related vasculitis, extending the spectrum of vascular changes raised by pathogenic aPL. Differentiation between thrombotic and vasculitic forms of vascular lesions is essential for appropriate therapeutic decision to include additional immunosuppression therapy. We also perform a systematic review to characterize the prevalence and clinical features of new-onset APS and APS relapses after COVID-19 for the first time, indicating the pathogenicity of aPL in a subset of COVID-19 patients.

KEYWORDS

**antiphospholipid antibodies, COVID-19, pediatrics, vasculitis, non-thrombotic manifestation, vasculopathy**

# 1 Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characteristic of arterial, venous, or microvascular thrombosis, obstetric morbidity, and well-defined non-thrombotic manifestations in the setting of persistent antiphospholipid antibodies (aPL) (1, 2). aPL, composed of a diverse family of acquired autoantibodies, are recognized as causative factors for clinical manifestations of APS (3). Both genetic and environmental elements could exert as precipitating factors for aPL production, with infection being the most prevalent trigger (4–6). In the recent COVID-19 pandemic, the observed high prevalence of aPL has been reported, yet the potential pathogenicity of these antibodies remains uncertain and controversial (7). The molecular mimicry between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral proteins and native tissues and the neoepitope caused by SARS-CoV-2-induced oxidative stress probably contribute to aPL generation (8). In addition to widely reported aPL-related thrombosis, associated non-thrombotic manifestations are emerging with considerable evidence (9). Compared with adult patients, aPL-related non-thrombotic complications, both criteria and non-criteria, are more frequently presented in pediatric patients (10). aPL-related vasculitis is characterized as the inflammation of vessel walls and is only well-confirmed in pulmonary capillaries as diffuse alveolar hemorrhage (DAH) (11). This rare manifestation can result in occlusion of vessel lumen in the absence of thrombus, which might make it clinically indistinguishable to thrombotic events. Differentiation between thrombotic and vasculitic causes of aPL-related vascular damage is essential for proper therapeutic decision to adequately include immunosuppression therapy (12). Here, we describe an uncommon case of a young girl with aPL-related vasculitis-induced liver infarction after non-severe COVID-19 infection, providing valuable information for development of pathogenic aPL in infectious diseases and aPL-related vasculitic manifestations.

# 2 Case report

A 15-year-old girl presented to the emergency department with hyperpyrexia and abdominal pain persisting for over a month. Initial laboratory results revealed elevated inflammation markers, liver dysfunction, and prolonged activated partial thromboplastin time (aPTT) (62.2 s; normal: 25–37 s) and prothrombin time (PT) (17.8 s; normal: 11–14 s). There were no bleeding signs clinically. Abdominal CT demonstrated liver "abscess-like" lesions (Figures 1A, B) as well as possible cholecystitis (Figures 1C, D), and the histopathological examination of liver biopsy specimens

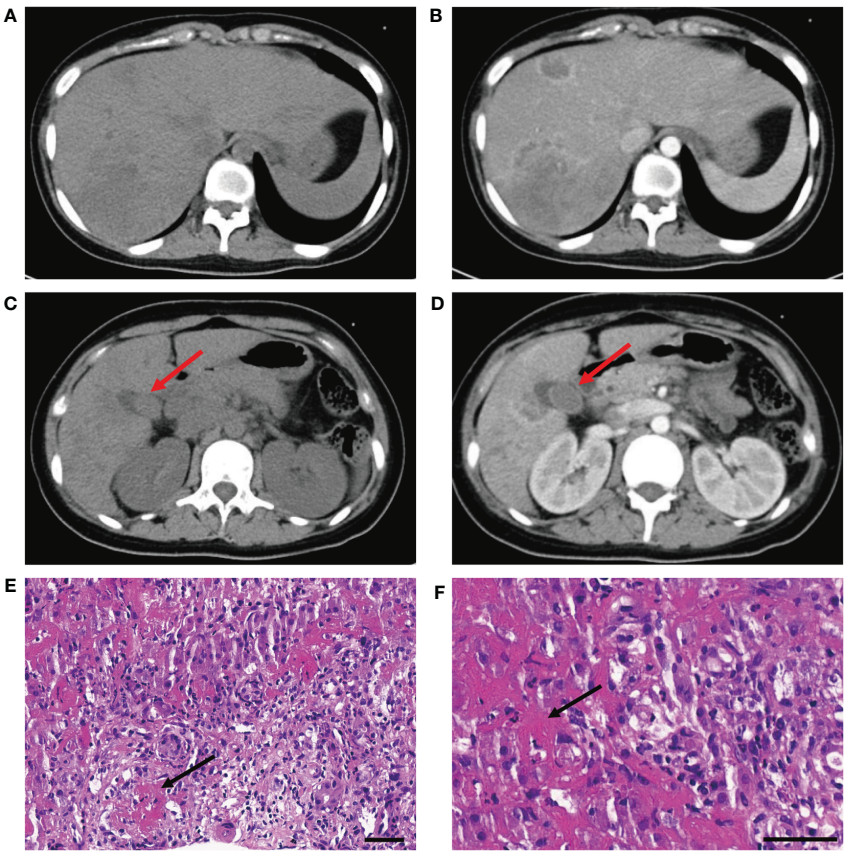



FIGURE 1
**(A, B)** CT scan without and with contrast demonstrates liver "abscess-like" lesions. **(C, D)** CT scan without and with contrast demonstrates possible cholecystitis (red arrowhead). **(E, F)** Histopathological examination reveals vasculitis of hepatic arteries and resultant liver infarction (black arrowhead) (bar is 50 μm).

confirmed the acute hepatic necrosis. An empiric anti-infective therapy was initiated with intravenous ertapenem and changed to meropenem and metronidazole later. Vitamin K and plasma transfusion were applied for correction of coagulation disorders but turned out to be ineffective. Possible pathogens were under intense exploration, but all proved negative after following tests: traditional microbiologic culture and metagenomic next-generation sequencing of peripheral blood samples and liver biopsy specimens; serology screenings for fungi, SASR-CoV-2, hepatitis viruses, TORCH pathogens, Leishmania, and mycobacteria tuberculosis; Epstein–Barr virus DNA analysis; and microscopic examination of parasites in stool samples. In addition, tumor marker analysis, bone marrow examination, specific staining of liver biopsy specimens, and ceruloplasmin test showed no abnormalities. The efficacy of anti-infective therapy was undetermined with fluctuating inflammation markers and unrelieved abdominal pain. Elevated D-dimer (14.87 mg/L; normal: 0–0.55 mg/L), fibrin and fibrinogen degradation products (FDP) (27.6 μg/mL; normal: 0–5 μg/mL), and fibrinogen (7.52 g/mL; normal: 1.8–3.5 g/mL) were also indicated. Repeated CT demonstrated enlargement or reduction of some liver lesions, as well as the emergence of new lesions. The antibiotics were improved to intravenous ertapenem and vancomycin after the re-elevation of C-reactive protein. Unexpectedly, her symptoms worsened with a re-elevated fever peak and persistent coagulation disorders (Figure 2).

The young girl had a medical history of mild SARS-CoV-2 Omicron variant infection, presented with only nasal congestion and fatigue. The onset of abdominal pain occurred 7 days after testing negative for SARS-CoV-2 antigen and complete remission of COVID-19 symptoms. As the efficacy of low-dose dexamethasone given during plasma transfusion could not be excluded for transient improvement of the patient (Figure 2), an immune dysregulation secondary to infection was considered. Serologic testing of antinuclear antibodies and autoimmune hepatitis antibodies only revealed the presence of low titers of antinuclear antibody (1:80) and smooth muscle antibody (1:80). Autoimmune liver diseases were ruled out. Antibodies associated with other systemic autoimmune diseases were comprehensively evaluated, and the presence of IgG anticardiolipin (aCL) and IgG anti-β2-glycoprotein I (anti-β2GPI) antibodies, as well as lupus anticoagulant (LA), was demonstrated (Table 1). Other autoantibodies were undetected. The aPTT and PT correction tests showed negative results. Consecutive examinations demonstrated disease progression following changes of aPL titers, and hepatic lesions were considered to be related to aPL. Considering the hypercoagulable state of pathogenic aPL, the patient underwent CT scan, MRI, MRA, and vascular ultrasound and multiple small acute to subacute cerebral infarcts were indicated. No thrombus and other abnormalities were detected. The liver biopsy specimen was histologically re-evaluated. Immune infiltration with a large number of neutrophils and fibrinoid necrosis were evident in some small- and medium-sized arteries, and adjacent hepatic tissues underwent ischemic infarction consequently (Figures 1D–F). The patient traversed the most severe phase because of administered low-dose dexamethasone. Further therapy included 40 mg prednisone once a day, 500 mg mycophenolate mofetil (MMF) twice a day, and 200 mg hydroxychloroquine twice a day for immunosuppression, along with 100 mg aspirin once a day to prevent future thrombosis. The patient were discharged from the hospital with reduced inflammation markers, diminished abdominal pain, and healed liver lesions as shown in CT examination. The administration of MMF, hydroxychloroquine and aspirin remained unchanged after discharge, whereas prednisone was gradually tapered. The dose reduction proceeded at 5 mg per week until reaching a daily dose of 20 mg, followed by a weekly reduction of 2.5 mg until reaching a daily dose of 15 mg. Scheduled follow-up appointments were conducted. Six months after discharge, the patient discontinued medication autonomously and subsequently experienced a relapsed right-upper quadrant pain with re-elevated aPL titers and significantly prolonged aPTT (Table 1). D-dimer, FDP, and fibrinogen were within normal ranges. Resumption of treatment yielded amelioration. Considering the persistence of medium-to-highly positive aCL and LA for over 12 weeks, as well as aPL-related hepatic vasculitis and cerebral infarction, the diagnosis was made as highly probable APS with vasculitis as a non-criteria manifestation.

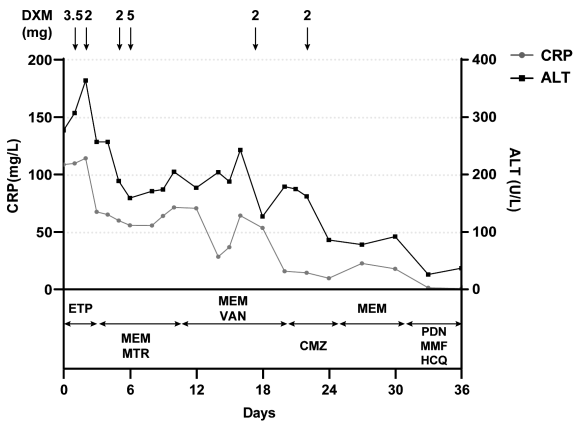



FIGURE 2
Positive correlation between clinical course and the administration of dexamethasone but not antibiotics. Laboratory reference range for indicators: CRP<3.0 mg/L; ALT: 9–50 U/L. CRP, C-reactive protein; ALT, alanine aminotransferase; DXM, dextromethorphan; ETP, ertapenem; MEM, meropenem; MTR, metronidazole; VAN, vancomycin; CMZ, cefmetazole; PDN, prednisone; MMF, mycophenolate mofetil; HCQ, hydroxychloroquine.

## 3 Discussion

Compared with the updated Sapporo criteria with only vascular thrombosis and pregnancy morbidity as diagnostic manifestations of APS (1), the new 2023 ACR/EULAR criteria has introduced several well-defined non-thrombotic manifestations into the clinical criteria for APS classification, including microvascular diseases, cardiac valve diseases, and thrombocytopenia (2). A progression and advancement of the comprehension of aPL-related clinical manifestations is indicated. However, limitations still exist as patients with criteria aPL and comparatively uncommon non-thrombotic manifestations and patients with fulfillment of clinical

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TABLE 1 Disease parameters and titers of autoantibodies.

| Days post hospital admission | Day 11 | Day 22 | Day 30 (discharge) | Day 76 (follow-up) | Day 181 (follow-up) | Day 215 (relapse) | Reference range |
|---|---|---|---|---|---|---|---|
| aPTT (s) | 45.2 | 71.9 | 53.8 | / | / | 50.6 | 23.3–32.5 |
| PT (s) | 20.1 | 15.1 | 13.3 | / | / | 14.4 | 10.4–12.6 |
| INR | 1.70 | 1.25 | 1.09 | / | / | 1.24 | 0.86–1.14 |
| ANA | (+) S1:80 | (+) S1:80 | / | (-) | (-) | (-) | (-) |
| IgG anti-β2GPI* (U/mL) | (+) 34.3 | (+) 42.8 | (+) 33.6 | (-) | (-) 11.6 | (+) 29.1 | <20 |
| IgG aCL* (U/mL) | (+) 39.8 | (+) 51.0 | (+) 41.3 | (+) 12.4 | (+) 12.3 | (+) 33.2 | <10 |
| LA† | 2.36 | / | 2.85 | / | 1.64 | 2.09 | (-) |

(/), not tested.
aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; ANA, anti-nuclear antibody; anti-β2GP I, anti-β2-glycoprotein I; aCL, anticardiolipin; LA, lupus anticoagulant.
*aCL and anti-β2GPI were measured using chemiluminescent immunoassay (CLIA) (iFlash CLIA kits provided by YHLO Biotech Co., Shenzhen, China). According to the manufacturer's instructions, a titer exceeding 10 U/mL was defined as medium or high level for aCL, while a titer exceeding 20 U/mL was defined as medium or high level for anti-β2GPI. The assay demonstrated robust sensitivity and specificity in previous cohort study (13).
†LA assay was performed based on a three-step procedure with two screening test systems recommended by the International Society of Thrombosis and Hemostasis guidelines (14).

criteria but seronegative conventional aPL might be inadequately excluded. These conditions are therefore suggested to be referred as "probable APS" or "non-criteria APS" (15). Our case met the laboratory criteria based on persistence of medium-to-highly positive aCL and LA. The complete and sustained remission of hepatic vasculitis was achieved only when aPL were managed at lower titers with pathogenic effects effectively suppressed. The development of cerebral infarction happened in the setting of highly positive aPL and in the absence of other vascular risk factors. Hepatic vasculitis and cerebral infarction were therefore considered to be associated manifestations. The pathophysiology of cerebral infarcts was undetermined, yet the remarkably elevated D-dimer and FDP suggested a possibility of thrombotic events. Accordingly, our case was assessed as highly probable APS with aPL-related hepatic vasculitis as a non-criteria manifestation, and the development of pathogenic aPL was associated with prior COVID-19 infection.

Infections have been implicated in induction of autoimmunity including aPL production (16), with the recent COVID-19 pandemic being no exception (7). A large number of studies have reported high prevalence of aPL (5%–71%), both criteria and non-criteria types, in COVID-19 patients (7, 17). Several potential mechanisms have been proposed but require further validation (8). Molecular mimicry supposes that the S1 and S2 subunits of the SARS-CoV-2 viral S protein might form a phospholipid-like epitope shared with native tissues, triggering aPL production and provoking an immunogenic response (18–20). The neoepitope model posits that oxidative stress induced by SARS-CoV-2 can alter the conformation of β2GPI (21, 22) and create a neoepitope for antibody generation (23).

Despite the observed high prevalence, the pathogenicity of COVID-19-associated aPL remains uncertain and controversial. To explore the potential roles of aPL, numerous studies have analyzed the correlations of aPL and clinical manifestations in COVID-19 patients, yet a consensus could not be reached. COVID-19-associated aPL were demonstrated to be natural or nonpathogenic in most studies (24–50), which was also shown in the largest meta-analysis published in 2021 (51). Additionally, anti-β2GPI in COVID-19 was reported to rarely (5%) recognize domain I of β2GPI, the molecular region most commonly associated with pathogenicity (24). On the contrary, associations of aPL with disease severity and thrombosis in COVID-19 patients were also reported (52–67). Notably, the largest cohort study demonstrated a correlation between the presence of aCL or IgA anti-β2GPI and thrombotic events (65). IgG antibodies purified from COVID-19 patients with high aPL titers were found to trigger neutrophil extracellular trap release and potentiate thrombosis in mice, similarly to IgG isolated from individuals with definite APS (59). Additionally, infections have been reported as the most common causative factor of catastrophic APS (CAPS), suggesting that infection-induced aPL could exhibit biological activity in a subset of patients (6). Several theories have been proposed to explain the heterogeneity. The "two hits" theory holds that aPL (first hit) induce a thrombophilic state, but clotting requires additional thrombophilic condition (second hit), often involving an innate immunity activator like inflammation, infection, or surgery (3). Furthermore, infections are proposed to more likely trigger APS in individuals with genetic propensity, immune defects, or hormonal abnormalities (16). Therefore, the pathogenicity of aPL exhibits heterogeneity across COVID-19 patients and susceptible individuals with predisposing factors might present aPL-related manifestations in the presence of COVID-19-associated aPL.

Albeit the intense exploration of aPL in COVID-19 patients by multiple studies, most of them neither specify the duration of aPL positivity nor subgroup patients according to antibody levels. All COVID-19 patients with positive aPL were incorporated, and individuals with or without pathogenic aPL were merged together for characterization and analysis, contributing to the debatable

pathogenicity of aPL. Systematic analyses based on these studies could not reveal the prevalence and features of patients developing pathogenic aPL after COVID-19. Conversely, new-onset APS in COVID-19 patients have also been reported, wherein persistently high-titer aPL, associated thrombotic and non-thrombotic manifestations, and recovery following treatments based on APS management guidelines substantially indicate the pathogenicity of aPL. Therefore, new-onset APS cases could be a narrow representative of COVID-19 patients with pathogenic aPL. We systematically reviewed the literature of relevant cases up to February 2024 using PubMed and EMBASE to analyze the APS onset after COVID-19 for the first time. The cases reported as APS after COVID-19 infection with sufficient information to meet the updated Sapporo criteria or the new 2023 ACR/EULAR criteria (1, 2) or with limited information but compelling evidence to support the diagnosis of APS were included. The former and the latter were annotated as definite APS and highly probable APS respectively. Nine cases (68–76) were identified and evaluated together with our case (Table 2). The patients ranged from 15 to 89 (mean = 41.10) years of age and most of the patients were female, consistent with the epidemiology of APS that is more common in middle-aged women (82). According to WHO-issued guidelines (83), COVID-19 severity of these cases encompassed a spectrum from non-severe to critical, indicating that aPL-related manifestations did not merely develop on the basis of cytokine storms in critical patients. The time interval from COVID-19 to the onset of APS varied from 7 to 41 days (mean = 18 days) and a probably more frequent occurrence during the convalescent period was suggested. Definite or probable CAPS was reported in three cases (30%), significantly higher than the approximate 1% incidence of CAPS in all APS patients (84). Thrombosis and corresponding organ infarctions (80%) were the most common manifestation, followed by thrombocytopenia (30%). There were 12 patients mentioned in four cohort studies who also fulfilled the inclusion criteria but were not included due to the lack of individualized information (50, 64, 67, 77–81, 85). In addition to newly diagnosed APS, five cases have reported relapses of completely remitted APS following COVID-19 infections (Table 2), reiterating SARS-CoV-2 as a potential trigger for pathogenic effects of aPL and exacerbation of APS in some patients. Here, we report the first case of developing pathogenic aPL in a juvenile after non-severe COVID-19, diagnosed as highly probable APS. Notably, the absence of any medical history in the patient alerts the possibility of developing severe aPL-related symptoms following non-severe COVID-19 infection in previously healthy individuals, which was also indicated in a healthy woman developing obstetric APS (OAPS) after non-severe COVID-19 infection (73).

Differences in distribution, clinical presentations, and outcomes exist between pediatric and adult APS (86). Compared with adult patients, juvenile patients more frequently exhibit non-thrombotic aPL-related manifestations (10). A study including 121 juveniles fulfilling the updated Sapporo criteria demonstrated a high prevalence of associated non-thrombotic manifestations with neurologic, hematologic, and skin disorders being the most common (87). Non-thrombotic manifestations sometimes precede later thrombotic events (88), leaving pediatric patients with isolated non-thrombotic manifestations being inadequately excluded from APS patient population. Accordingly, diagnostic criteria for definite APS are inapplicable in juveniles. Recommendations for management of pediatric APS published by SHARE initiative advocated for the incorporation of non-criteria manifestations into classification criteria for pediatric APS (86). Therefore, recent studies in pediatric APS have concentrated mainly on pathogenic aPL and associated manifestations rather than definite APS. A study of pediatric APS including definite and probable cases revealed high percentage of hematologic and skin disorders (89). Moreover, another analysis of children with medium or highly positive aPL suggested that more than half exhibited non-thrombotic aPL-related manifestations alone (90).

In our case, the histopathology of liver biopsy specimens revealed immune infiltration and fibrinoid necrosis of arteries without granulomatosis, indicating the existence of hepatic vasculitis that has not been reported in association with pathogenic aPL before. The resultant occlusion of arteries gave rise to liver ischemic necrosis in the absence of any notable thrombus or microthrombus. The patient was successfully treated with immunosuppression, further supporting a vasculitic other than thrombotic etiology.

Although debatable, vascular lesions raised by aPL could be inflammatory. DAH, characterized by bleeding into the alveolar space resulting from disruption and injury of pulmonary microcirculation, represents a genuine inflammatory complication of APS and has been included into clinical criteria for APS in the 2023 ACR/EULAR criteria (2, 91). Several studies have investigated the primary APS-associated DAH in recent years (11, 92–94). Surgical or transbronchial biopsies were performed in 20 cases and capillaritis without thrombus or microthrombus was histologically documented in 11 of them (55%), indicating an isolated inflammatory vasculopathy in DAH development. The recommended and efficient treatment of DAH in APS with glucocorticoids and immunomodulatory agents re-emphasizes an inflammatory instead of thrombotic etiopathology of DAH (91). Additionally, mesenteric vasculitis is considered to be one of aPL-related microvascular manifestations as well (95). Sporadic cases with authentic associated vasculitic manifestations have also been reported in cerebral (96), renal (97), aortic (98), and cutaneous (99) vasculature, and no local thrombus or microthrombus was noted in these inflammatory lesions.

Therapy for APS is diverse and individualized based on a broad spectrum of manifestations. Long-term oral anticoagulants like warfarin are recommended for thrombotic APS (100), and alternative therapies such as extended therapeutic dose of low-molecular-weight heparin can be utilized for patients with recurrent thrombotic events despite warfarin (101). For aPL carriers with high-risk profiles or OAPS patients, low-dose aspirin is proposed for primary thrombosis prevention, particularly in individuals with additional vascular risk factors (100, 102). Glucocorticoids; immunomodulatory agents including MMF, cyclophosphamide, and azathioprine; and B-cell-modulating agents like rituximab and belimumab, are recommended in cases with non-thrombotic manifestations (103, 104). Notably, these recommendations, based on adult-derived studies, might be improper for pediatric populations due to differences in physiological conditions,

TABLE 2 Demographic and clinical characteristics of APS after COVID-19.

| Patients | Age (years) | Sex | Medical history of autoimmune diseases | COVID-19 severity | Time from COVID-19 to onset of APS symptoms (days) | Antiphospholipid antibodies | Primary manifestations | Inclusion criteria |
|---|---|---|---|---|---|---|---|---|
| **Definite new-onset APS** | | | | | | | | |
| 1 (68) | 89 | Female | None | Severe | 14 | IgM aCL<br>IgM anti-β2GP I<br>LA | Deep venous thrombosis | Thrombosis<br>Persistent aPL>12 weeks |
| 2 (69) | 46 | Female | AIH | Severe | 41 | aCL<br>LA | Adrenal infarcts | Thrombosis<br>Persistent aPL>12 weeks |
| 3 (70) | 22 | Female | SLE | Non-severe | 7 | IgG aCL<br>IgG anti-β2GP I<br>LA | Deep vein thrombosis<br>Thrombocytopenia<br>Pulmonary emboli | Thrombosis<br>Thrombocytopenia<br>Persistent aPL >12 weeks |
| 4 (71) | 63 | Female | SLE | Severe | 14 | aCL<br>LA | Thrombosis<br>Refractory thrombocytopenia | Thrombosis<br>Thrombocytopenia<br>Persistent aPL >12 weeks |
| 5 (72) | 36 | Female | SLE | N/A | N/A | aCL<br>anti-β2GP I<br>LA | Budd–Chiari syndrome<br>Thrombocytopenia | Budd–Chiari syndrome<br>Thrombocytopenia<br>Persistent aPL>12 weeks |
| 6 (73) | 39 | Female | None | Non-severe | N/A | IgG aCL<br>IgG β2GP I | Preeclampsia<br>HELLP syndrome | Preeclampsia<br>Persistent aPL>12 weeks |
| **Highly probable new-onset APS** | | | | | | | | |
| 7 (74) | 47 | Female | None | Non-severe | 30 | IgG aCL, IgM aCL<br>IgG anti-β2GP I,<br>IgM anti-β2GP I | Splenic infarcts<br>Bilateral renal infarcts | Thrombosis<br>Double positive aPL with remarkably high titers |
| 8 (75) | 26 | Male | None | Critical | 7 | aCL<br>anti-β2GP I<br>LA | Splenic infarcts<br>Celiac trunk and superior Mesenteric artery thrombosis | Thrombosis<br>Triple positive aPL with high titers |
| 9 (76) | 28 | Female | SLE | Severe | N/A | IgM aCL<br>IgM anti-β2GP I | Diffuse alveolar hemorrhage | Diffuse alveolar hemorrhage<br>Double positive aPL with high titers |
| 10 (our case) | 15 | Female | None | Non-severe | 13 | IgG aCL<br>IgG anti-β2GP I<br>LA | Liver infarcts<br>Cerebral infarcts | aPL-related non-criteria manifestation<br>Probable thrombosis<br>Persistent aPL >12 weeks |
| **Relapse of APS** | | | | | | | | |
| 11 (77) | 51 | Female | Remitted APS | Severe | N/A | N/A | Severe thrombocytopenia<br>Suspicious pulmonary hemorrhage | Onset of APS manifestations after COVID-19 |

*(Continued)*





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TABLE 2 Continued

| Patients | Age (years) | Sex | Medical history of autoimmune diseases | COVID-19 severity | Time from COVID-19 to onset of APS symptoms (days) | Antiphospholipid antibodies | Primary manifestations | Inclusion criteria |
|---|---|---|---|---|---|---|---|---|
| Relapse of APS | | | | | | | | |
| 12 (78) | 38 | Female | Remitted APS | Severe | 12 | IgG aCL, IgM aCL IgG anti-β2GP I, IgM anti-β2GP I | Adrenal glands hemorrhage Limb arterial ischemia | Onset of APS manifestations after COVID-19 |
| 13 (79) | 64 | Female | Remitted APS | Critical | N/A | IgG aCL, IgA aCL IgG anti-β2GP I, IgA anti-β2GP I LA | Stroke Venous thrombosis Adrenal hemorrhage | Onset of APS manifestations after COVID-19 |
| 14 (80) | 66 | Female | Remitted APS | Severe | 5 | IgG aCL, IgM aCL IgG anti-β2GP I LA | Venous thrombosis Adrenal hemorrhage | Onset of APS manifestations after COVID-19 |
| 15 (81) | 43 | Female | Remitted APS | Non-severe | 14 | N/A | Stroke | Onset of APS manifestations after COVID-19 |

N/A, not available.

Remitted APS: years of remission under effective treatment.

APS, antiphospholipid syndrome AIH, autoimmune hepatitis; SLE, systemic lupus erythematosus; anti-β2GP I, anti-β2-glycoprotein I; aCL, anticardiolipin; LA, lupus anticoagulant HELLP: hemolysis, elevated liver enzymes and low platelet; aPL, antiphospholipid antibodies.





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metabolic capacities and duration of medication. Additionally, the low prevalence and heterogeneity of APS in juveniles impede the formation and limit the strength of evidence-based guidelines (86, 105), contributing to substantial variations in treatment regimens that are mostly based on physicians' experience or observational studies.

In our case, aspirin was administered without anticoagulants. The decision was made based on vasculitis-induced hepatic infarction as the major clinical presentation, repair of cerebral lesions with indefinite pathology before systemic treatment, impaired liver synthetic function for coagulation factors, and the absence of other thrombosis risk factors. As concurrent thrombosis risk factors like arterial hypertension, hyperlipidemia, atherosclerosis and smoking are rarely observed in younger subjects, long-term anticoagulation therapy is not indicated in pediatric thrombotic APS patients harboring discontinuous aPL (106–108). Likewise, immunosuppressive therapy in our case reduced aPL titers close to baseline levels and suppressed their pathogenicity, reminiscent of patients with discontinuous aPL. Combined together, anticoagulants were not administered temporarily. However, the patient underwent intensive and regular follow-up to monitor for emergence of any additional thrombosis risk factors, in which scenario, anticoagulants would be introduced as a replacement of aspirin.

aPL-related thrombosis and vasculitis can cause similar clinical presentations including organ infarctions, whereas the treatment decision is different due to the underlying pathologies. The histopathologic results helped us to confirm the inflammatory vasculopathy and guided the treatment to adequately include immunosuppression comprising glucocorticoids and immunomodulatory agents. Therefore, when no thrombus is detected by non-invasive examinations, biopsy for confirmation of the underlying vasculopathy is suggested in APS, if possible and especially when liver is involved.

Our treatments were individualized based on an atypical case. Although the outcome was favorable, the efficacy and safety of aspirin without anticoagulants require further validation during extended follow-up. We merely recommend the addition of immunosuppressants to conventional therapy for managing aPL-related vasculitis.

## 4 Conclusion

Given the perplexing and contentious nature of aPL produced during infections, the COVID-19 pandemic provides a distinctive opportunity to comprehensively assess this issue. The literature review and analysis evaluate the onset and relapse of APS after COVID-19 infection, suggesting that SARS-CoV-2-triggered aPL may exert pathogenic effects in a subset of COVID-19 patients.

Altogether, we endorse the hypothesis that pathogenic aPL can raise vascular damage manifested as vasculitis other than thrombosis, conveying distinct therapeutic considerations to include immunosuppression therapy. In addition to vasculitis, other forms of vascular lesions including proliferative vascular diseases have also been described in APS (109), extending the spectrum of vascular changes associated with pathogenic aPL. Such cumulative evidence supports the statement that the nature of APS should be extended to both thrombophilia and vasculopathy.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

QL: Conceptualization, Formal analysis, Investigation, Writing – original draft. JL: Conceptualization, Formal analysis, Investigation, Writing – original draft. MZ: Writing – review & editing. YG: Writing – review & editing. ZL: Funding acquisition, Writing – review & editing. TL: Funding acquisition, Writing – review & editing. LZ: Resources, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Imatinib-induced dermatomyositis *sine dermatitis* - a rare case report

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Idiopathic Inflammatory Myopathies are rare conditions with several heterogeneous disease subtypes. They can range from limited muscle or skin involvement to severe, systemic, life-threatening disease. Although the etiology is unknown, some evidence suggests a role for external agents, particularly drugs. Herein, we present a case of a 71-year-old woman with chronic myeloid leukemia who developed imatinib-induced dermatomyositis *sine dermatitis*. The presentation was predominantly muscular, characterized by proximal muscle weakness and myalgia of the lower limbs, with positive anti-Mi2a antibodies. Spontaneous recovery was observed after drug discontinuation, without the need for immunosuppressive therapy. This is the first confirmed description of an imatinib-induced dermatomyositis *sine dermatitis*. It reflects the importance of a high awareness from rheumatologists and hematologists to accurately anticipate and identify similar situations.

KEYWORDS

**inflammatory myopathies, dermatomyositis *sine dermatitis*, autoantibodies, proximal muscle weakness, imatinib mesylate**

## 1 Introduction

Idiopathic Inflammatory Myopathies (IIM) are rare systemic inflammatory diseases, that include dermatomyositis (DM), polymyositis, immune-mediated necrotizing myopathy, overlap myositis, antisynthetase syndrome and inclusion body myositis (1–3).

DM is a clinical heterogeneous disease characterized by distinct skin lesions. These can be highly suggestive (e.g., Gottron's papules/sign, heliotrope rash), characteristic (e.g., ragged cuticles and periungual erythema, shawl sign, V sign and holster sign), compatible (e.g., poikiloderma and periorbital edema), less common (e.g., ulcerative lesions and cutaneous vasculitis), rare (e.g., mechanic's hands), and non-specific (Raynaud's phenomenon). A constellation of systemic manifestations can also be present, including

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constitutional symptoms (weight loss, fever, night sweats) and specific organ involvement, such as pulmonary, cardiovascular, gastrointestinal or vascular involvement (4).

In patients without skin disease (DM *sine dermatitis*) or without evident myositis (amyopathic or hypomyopathic DM), DM can be difficult to diagnose (4). The European Neuromuscular Centre (ENMC) criteria recognize DM *sine dermatitis*, characterized by subacute proximal muscle weakness, marked elevation of CK and a muscle biopsy consistent with DM, while lacking cutaneous features (1, 2). Diagnosis is based on the clinical examination in combination with raised CK, presence of myositis specific/associated autoantibodies (MSA or MAA respectively), electromyography (EMG) and muscle biopsy (1). Some MSA are exclusively associated with a diagnosis of DM, namely anti-Mi2, anti-MDA5, anti-NXP2, anti-TIF1, and anti-SAE (4). The use of muscle magnetic resonance imaging (MRI) can aid in guiding muscle biopsy and in the differential diagnosis with other muscle diseases, such as muscular dystrophies (1).

The pathogenesis of DM is multifactorial, complex, and incompletely understood. Genetic, environmental, and immune mechanisms are thought to play an important role in DM development (4). The etiology remains unclear, but some external factors may be important, most notably drugs (1). Drug-induced myopathy is among the most common causes of muscle disease and includes alcohol, glucocorticoids, statins, cocaine, antimalarial drugs, antipsychotic drugs, colchicine, zidovudine, interferon, tumor necrosis factor inhibitors, and chemotherapeutic agents (e.g., gemcitabine and immune checkpoint inhibitors) (5, 6). Rare reports of inflammatory myopathy, possibly translating a hypersensitivity reaction to the drug, have been described with D-penicillamine, cimetidine, procainamide, levodopa, and phenytoin (7). Myositis has been reported only seldomly in patients with chronic myeloid leukemia (CML), and it is usually associated with hydroxyurea or alpha-interferon administration (8).

# 2 Case description

## 2.1 Demographic information and clinical findings

A 71-year-old woman, with a three-year history of CML treated with imatinib mesylate presented with lower limb myalgia mainly during the night, inflammatory polyarthralgia of the wrists and metacarpophalangeal joints, and muscle weakness of the thighs. The complaints had begun six months after starting imatinib and worsened over time. There were no relevant comorbidities, tobacco or alcohol consumption. On examination, she had a Manual Muscle Testing-8 (MMT-8) score of 70/80. No other alterations, particularly in the skin, scalp, joints or cardiopulmonary examination were noted.

## 2.2 Diagnostic assessments

Blood tests showed anemia and mildly elevated acute phase reactants and muscle enzymes (Table 1). Antinuclear antibodies were positive at 1/640 (citoplasmatic linear (AC-15) and nuclear fine speckled (AC-4) pattern), with negative extractable nuclear antigen antibodies, while myopathies panel came strongly positive for anti-Mi2a. Detection electromyography showed rich tracings with a slight increase in polyphasia upon maximum contraction of bilateral vastus medialis, anterior tibialis, trapezii and biceps brachii, without activity at rest, compatible with diffuse muscle fiber damage, without active necrosis. Muscle thigh MRI scans revealed fatty infiltration between the fibers and atrophy of the biceps femoris and semitendinosus muscles (Figure 1). According to the Neurology protocol, a deltoid muscle biopsy was performed which revealed a few scattered, non-specific, atrophic fibers suggestive of myositis. Figure 2 presents the entire clinical course of the reported case.

TABLE 1 Blood test results of the patient.

| Parameter | Result | Reference range |
|---|---|---|
| Hemoglobin | 10.6 g/dL | 12-15,3 g/dL |
| Mean Corpuscular Volume | 97.9 fL | 80-97 fL |
| Mean Corpuscular Hemoglobin | 33.8 pg | 27-33 pg |
| Leukocytes | 5.9x10$^9$/L | 4-11x10$^9$/L |
| Erythrocyte sedimentation rate | 32 mm/h | < 15 mm/h |
| C-reactive protein | 1.56 mg/dL | < 0.5 mg/dL |
| Creatinine | 1.14 mg/dL | 0.7-1.2 mg/dL |
| Aspartate aminotransferase | 18 U/L | 0-32 U/L |
| Alanine aminotransferase | 11 U/L | 0-33 U/L |
| Lactate dehydrogenase | 213 U/L | 100-250 U/L |
| Creatinine kinase | **207 U/L** | 26-192 U/L |
| Aldolase | 3.8 U/L | 1.2-8.8 U/L |
| Myoglobin | **68 U/L** | 25-58 U/L |
| Troponin T | **23 ng/L** | < 14 ng/L |
| Antinuclear antibodies | 1/640 (AC-4 and AC-15) | Negative |
| IIM immunoblot | Strongly positive for anti-Mi2a | Negative |

The bold values are those that are high compared to the reference values and are clinically relevant.

## 2.3 Therapeutic interventions and follow-up

Given the mild muscle manifestations, no immunosuppressive or glucocorticoid therapy was started. Following discussion with the assisting hematologist, and considering the sustained clinical and molecular CML remission after five years of treatment, imatinib was discontinued. Approximately four months after stopping imatinib,

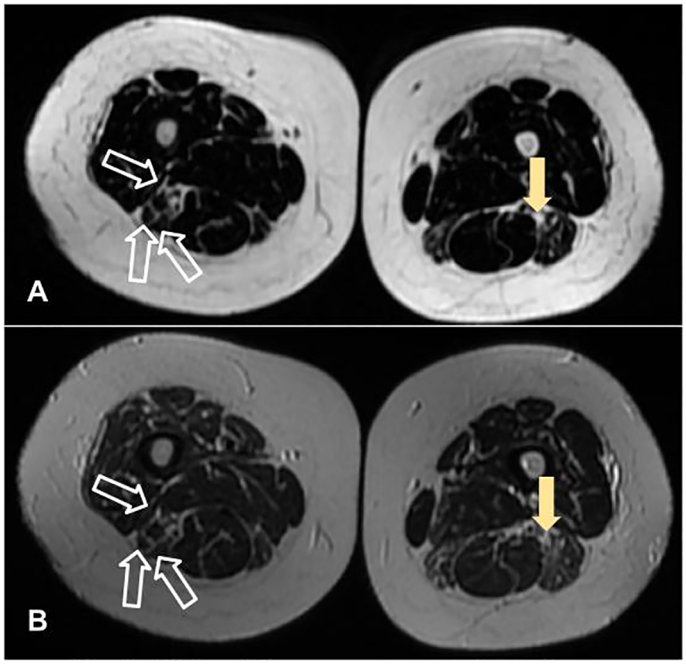



FIGURE 1
Muscle thigh magnetic resonance imaging scans, in axial plans, revealing fatty infiltration between the fibers (filled arrow) and atrophy of the biceps femoris and semitendinosus muscles (unfilled arrow). **(A, B)** were acquired in LAVA Flex and T2 sequences, respectively.

the patient repeated the biopsy targeting one of the most affected muscles in the MRI scan (which revealed no changes) and showed spontaneous resolution of the myalgia, as well as an improvement in muscle strength (MMT-8 = 74), normalization of muscle enzymes, ANA repetition showed a titre of 1/160 nuclear fine speckled AC-4 pattern and, notably, anti-Mi2a antibodies turned negative. The strict time association between improvement and treatment suspension confirmed the diagnosis of imatinib-induced myositis.

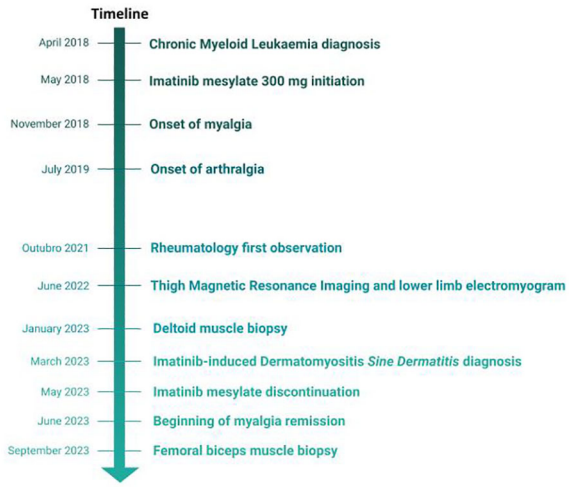



FIGURE 2
Clinical course of the Imatinib-induced Dermatomyositis *sine dermatitis*.

## 3 Discussion

To the best of our knowledge this is the first confirmed report of IIM induced by imatinib described in the literature. The results of EMG, muscle biopsy and MRI scans, combined with the presence of a strongly positive anti-Mi2a autoantibody, strongly supported the diagnosis of IIM. On the other hand, the temporal relationship between the onset of IIM symptoms and imatinib intake, as well as the spontaneous and nearly full recovery of muscle strength and myalgia after its suspension.

Autoantibodies directed against chromodomain helicase DNA binding protein 4 (Anti-Mi2a and Anti-Mi2b) are found in 11–59% of adult DM patients. Clinically, patients with anti-Mi2 can present a range of cutaneous features, but usually have a more favorable prognosis, with mild muscle involvement and a decreased risk of interstitial lung disease and malignancy (9).

Acquired inflammatory myopathies arise from sustained activation of the innate and adaptive immune system, resulting in damage to internal organs. Auto-antibodies are found in a majority of cases, which makes the immune serology an important diagnostic tool (10). Using indirect immunofluorescence, antinuclear antibodies can be detected until 76% of the patients with polymyositis or dermatomyositis, and the most common pattern is a nuclear fluorescence, while the speckled pattern on HEp-2 smears is the most common presentation (11).The

International Consensus on ANA Patterns (ICAP) had classified an anti-Mi2-positive pattern into AC-4, also named nuclear fine speckled, which referred to fine tiny speckles throughout the nucleoplasm (12). The patient initially had an ANA titre of 1/640 which, after imatinib suspension, fell to 1/160, maintaining the AC-4 nuclear pattern while the AC-15 cytoplasmic pattern disappeared.

Imatinib mesylate is a selective tyrosine kinase inhibitor targeting the Philadelphia chromosome (BCR-ABL fusion oncoprotein) in CML (7). Despite being well tolerated, myalgias can be frequent and occur in 21% to 52% of patients taking imatinib (8, 13, 14). High CK levels have been reported only rarely (<1%), and rhabdomyolysis was described in a few patients (15, 16). In one anecdotal report, the myositis was possibly coincidental and unrelated to imatinib therapy, since after interrupting imatinib muscle weakness still progressed and serum CKs remained elevated (800-1100 IU/L) (9). Myositis has been reported only rarely in CML, and has been mostly attributed to treatment with hydroxyurea or alpha-interferon.

## 4 Conclusion

We report the first case of DM *sine dermatitis* associated with imatinib. The strong temporal relationship between onset and resolution of signs and symptoms of IIM and the start and discontinuation of imatinib, respectively, strongly suggest a drug-induced etiology. Complementary exams further supported a diagnosis of myositis. In conclusion, this case reveals the importance of a detailed anamnesis and the framing of the temporal and cause-effect relationship in establishing the diagnosis of a drug-associated myositis. This applies even when no similar cases have been described in the literature, underlining the importance of both rheumatologists and hematologists being alert to this type of manifestation.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

AS: Conceptualization, Writing – original draft. VR: Supervision, Validation, Writing – review & editing. RC-M: Supervision, Visualization, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Isolated brainstem-cerebellar symptoms in a patient with anti-NMDA receptor encephalitis

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Cerebellar ataxia is an uncommon and atypical manifestation of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, often accompanied by seizures, psychiatric symptoms, and cognitive deficits. Previous cases of isolated brainstem-cerebellar symptoms in patients with anti-NMDAR encephalitis have not been documented. This report presents a case of anti-NMDAR encephalitis in which the patient exhibited cerebellar ataxia, nystagmus, diplopia, positive bilateral pathological signs, and hemiparesthesia with no other accompanying symptoms or signs. The presence of positive CSF anti-NMDAR antibodies further supports the diagnosis. Other autoantibodies were excluded through the use of cell-based assays. Immunotherapy was subsequently administered, leading to a gradual recovery of the patient.

KEYWORDS

**Isolated brainstem-cerebellar symptoms, anti-NMDAR encephalitis, encephalitis, ataxia, brainstem symptoms**

## Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a form of autoimmune encephalitis that typically responds well to immunotherapy, as reported by Titulaer et al. Ovarian teratomas are identified as the underlying pathogenesis in approximately one-third of patients with this condition (1). Common clinical manifestations of the disease include neuropsychiatric symptoms, language dysfunction, altered consciousness, seizures, dyskinesias, dysautonomia, and central hypoventilation (1). In pediatric cases, cerebellar ataxia, speech dysfunction, and hemiparesis are more prevalent, often presenting alongside other symptoms (1). In the adult population, cerebellar ataxia presenting as the initial symptom is uncommon and typically occurs in conjunction with psychiatric symptoms and cognitive impairment (2). The occurrence of isolated brainstem-cerebellar symptoms in patients with anti-NMDAR encephalitis has not been previously documented. This case study presents a unique instance of a woman with anti-NMDAR encephalitis displaying isolated brainstem-cerebellar symptoms.

## Case presentation

A healthy 36-year-old woman experienced right-sided numbness, double vision, and difficulty walking. One month prior to admission, the patient experienced initial symptoms of numbness in the distal end of the lower right extremity, which progressed upwards over time. Approximately 5 days later, the patient reported numbness in the right upper limb, starting from the palm of the hand and advancing proximally. This was followed by the development of facial numbness. After approximately 7 days, the patient began to experience difficulty walking, resembling a drunken gait, which worsened to the point of being unable to walk unassisted. Additionally, the patient gradually developed instability in writing with the right hand, as well as bilateral holding instability, with the right hand particularly affected. The patient presented with normal left limb and facial sensation. Approximately 10 days prior to admission, the patient experienced double vision that worsened gradually, with the absence of double vision when viewing with one eye. Throughout this progression, there were no reported symptoms of headache, fever, mental disorders, memory loss, speech or swallowing difficulties, or incontinence.

Neurological exam revealed sensory abnormalities on the right limbs and face, diplopia, downbeat nystagmus, ataxia, and difficulty walking. Positive Babinski's sign was present bilaterally. The Mini-Mental State Examination Scale (MMSE) and the Montreal Cognitive Assessment (MoCA) score were both 29/30.

Contrast-enhanced brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and chest computed tomography (CT) revealed no abnormalities. Lumbar puncture indicated normal pressure. Cerebrospinal fluid (CSF) analysis and extensive laboratory investigations showed pleocytosis (Table 1). Anti-NMDAR antibodies were positive in CSF (cell-based assay, EUROIMMUN product), but negative in serum. A pelvic MRI revealed bilateral benign cystic lesions in the adnexa. The patient received treatment with intravenous immunoglobulin at a dose of 0.4 g/kg per day for 5 days, in combination with intravenous methylprednisolone at a daily dose of 500 mg for 5 days, followed by an oral therapeutic regimen.

One month post-treatment, the patient was assessed for functional abilities. The patient demonstrated independent ambulation, albeit with a sense of instability, and was able to ascend stairs normally but descended at a slower pace. Manual dexterity, particularly in holding objects with both hands, showed improvement, with the right hand demonstrating the ability to write. Sensory deficits persisted on the right side of the face and limbs, accompanied by intermittent electric shock-like sensations, albeit with reduced frequency. While diplopia was absent during forward gaze, it persisted when looking to the right. The physical examination revealed the absence of significant nystagmus, normal legibility of his name, and continued presence of bilateral pathological signs. The lumbar puncture was repeated, and CSF white blood cell count decreased (Table 1). Additionally, the presence of a positive CSF antibody against NMDAR (cell-based assay, CBA, EUROIMMUN product) was noted, while serum antibody against NMDAR was negative. Oligoclonal bands (OBs) were detected in the CSF sample. The patient was advised to maintain oral corticosteroid therapy with tapering and was prescribed mycophenolate mofetil. Instructions were given for regular monitoring of teratoma. A recent follow-up by phone indicated the patient's stable condition, although the patient continued to experience numbness in the right limb and unstable walking, with minimal impact on daily activities. Following our recommendation, the patient underwent whole-body positron emission tomography (PET)-CT scan at a local hospital, which revealed no evidence of tumor presence.

TABLE 1 Overview of investigations.

| CSF analysis | Time | |
|---|---|---|
| White blood cells | Admission | *100 [ref: 0–8]/μL* |
| Protein | Admission | *104.7 [ref: 15–45] mg/dL* |
| Glucose | Admission | 2.77 [ref: 2.5–4.4] mmol/L |
| Gram stain and culture | Admission | Negative |
| CSF NGS | Admission | Negative |
| IgG index | Admission | *1.39 [ref: ≤0.7]* |
| Oligoclonal bands | Admission | *Present* |
| Cytology testing | Admission | Negative |
| Laboratory tests | Admission | |
| Complete blood cell count, blood culture, levels of calcium, phosphorus, magnesium, liver function, thyroid-stimulating hormone, antinuclear antibody, ANCA, anti-thyroid peroxidase antibodies, and anti-thyroglobulin | Admission | Within normal limits |
| **Antibodies in serum and CSF** | | |
| Anti-NMDAR in CSF (cell-based assay) | Admission | *1:10* |
| Anti-NMDAR in serum | Admission | Negative |
| Anti-AMPAR, anti-LGI1, anti-CASPR2, anti-GABAbR, anti-DPPX, anti-IgLON5, anti-mGluR5, anti-MOG, anti-AQP4, anti-MBP, anti-flotillin-1/2, and anti-GFAP | Admission | Negative |
| Serum paraneoplastic autoantibodies including anti-Hu, anti-Yo, anti-Ri, anti-Ma2, anti-CV2, anti-amphiphysin, anti-ANNA-3, anti-Tr, anti-PCA2, and anti-GAD65 | Admission | Negative |
| Serum antibodies including anti-VGCC, anti-GQ1b, anti-ATP13A, anti-ARHGAP26, anti-NCDN, anti-Homer3, anti-KLHL11, anti-PCA2 (MAP1B), anti-DNER, anti-ITPR1, and anti-CARPVIII | Admission | Negative |

*(Continued)*

TABLE 1 Continued

| CSF analysis | Time | |
|---|---|---|
| CSF analysis | | |
| White blood cells | Follow-up | *20 [ref: 0–8]/μL* |
| Protein | Follow-up | 34 [ref: 15–45] mg/dL |
| Glucose | Follow-up | 3.76 [ref: 2.5–4.4] mmol/L |
| Oligoclonal bands | Follow-up | *Present* |
| Antibodies in serum and CSF | Follow-up | |
| Anti-NMDAR in CSF (cell-based assay) | Follow-up | *1:3.2* |
| Anti-NMDAR in serum | Follow-up | Negative |

Follow-up was conducted 1 month after the initial assessment.
NGS, Next-Generation Sequencing; ANCA, Anti-Neutrophil Cytoplasmic Antibody; NMDAR, N-Methyl-D-Aspartate Receptor; AMPAR, α-Amino-3-hydroxy-5-Methyl-4-isoxazole-Propionic acid 1 Receptor; LGI1, Leucine-rich Glioma Inactivated-1 (LGI1); CASPR2, Contactin-Associated Protein-like Receptor 2 (CASPR2); GABAbR, γ-Aminobutyric Acid-B Receptor; DPPX, Dipeptidyl-Peptidase-like Protein 6; mGluR5, metabotropic glutamate Receptor 5; MOG, Myelin Oligodendrocyte Glycoprotein; AQP4, Aquaporin 4; MBP, Monobutyl Phthalate; GFAP, Glial Fibrillary Acidic Protein; ANNA-3, Anti-Neuronal Nuclear Antibody-type 3; PCA2, Purkinje cell Cytoplasmic Antibody type 2; GAD65, Glutamic Acid Decarboxylase-65; VGCC, Voltage-Gated Calcium Channel; ATP13A, ATPase type 13A; ARHGAP26, RhoA GTPase-Activating Protein 26; NCDN, Neurochondrin; KLHL11, Kelch-like protein 11; MAP1B, Microtubule-Associated Protein 1B (MAP1B); DNER, Delta/Notch-like EGF-related Receptor; ITPR1= Inositol 1;4;5-trisphosphate receptor type 1; CARPVIII, Carbonic Anhydrase-Related Protein VIII.
Abnormal values are shown in italic font.

## Discussion

This case report details a patient presenting solely with brainstem-cerebellar symptoms in the context of anti-NMDAR encephalitis, following the exclusion of central nervous system infection and carcinomatous meningitis. While the possibility of co-occurring autoimmune brainstem-cerebellar syndromes cannot be definitively ruled out, it is deemed improbable.

MRI abnormalities of the cerebellum have been documented in 6% of individuals with anti-NMDAR encephalitis (3). Additionally, Iizuka et al. reported that two patients with anti-NMDAR encephalitis exhibited progressive cerebellar atrophy on MRI, which was correlated with a poor clinical prognosis (4). Furthermore, [123I] CLINDE-SPECT imaging has shown a significant increase in binding to the translocator protein 18 kDa (TSPO) in the brainstem and cerebellum of patients with anti-NMDAR encephalitis. TSPO, found on activated microglia, may serve as a marker of regional neuroinflammation (5). Only a small percentage of patients, approximately 5%, exhibit cerebellar complaints, the etiology of which remains unclear. Turner et al. documented a case of a 28-year-old man presenting with a rapidly fatal form of progressive encephalomyelitis with rigidity and myoclonus (PERM). Postmortem analysis revealed the presence of serum antibodies targeting both NMDAR and glycine receptors, suggesting a potential pathogenic role for these antibodies. The authors further observed direct interaction between $CD8^+$ cytotoxic T cells and granule cell neurons of the hippocampus and Purkinje cells (6).

In the cerebellum, Purkinje cells typically lack expression of NMDA receptors, while granule cells exhibit NMDA receptor expression. The cerebellar input layer is composed of granule cells, which represent the most abundant neuronal subtype in the brain. Axons of granule cells ascend to bifurcate into parallel fibers along the mediolateral axis, ultimately making contact with the dendrites of Purkinje cells (7). Traditional theories of cerebellar motor learning have historically emphasized plasticity at the parallel fiber-to-Purkinje cell synapse, neglecting the role of granule cells. However, recent research has demonstrated that granule cells are heavily involved in movement and sensory processing (8, 9). Therefore, a comprehensive understanding of cerebellar learning must also consider the contributions of granule cells.

Armangue et al. reported the presence of brainstem-cerebellar symptoms, such as ocular movement abnormalities, opsoclonus–myoclonus syndrome, and low cranial nerve involvement, in patients with ovarian teratomas. However, no anti-NMDAR antibodies were detected in these patients. In contrast, patients with anti-NMDAR encephalitis rarely present with cerebellar complaints, which are typically accompanied by other symptoms (10).

Cerebellar manifestations are predominantly observed in pediatric populations and typically manifest later in the course of the disease. Ataxia is notably uncommon as an initial symptom in adults. Poorthuis et al. documented a case of a woman presenting with ataxia as the initial symptom in the context of anti-NMDAR encephalitis, accompanied by the discovery of ovarian teratomas and subsequent development of psychiatric symptoms and mutism (2). Wang et al. documented dizziness and gait ataxia as the presenting symptoms in a man diagnosed with anti-NMDAR encephalitis. Subsequently, the patient exhibited symptoms of drowsiness, cognitive impairment, and abnormal behavior 2 weeks later. Brain MRI revealed hyperintense lesions affecting the cerebellum (11).

There are certain restrictions in this case. Owing to limitations, CSF rodent brain immunohistochemistry (IHC) was not performed in this study. In cases of anti-NMDAR encephalitis and anti-LGI1 encephalitis presenting with characteristic symptoms (such as anti-NMDAR encephalitis symptoms, faciobrachial dystonic seizures, etc.), a single antibody assay (e.g., CBA) may be adequate for confirmation. However, in instances where symptoms are atypical, it is recommended to confirm antibodies using at least two different techniques. In the case of detecting anti-NMDA receptor antibodies in CSF, IHC is recommended due to the presence of non-typical clinical symptoms. Furthermore, our study did not include testing for mGluR1, mGluR2, GluK2, and various other antibodies, thus limiting our ability to definitively exclude the potential for synergistic effects with other antibodies. Nevertheless, through antibody detection and repeated CSF analysis, we were able to eliminate the likelihood of most other autoimmune encephalitis, infections, and tumors. Ultimately, the positive identification of anti-NMDAR antibodies in the CSF supports our conclusion that the clinical manifestations exhibited by this patient are associated with anti-NMDAR antibodies.

In conclusion, isolated brainstem-cerebellar symptoms have not been reported in adult patients with anti-NMDAR encephalitis. This case shows that anti-NMDAR encephalitis should be included in the list of possible diagnosis when patients present with brainstem-cerebellar symptoms.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Ethics Committee of the Second Affiliated Hospital School of Medicine, Zhejiang University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YX: Conceptualization, Writing – original draft, Writing – review & editing. QT: Data curation, Methodology, Validation, Writing – review & editing. YD: Conceptualization, Formal Analysis, Writing – review & editing. YZ: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Writing – review & editing.

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# Case report: A highly active refractory myasthenia gravis with treatment of telitacicept combined with efgartigimod

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There is always a lack of effective treatment for highly active refractory generalized myasthenia gravis (GMG). Recently, telitacicept combined with efgartigimod significantly reduces circulating B cells, plasma cells, and immunoglobulin G, which brings promising therapeutic strategies. We report a case of a 37-year-old female patient with refractory GMG, whose condition got significant improvement and control with this latest treatment after multiple unsuccessful therapies of immunosuppressants. The new combination deserves further attention in the therapeutic application of myasthenia gravis.

KEYWORDS

**myasthenia gravis, telitacicept, efgartigimod, highly active, refractory, case report**

## 1 Introduction

Myasthenia gravis (MG) is a rare autoimmune neuromuscular junction disorder characterized by autoantibody-mediated and complement-involved mechanisms (1, 2). In addition to the most common acetylcholine receptor antibodies (AChR-Ab), studies have progressively identified muscle-specific tyrosine kinase antibodies (MuSK-Ab), lipoprotein receptor–related protein 4 antibodies, ryanodine receptor antibodies (RyR-Ab), titin antibodies, and other pathogenic antibodies (2). Although conventional treatments based on acetylcholinesterase inhibitors, corticosteroids, and immunosuppressants are usually effective, patients continue to experience recurrent exacerbations and other safety concerns related to long-term immunosuppressants (3). Therefore, it is an urgent issue to search for safe and effective emerging therapies.

The 2023 Germany's guideline (4) for MG has proposed a new concept about highly active GMG (including "refractory" MG), which can be defined that moderate/high Myasthenia Gravis Foundation of America (MGFA) status (≥MGFA IIb) and/or at least two recurrent severe exacerbations/myasthenic crises with the need for therapeutic intervention. Neonatal Fc receptor modulators (currently efgartigimod) are recommended

for AChR-Ab–positive status. As the FcRn inhibitor, efgartigimod blocks immunoglobulin G (IgG) binding to FcRn, resulting in IgG degradation (5). In addition, as an inhibitor for the activity of BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand), telitacicept was originally designed to diseases such as systemic lupus erythematosus (6) and rheumatoid arthritis (7). However, according to its mechanism that achieves multistage inhibition of B-cell maturation and differentiation (8), it can be a potential efficacy treatment for patients with MG.

We herein report a young female patient with highly active refractory GMG after multiple unsuccessful therapies of immunosuppressants (adequate quantity and course), who was positive for AChR-Ab (early onset) and RyR-Ab and acquired recurrent intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) after recurrent myasthenic crises. With telitacicept combined with efgartigimod, this patient's condition got significant improvement and control.

## 2 Case description

A 37-year-old female patient was diagnosed with MG in 2011 when she was first admitted to our hospital with clinical presentation of fluctuating ptosis, diplopia, upper and lower limb weakness, dyspnea, dysphagia, and dysarthria. Serology was positive for AChR-Ab (>20 nmol/L, reference value < 0.45 nmol/L) and RyR-Ab by enzyme-linked immunosorbent assay. Low-frequency repetitive nerve stimulation showed an abnormal amplitude decrease, and neostigmine test showed a positive result. Autoimmune-related antibodies, including antinuclear antibodies, anti-Sjögren's-syndrome-related antigen A (SSA) antibodies, and anti-SSB antibodies, all tested negative. By the way, she has no thymic pathology. Her clinical manifestation was well controlled by pyridostigmine (180 mg/day) in the early years. Since 2018, she had frequent exacerbations or myasthenic crises and required hospitalization for a pulmonary infection. In February 2022, she was hospitalized again with dyspnea due to pregnancy. Fortunately, she delivered a healthy baby. Throughout the multiple crises, IVIg, PLEX, and high-dose steroid treatment were indispensable, with endotracheal intubation to assist ventilation and a gastric tube, even a gastrostomy, to assist food and drug intake. Multiple immunosuppressants such as tacrolimus, rituximab (RTX), azathioprine (AZA), mycophenolate mofetil (MMF), and cyclosporine A (CsA) did not significantly improve symptoms. Consistent high doses of prednisone and pyridostigmine result in various complications such as hyperprolactinemia, hyperglycemia, hyperlipidemia, myelosuppression, lower limb venous thrombosis, and anal fistula. Since late June 2023, when she started receiving subcutaneous injections of telitacicept (160 mg/week), her symptoms of dyspnea and dysphagia have improved well, and her limb weakness is better than before. Her QMG (quantitative myasthenia gravis) and ADL (activity of daily living scale) scores have also decreased significantly to date (February 2024). Meanwhile, to further reduce the amount of prednisone, we combined it with efgartigimod (10 mg/kg, 800 mg/week) in January 2024. The details of the treatment regimens and drug doses are shown in Figure 1.

## 3 Treatment outcome and follow-up

The QMG and ADL scores have decreased significantly because the patient was injected with telitacicept for 4 weeks (decrease in

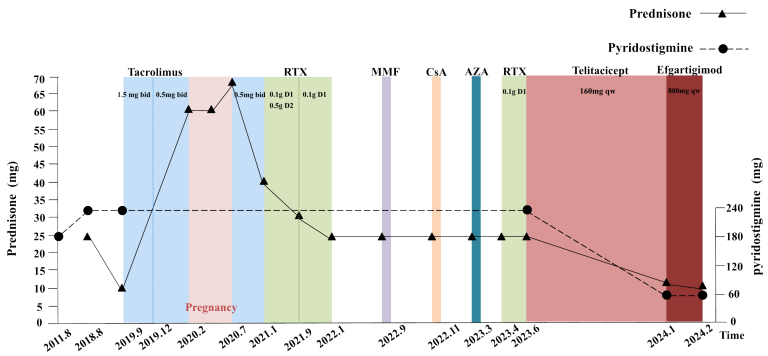



FIGURE 1
Previous therapeutic strategies and the dose of prednisone and pyridostigmine. Each time point represents a MC, which used rapid treatment of IVIg, PLEX, and high-dose steroid (before June 2023). Abbreviations: MC, myasthenic crises; RTX, rituximab; MMF, mycophenolate mofetil; CsA, cyclosporine A; AZA, azathioprine; IVIg, intravenous immunoglobulin; PLEX, plasma exchange. Details: The dose of pyridostigmine was 60 mg ter in die (tid) during 2011 to 2018 and increased to 60 mg quater in die (qid) until June 2023. The prednisone's dosage was 25 mg qd in August 2018 and declined to 10 mg quaque die (qd) when combining tacrolimus (1.5 mg bid) in September 2019. In February 2020, the patient found an intrauterine pregnancy of 7+ weeks and chose to continue the pregnancy. She discontinued tacrolimus, and the dose of prednisone was increased to 60 mg qd. In July 2020, a segment cesarean section was performed, whose procedure was successful, resulting a live infant. Following discharge, the patient was prescribed tacrolimus of 1 mg bid and prednisone of 70 mg qd. In January 2021, the patient received rituximab treatments on three occasions with doses of 0.1 g d1 and 0.5 g d2 initially, followed by 0.1 g d1 in subsequent two treatments. The prednisone dose was reduced to 40 mg qd after the first treatment and further decreased, respectively, to 30 mg qd and 25 mg qd in September 2021 and January 2022. MMF (1 g bid) was added in September 2022 but discontinued after 18 days. CsA (25 mg bid) was added in November 2022 but, later, discontinued after 14 days. AZA (50 mg qd) was added in March 2023 but discontinued in April 2023 when the fourth rituximab treatment was administered (0.1 g d1). In June 2023, the patient was prescribed telitacicept (160 mg quaque semana (qw)) and added efgartigimod (800 mg qw) in January 2024.

QMG and ADL scores by 8 and 12 points, respectively), especially with regard to upper and lower limb weakness, dyspnea, and dysphagia. After 8 weeks of injections, prednisone was reduced to 15 mg/day (dose reduction of 10 mg/day), and pyridostigmine was reduced to 120 mg/day (dose reduction of 120 mg/day). The patient now attends the hospital weekly for regular telitacicept doses. In order to further reduce the dose of prednisone and pyridostigmine for less side effects, we combined it with efgartigimod in January 2024. By February 2024, she had received 31 regular injections of telitacicept (160 mg qw) and four regular injections of efgartigimod (800 mg qw), with a remarkable clinical improvement (QMG and ADL decreased to 10 and 1 points from baseline, respectively), and the doses of prednisone and pyridostigmine were reduced to 10 mg/day and 60 mg/day, respectively (Figure 2). During treatment with telitacicept and/or efgartigimod, symptoms were well controlled, and no exacerbation/myasthenic crisis occurred. In addition, serum B-cell, lymphocyte, and immunoglobulin levels showed a decreasing trend (Figure 3). With the combination of efgartigimod, the presentation of ptosis was well improved. However, the patient complained of hyperphagia after injection of efgartigimod and a slight swelling at the subcutaneous injection site, which disappeared in 1–2 days. In addition, hepatorenal function was within normal limits, and there were no infections or other adverse reactions.

# 4 Patient perspective

As a young woman with recurrent dyspnea and dysphagia who was diagnosed with MG 13 years ago, the previous multiple ineffective immunosuppressive therapies have greatly increased her anxiety, with invasive therapies such as PLEX and endotracheal intubation. Then, the stress of pregnancy and the complications of prolonged high-dose corticosteroids came. Fortunately, with the introduction of telitacicept and efgartigimod, her clinical presentation improved dramatically in terms of breathing and swallowing, and the dosage of steroids was gradually reduced. In the meantime, we have obtained individual informed consent and satisfaction with this combination therapy.

# 5 Discussion

## 5.1 Selection and deactivation of tacrolimus

Although the guideline and related research support that glucocorticosteroids and AZA are the basic immunotherapeutic agents for the treatment of mild/moderate to highly active GMG (4), AZA has a relatively slow therapeutic effect and side effects such as myelosuppression and liver injury. Therefore, we choose tacrolimus, which is faster than AZA, to combine with prednisolone. Compared with cyclosporine, tacrolimus is given in lower doses and has a lower nephrotoxic potential, although both are calcineurin inhibitors. It is suitable for patients who are unable to tolerate the side effects of prednisolone or other immunosuppressants to choose tacrolimus, especially patients with MG positive for RyR-Ab. It has been reported that intervention with calcineurin inhibitors is beneficial for early achievement of minimal manifestations (9). When she was diagnosed at 7 weeks of gestation in February 2020, with an urgent request to continue the pregnancy, we had to discontinue this inhibitor given the teratogenic potential of tacrolimus. Given the lack of clear guidelines or expert consensus on the treatment of MG during pregnancy, traditional therapies such as IVIg and PLEX are still being chosen. Fortunately, the patient had a smooth pregnancy and delivered a healthy baby by cesarean section. It has been found that the mothers who received immunotherapy during pregnancy, especially early and regular IVIG and/or PLEX, would have less severe complications and higher survival rate of offspring (10). Our case seems to confirm this point as well.

## 5.2 Choose of rituximab

RTX, a chimeric monoclonal antibody directed against the B-cell membrane marker CD20, acts through the mechanisms of complement- and antibody-dependent cytotoxicity (11, 12). Our therapy regimen with RTX was in regulation every 6 months (0.1 g D1 and 0.5 g D2) from January 2021, during which the B cells were kept at a low level. In addition, the dose of prednisone was reduced

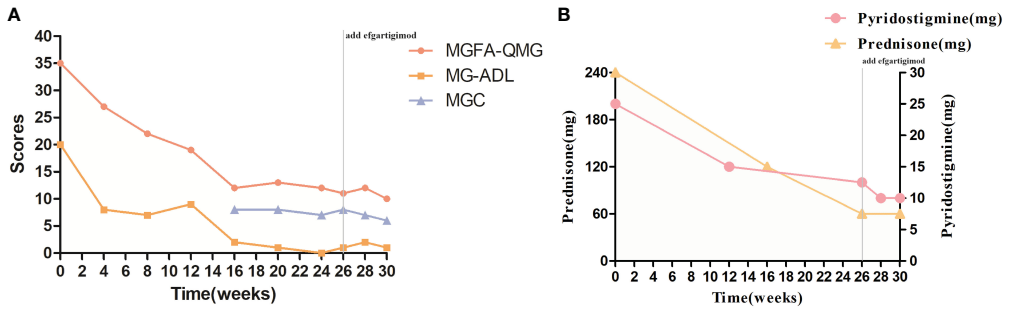



FIGURE 2
Evolution of clinical severity after injecting telitacicept. **(A)** Changes in MGFA-QMG, MG-ADL, and MGC. **(B)** Changes in levels of dose of prednisone and pyridostigmine. Abbreviations: QMG, quantitative myasthenia gravis score; MG-ADL, myasthenia gravis-specific activities of daily living scale; MGC, myasthenia gravis composite; W0, the week before the first injection of telitacicept (June 2024).

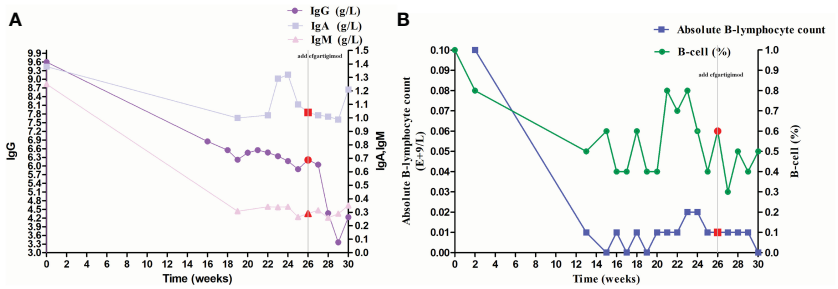



FIGURE 3
Changes in serum marker during follow-up. **(A)** Changes in immunoglobulin. **(B)** Changes in lymphocyte. The red point means the time of combination. IgG, immunoglobulin G.

from 40 mg/day to 25 mg/day. However, the efficacy was not really significant, and the clinical symptoms still worsened repeatedly and recurrently. It has been reviewed that, despite initial responsiveness to RTX, many patients experience relapse during the reconstitution of B cells. This relapse can occur due to the re-encounter of antigens by RTX-resistant B cells or the reactivation of autoimmune responses by newly generated B cells during the process of B-cell repopulation (13). In exploring the reasons for the poor efficacy of RTX in this case, we contribute the following opinions. Firstly, as a B-cell depleting agent that directly targets CD20, RTX shows inadequate clearance of plasma cells, especially those long-lived plasma cells that continue to secrete antibodies that are located in the bone marrow or at sites of inflammation (14). Secondly, germinal center/memory B cells counteract the depletion of RTX by persistently producing pathogenic short-lived plasma cells, which are also involved in the pathogenesis of neurological autoimmune diseases. In addition, a study showed that the effects of RTX treatment were significantly better in patients with MuSK-MG than in those with AChR-MG (15).

## 5.3 Temporary attempt with MMF, CsA, and AZA

MMF selectively inhibits the proliferation of T and B lymphocytes by inhibiting enzymes involved in purine biosynthesis (16). In this case, the patient developed severe gastric reflux symptoms within half a month of taking MMF, and the drug was immediately discontinued in view of the patient's gastrostomy status and the fear that the refluxed material would block the airway, causing respiratory distress or aspiration pneumonia. Compared to tacrolimus, CsA has a higher nephrotoxic potential and several other side effects such as hypertension, myalgia, and influenza-like symptoms (17). Unfortunately, the woman developed severe drug-induced liver injury with renal insufficiency and had to stop taking cyclosporin after 10 days. AZA is an effective therapeutic drug for all subtypes of MG that interferes with DNA synthesis by inhibiting the synthesis of purine nucleotides in rapidly proliferating T and B cells (16). After taking AZA for 1 month, the patient developed severe myelosuppression and a lung infection, so the drug was stopped immediately.

## 5.4 A new attempt with telitacicept

The main role of B cells in the body's immune response involves complement activation, antigen presentation, antibody secretion, and cytokine release. Activated B cells can differentiate into plasma cells, which can further differentiate into short-lived plasma cells and long-lived plasma cells, thereby secreting a large amount of antibodies in a short period, leading to the recurrence of autoimmune diseases.

The BLyS and APRIL are critical factors in maintaining the B-cell pool and humoral immunity, and both play different roles during B-cell maturation and differentiation. BLyS inhibits the development and maturation of immature B cells and regulates their differentiation into mature B cells. APRIL affects the secretion of autoantibodies by autoreactive plasma cells by inhibiting the differentiation of mature B cells into plasma cells. Blocking both BLyS and APRIL can directly contribute to the reduction of plasma cells (18). Therefore, the B-cell targeted drug by blocking the maturation of plasma cells is a new approach in autoimmune diseases. Mono inhibition of BLyS or APRIL has little effect on plasma cell depletion (19). For example, belimumab, which interferes with the binding of BAFF to BCR, thereby inhibiting B-cell differentiation and preventing antibody production, showed a poor outcome in its phase 2 clinical trial (20, 21).

Telitacicept is a novel recombinant fusion protein of the ligand-binding domain of the TACI receptor and the Fc component of human IgG. By competitive inhibition of calmodulin cyclin ligand interaction factor (TACI) to neutralize BAFF and APRIL activity, it achieves multistage inhibition of B-cell and plasma cell maturation and differentiation (8). Meanwhile, due to the presence of TACI receptors on the surface of T cells, telitacicept also inhibits T-cell activation (8). In its phase 2 clinical trial, we find that telitacicept has good clinical efficacy and favorable safety in patients with GMG. Telitacicept has been shown to be a way to improve B-cell depletion and improve the safety and efficacy of RTX (22). Telitacicept targets BLyS/APRIL to inhibit the maturation and differentiation of B cells and plasma cells in multiple stages, thereby further suppressing the secretion of autoantibodies such as IgG. Therefore, compared to FcRn antagonists (e.g., efgartigimod) that directly act on IgG levels in the serum, telitacicept takes longer to take effect. The reasons for choosing telitacicept as a new attempt in June 2023, which takes

effect relatively slower than efgartigimod, are as follows: 1. The half-life of IgG antibodies is approximately 16–24 days, meaning the maintenance period after clearing serum IgG with efgartigimod is short. Telitacicept targets inhibition from the upstream of the immune mechanism, resulting in a relatively longer maintenance period compared to efgartigimod. 2. During the last critical admission period in April 2023, the patient underwent rapid therapy of PLEX in the ICU. Considering that PLEX also works by clearing antibodies, complement, cytokines, and other substances in the plasma, similar to the mechanism of action of efgartigimod, telitacicept was chosen after this exacerbation. 3. At that time, efgartigimod has not yet been included in medical insurance coverage. Considering the patient's 13-year illness history and comprehensive economic considerations, we have chosen telitacicept as the first choice for a new attempt.

In our case report, the woman experienced significant improvement after approximately 16 weeks of telitacicept (QMG and ADL scores decreased to 12 and 2 points, respectively) (Figure 2). In addition, serum levels of B cells, lymphocytes, and immunoglobulins showed a decreasing trend, demonstrating the efficacy of telitacicept (Figure 3). Finally, no infections or other adverse events were observed during the entire follow-up period, demonstrating the tolerability and safety of telitacicept, which are as important as efficacy from the patient's perspective. Following the recent administration of RTX in early April 2023, which can result in peripheral B-cell depletion lasting approximately 6 months, the efficacy of RTX may persist until early October (around week15). Consequently, the potential role of RTX cannot be entirely discounted in the initial phase of telitacicept treatment. Further rigorous randomized controlled clinical trials are necessary to confirm the efficacy and safety of telitacicept.

### 5.5 The combination with efgartigimod

Due to enhancements in the medical insurance system, efgartigimod was officially incorporated into medical coverage in January 2024. To further reduce the amount of prednisone and even reduce the amount of pyridostigmine, we considered combining it with efgartigimod. In the pivotal phase 3 ADAPT trial of efgartigimod, efgartigimod was shown to improve muscle function and strength in all muscle groups, leading to the observed efficacy in participants with GMG (5). Research has shown that efgartigimod may serve as a potentially effective option for myasthenic crisis (23). The IgG antibody has a half-life of approximately 16–24 days. FcRn plays a direct role in the recycling and upkeep of IgG levels in the serum, leading to a faster onset of action. Figure 3 illustrates a noticeable decrease in IgG levels and lymphocyte count especially following the administration of efgartigimod (highlighted by the red data point). Following the second administration of efgartigimod at week 28, we observed a halving of IgG levels compared to week 26 (Figure 3), with this decline persisting after the third injection. While a slight upward trend was noted at week 30, the IgG levels remained lower than those at week 26. Our patient's blurred vision improved significantly after the combination of efgartigimod (QMG and ADL scores decreased to 10 and 1 points, respectively). Compared to PLEX, FcRn inhibitors are less invasive, more specific (particularly the removal of IgG), and independent (no effect on other therapeutic drug levels) (24). During acute phases, utilizing efgartigimod for its direct impact on IgG to rapidly take effect, inducing symptom relief, and then transitioning to telitacicept for sustained B-cell modulation may be a new combined approach.

## 6 Conclusion

Considering the pathogenesis of MG and the mechanism of telitacicept, despite its slower onset of action, it is reasonable to anticipate a promising future for telitacicept in MG treatment. Moreover, our research suggests that the combination of telitacicept with the faster-acting efgartigimod could represent an effective and safe therapeutic approach for highly active refractory MG. However, the sequencing of these two targeted agents and the treatment cost require careful consideration. Efgartigimod has a rapid onset of action and can more specifically remove IgG compared to PLEX, without affecting the levels of other therapeutic drugs, but its maintenance period is short. Telitacicept has a slower onset of action but a longer duration of effect. Considering the differences in the mechanisms of action of the two drugs mentioned above, we recommend prioritizing efgartigimod during the acute exacerbation phase, followed by maintenance therapy with telitacicept. During non-acute phases, telitacicept may be preferred initially, with the option to add efgartigimod if the treatment response is inadequate. The advantages and disadvantages of sequentially using telitacicept followed by FcRn versus FcRn followed by telitacicept are currently unclear due to the insufficient clinical data. Further large-scale studies are required to validate these approaches.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

CZ: Writing – original draft, Writing – review & editing, Investigation. YL: Writing – review & editing, Data curation, Investigation. QK: Writing – review & editing, Data curation, Investigation. HL: Writing – review & editing, Data curation, Investigation. QJ: Supervision, Writing – review & editing. XY: Supervision, Writing – review & editing.

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# Immune checkpoint inhibitor therapy associated with IgA nephropathy: a case report and literature review

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Immune checkpoint inhibitors (ICIs) dramatically improve the prognosis of many malignancies but at the cost of numerous side effects, which may limit their benefits. Acute kidney injury associated with immune checkpoint inhibitors most frequently are acute tubulointerstitial nephritis (ATIN), but various cases of glomerulonephritis have also been reported. Herein, we report a case of severe IgA nephropathy (IgAN) associated with ICIs and carry out a literature review. IgAN was diagnosed in a median time of 5 months (range 1–12 months) after the initiation of ICIs, with heterogeneous severity, and usually treated by corticosteroid and discontinuation of ICIs. In contrast to our case, renal outcomes in literature were often favorable, with recovery of renal function and a reduction in proteinuria on treatment. Although IgAN related to ICIs is a much rarer complication than ATIN, it may still be underdiagnosed. Careful questioning and screening for asymptomatic hematuria should be performed before using ICIs.

KEYWORDS

**IgA nephropathy, IgAN, immune check inhibitor (ICI), pembrolizumab, glomerulonephritis, immune-related adverse events (IRAE), AKI (acute kidney injury)**

## Introduction

Onco-nephrology is an emerging discipline for multiple reasons. Chronic kidney disease leads to a greater risk of cancer. Conversely, several oncological treatments or paraneoplastic syndromes may result in renal injury (1). More recently, the discovery and understanding of the role of immune checkpoint in T-cell activation and function, and of the way cancer cells hijack this system, have been a major progress in the field of oncology. Immune checkpoint inhibitors (ICIs) such as PD1 (*e.g.*, nivolumab or pembrolizumab), programmed death-protein-ligand PD-L1 (*e.g.*, durvalumab), or cytotoxic T lymphocyte-associated protein 4 CTLA-4 (*e.g.*, ipilimumab) inhibitors have dramatically improved prognosis of cancers and are widely used. Despite their efficiency, ICIs are associated with a wide spectrum of autoimmune-related toxicities called immune-related adverse events (irAEs). The most affected organs are the skin, the gastrointestinal tract, and the liver ranging from 54% to 76% of cases (2). Acute kidney injury related to ICIs (ICI-AKI) is less common, ranging from 2% to 4.9% (2). Renal side effects of ICIs are mostly represented by acute tubulointerstitial nephritis (ATIN). Gupta et al. (3) have described an international retrospective cohort of 429 patients with ICI-AKI. Among them, 151 underwent kidney biopsy and 125 (82.7%) showed ATIN lesions. However, glomerulonephritis (GN) is also reported (2), and numerous glomerular lesions are described as well. In a retrospective study from Mamlouk et al. (4), 16 cases of ICI-AKI were reported among 6,412 patients. Of these, 14 had ATIN, which could be isolated in only five patients; other lesions were found such as pauci-immune GN, IgA nephropathy (IgAN) (two cases), membranous nephropathy, C3 GN, focal segmental glomerulosclerosis, and AA amyloidosis. In a recent meta-analysis by Kitchlu et al. (5), of 45 kidney biopsies demonstrating ICI-related glomerular disease, the most common GN was proliferative GN (pauci-immune and anti-GBM GN n = 15, C3 GN n = 5), immune-complex GN n = 2, and lupus-like nephritis n = 1, which accounted for half of the cases. The second most common (35%) was nephrotic syndromes such as podocytopathies (n = 11), AA amyloidosis (n = 4), and membranous nephropathy (n = 1). Only four cases (8.9%) were IgAN (5).

The following case report presents the case of a patient with severe IgA nephropathy, to highlight the difficulties of managing these patients and the need for close collaboration between oncology and nephrology teams.

## Case report

A 65-year-old man was diagnosed with non-small cell lung carcinoma (NSCLC) T4N0M0 and treated by chemotherapy and ICI infusion including carboplatin AUC 6, paclitaxel 200 mg/m$^2$, and pembrolizumab (a humanized monoclonal antibody against programmed death protein {PD-1}) 200 mg IV every 3 weeks. Three weeks after the second course of his treatment, he developed a severe acute kidney injury with an increase in creatinine from 108 µmol/L to 570 µmol/L in 1 week, associated with oliguria at 300 mL per day. The CT scan showed kidneys without morphological abnormalities or obstructive uropathy. AKI required two sequential dialysis sessions. He reported having microscopic hematuria a long time ago without any investigation. He had no history of chronic kidney disease, high blood pressure, urological disease, and gross hematuria (Figure 1).

The patient presented an impure nephrotic syndrome with lower-limb edema, a urinary protein/creatinine ratio of 3.4 g/g, and serum albumin at 18 g/L, associated with microscopic hematuria (1129/mm$^3$). There were no extra-renal manifestations. Immune testing revealed normal complement and negative anti-neutrophil cytoplasmic (ANCA) and anti-glomerular basement membrane antibodies (anti-GBM) of the IgG isotype. Serum protein electrophoresis was consistent with an inflammatory profile. Treatment with oral corticosteroids (1 mg/kg) was introduced in the context of rapidly progressing glomerulonephritis and the use of ICIs. The kidney biopsy, performed 7 days after the admission and the beginning of oral corticosteroid, contained 16 glomeruli (Figure 2). By light microscopy, we observed intense proliferative lesions consisting of mesangial hypercellularity, endocapillary proliferation in 80% of glomeruli, and five active glomerular crescents. Glomerular lesions were associated with interstitial inflammation with inflammatory elements but not enough to assess acute interstitial nephritis. By immunofluorescence, we observed intense mesangial IgA deposit with co-deposition of C3 but no fibrinogen deposit. A diagnosis of severe IgAN was made with MEST-C [i.e., a prognostic histological score (6)] scoring M1E1S0T1-C2. Therefore, chemotherapy and ICI therapy were discontinued, and immunosuppressive therapy was intensified with a pulse of cyclophosphamide (500 mg *i.v.*) in addition to the corticosteroid. Cyclophosphamide was stopped due to gross hematuria and radiotherapy initiation. Unfortunately, despite an improvement in renal function with cessation of dialysis 7 days after the start of treatment, the patient died 4 weeks later from a severe lung infection and multiple-organ failure due to the progression of the lung carcinoma.

## Discussion

Although IgAN is the most common primary GN in the world (7), only a few cases secondary to ICI treatment have been described. In the literature, we found 11 case reports (nine IgAN and two IgA vasculitis), which are briefly described in Table 1 [no clinical data are available in the four cases described by Kitchlu et al. (5)]. We excluded two cases, one due to the absence of histologic evidence (17) and the second because the final diagnostic was postinfectious GN (8). Nine were case reports and two cases were described by Mamlouk et al. (4) among 16 patients with ICI-induced irAEs. Patients were mostly male with a median age of 70 (range 50–78) years old, with no previous history of kidney disease. ICI-AKI occurred in a median time of 5 months (1 to 12 months) after the beginning of ICIs. Renal manifestations consisted of glomerular syndrome with proteinuria and microscopic hematuria in almost every case, associated with different severity levels of AKI. Histopathologic kidney biopsy analysis showed typical IgAN features in nine cases (9–14, 16) and IgA vasculitis

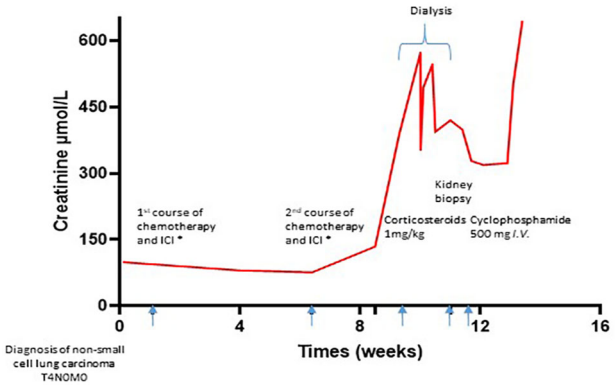



FIGURE 1
Timeline. Chemotherapy and ICI consisting of carboplatin AUC 6, paclitaxel 200 mg/m$^2$, and pembrolizumab 200 mg IV every 3 weeks. ICI, immune checkpoint inhibitor.

in two cases (15, 18) associated with mild ATIN in seven cases. In our case, patient characteristics were similar to that of the literature. Still, AKI appeared earlier after ICI initiation, and histopathologic features were much more severe with intense endocapillary proliferation and active crescentic GN. He also had nephrotic syndrome, which was not present in any of the other cases. Nephrotic syndromes are not a typical feature of IgAN and are often associated with segmental sclerosis. Cases of minimal change disease (MCD) associated with IgAN have also been described (19). In our case, there was no segmental sclerosis and no amyloidosis, and we did not perform electromicroscopy for confirmation of MCD. Other factors may have amplified the hypoalbuminemia, such as a chronic inflammatory syndrome associated with cancer and a recent lung infection.

Mechanisms of irAEs are not completely understood, including for ICI-AKI mechanisms. Common hypotheses are 1) aberrant self-reactive T-cell activation and 2) loss of peripheral tolerance toward an intrinsic kidney antigen (2). Most patients with ICI-AKI had concomitant medication, and the use of proton pump inhibitors was proven to be a major risk factor for developing ICI-ATIN (2, 3). These results supported the hypothesis of a loss of peripheral tolerance. The patient was taking PPIs and NSAIDs and had received antibiotics in the previous weeks. Although these drugs have a strong association with the risk of ATIN (3), their role in the

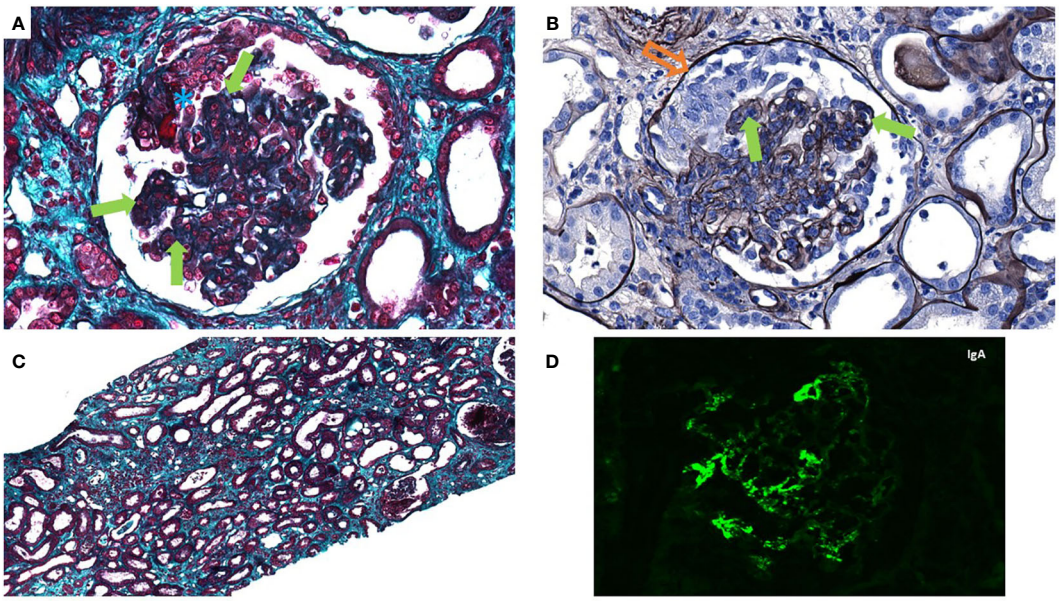



FIGURE 2
The patient's kidney biopsy shown by light microscopy: Glomeruli showing endocapillary hypercellularity (solid arrow, green), cellular crescent (hollow arrow, orange), and fibrinoid necrosis (asterisk, blue), ×40 magnification, Masson's trichrome stain **(A)** and Jones' silver stain **(B)**. Interstitium showing mild to moderate inflammation, edema, and diffuse acute tubular injury **(C)**, ×10 magnification, Masson's trichrome stain.
**(D)** Immunofluorescence showed IgA mesangial staining without other significant deposit.

TABLE 1 Clinical presentation of different IgA nephropathy related to immune checkpoint inhibitor.

| | Our case | Mamlouk et al., 2016 (2 cases) (4) | Kishi et al., 2018 (8) | Wang et al., 2020 (9) | Oki et al., 2020 (10) | Mitarai et al., 2022 (11) | Tanabe et al., 2020 (12) | Dougherty et al., 2021 (13) | Belkaid et al., 2020 (14) | Casafont-Solé et al., 2020 (15) | Palamaris et al., 2022 (16) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age/gender** | 65/M | 1) 69/M<br>2) 50/W | 72/M | 72/M | 75/W | 70/M | 78/M | 70/W | 70/M | 64/M | 73/M |
| **Basal kidney function serum creatinine (mg/dL)/eGFR (mL/min/1.73 m²)** | 0.9/89 | 1) 1.4/51<br>2) 0.8/86 | NA/69 | 1.15/47 | 0.65/87 | NA/70 | 0.64/93 | 0.8/64 | NA<br>No renal history | NA<br>No renal history | NA |
| **Others irAEs** | – | –<br>- | – | Adrenal insufficiency | | – | – | Malar-like rash | Arthralgia, purpura, and digestive disorder | Inflammatory rheumatism, | – |
| **Cancer type** | Lung NSCLC | 1) Uveal melanoma<br>2) Melanoma | Lung squamous cell carcinoma T3N2M0. | Lung mesothelioma T4N2M0 | Lung NSCLC | Lung squamous cell carcinoma | Gastric cancer T3N3M1 | Lung NSCLC stage IV | metastatic melanoma | Lung Squamous cell carcinoma pT1aN1M0 | Bladder Cancer |
| **Drug/lines** | Pembrolizumab/ I line | 1) Nivolumab + ipilimumab<br>2) Pembrolizumab | Nivolumab/ I line | Pembrolizumab/ II line | Pembrolizumab/ II line | Pembrolizumab/ II line | Nivolumab/III Line | Ipilimumab/II line<br>Prior use of pembrolizumab in I line | Nivolumab + ipilimumab/ II line | Durvalumab/ I line | Atezolizumab/ NA |
| **Delay before ICI-AKI since initiation of ICIs (delay before ICI-AKI since the last course of ICIs)** | 8 weeks (3 weeks) | 1) 6 weeks (NA)<br>2) 12 weeks (NA) | 24 weeks (NA) | 20 weeks (NA) | 36 weeks (NA) | 8 weeks (NA) | 32 weeks (12 weeks) | 4 weeks (4 weeks) | 15 weeks (3 weeks) | 20 weeks (NA) | 48 |
| **Renal presentation** | Nephrotic syndrome and AKI Stage 3[$] | 1)AKI stage 2<br>2) AKI stage 3 | AKI | AKI stage 1 | Glomerular syndrome [§§]/AKI grade 2 (CTCAE) | Glomerular syndrome/AKI | Glomerular syndrome and AKI Stage 3 | Glomerular syndrome/AKI stage 3 | Glomerular syndrome | Glomerular syndrome, no AKI | AKI |
| **Creatinine level (mg/dL)** | 4.77 | 1) 2.40<br>2) 3.08 | 1.35 | 1.57 | 0.79 | NA[§§§] | 1.45 | 2.5 | 0.94 | NA | 2 |
| **Proteinuria (g/g)/Hematuria*** | 3.4/+ | 1) 7.7/+<br>2) –/– | 1.69/+ | –/– | 1.7/+ | 3.0/+ | 3.59/+ | 3+ (dipstick)/+ | 1/+ | 0.539/+ | NA/+ |

*(Continued)*





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TABLE 1 Continued

| | Our case | Mamlouk et al., 2016 (2 cases) (4) | Kishi et al., 2018 (8) | Wang et al., 2020 (9) | Oki et al., 2020 (10) | Mitarai et al., 2022 (11) | Tanabe et al., 2020 (12) | Dougherty et al., 2021 (13) | Belkaid et al., 2020 (14) | Casafont-Solé et al., 2020 (15) | Palamaris et al., 2022 (16) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Oxford MEST-C score** | M1E1S0T1-C2 | 1) M?E1S1T0-C0 (according to biopsy description) 2)NA Focal segmentally sclerotic glomeruli. No active lesion | NA Mesangial proliferation WO endocapillary nor crescent described (M1E0C0)? | M1E0S0T0C0 | NA Mesangial and endocapillary proliferation. No crescent described (M1E1C0 )? | M0S0E1T2C1 Fibrotic crescent | M1S0E0T1C1 | NA Mesangial and endocapillary hypercellularity, 5 cellular crescents | NA Mesangial and endocapillary proliferation | NA | M1E0S0T1-C0 |
| **Associated ATIN** | +/− | 1) +mild 2) + mild | − | − | + | + | + focal | − | − | NA | Mild |
| **Treatment** ** | ICI discontinuation + CTS I.V. bolus then 1 mg/kg rapid tapering + CYP | 1) ICI discontinuation + oral CTS at.0.5 mg/kg 2) ICI discontinued + oral CTS 2 mg/kg + MMF 1 g + IBD infliximab (1 dose) | ICI discontinuation | ICI 2months discontinuation | ICI discontinuation | CTS I.V. bolus then 1 mg/kg rapid tapering | ICI discontinuation + oral CTS 0.6 mg/kg rapid tapering | ICI discontinuation + CTS I.V 1 mg/kg rapid tapering | ICI discontinuation + CTS I.V. bolus then 1mg/kg rapid tapering | ICI discontinuation + CTS 0,5mg/Kg | NA |
| **Outcomes (details if available)** | Death | 1) Renal recovery followed by relapsed 2) Renal recovery | Renal recovery at 4 months | No renal recovery (persistent CKD) | Renal recovery (proteinuria decreased after 6 months) | Renal recovery (decreased in proteinuria and creatinine) | No renal recovery (increased creatinine level at 1.82 mg/dL) | No renal recovery | Renal recovery (NA) | Renal recovery (NA) | NA |

*Always microscopic hematuria.
**Treatment always included symptomatic treatment.
$Glomerular syndrome: high blood pressure in association with proteinuria and/or hematuria.
$$Staging based on Kidney Disease: Improving Global Outcomes definition.
$$$Decrease of the eGFR to 55 mL/min/1.73 m².
Conversion factors for units: serum creatinine in mg/dL to µmol/L, ×88.4.
irAEs, immune-related adverse events; CKD, chronic kidney disease, CTCAE, common terminology criteria for adverse events; AKI, acute kidney injury; CYP, cyclophosphamide; IBD, inflammatory bowel disease; MMF, mycophenolate mofetil; NA, no available; IV, intravenous; CTS, corticosteroid; ESKD, end-stage kidney disease; Vs, versus.
- mean negative or absent; + mean positive or present.





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development of glomerulonephritis has not yet been established. IgAN is a multiple-hit disease (6) in which aberrantly galactosylated IgA1 acts as autoantigens that induce the production of IgG antibodies forming immune complexes that are deposited in the mesangium of the kidney and triggering an inflammatory reaction within the kidney. Recently, Nihei et al. (20) demonstrated the presence of IgA autoantibodies directed against a protein expressed on the membrane surface of mesangial cells in 30% of patients with IgAN. This mechanism, which remains to be confirmed, may be part of the breakdown in peripheral tolerance induced by ICIs. As reported, ICI-induced IgAN is very rare; however, its incidence may be underestimated because IgAN can be paucisymptomatic, with only microscopic hematuria and a low proteinuria level. The role of renal biopsy in diagnosing ICPI-AKI is controversial and currently debated (21). In our opinion, these data highlight the need for renal monitoring before, during, and after ICI therapy and the importance of rapidly performing a kidney biopsy in AKI situations. In our case, the patient probably had a history of renal disease, but this appeared only after careful questioning in our department. He reported positive dipstick to microscopic hematuria, screened at occupational medicine that had never been explored. We hypothesize that the patient had preexisting subclinical IgAN and became symptomatic after exposure to ICIs due to a rupture of peripheral tolerance. Alternatively, the severity of the lesions, particularly glomerular crescents, led us to hypothesize another autoimmune mechanism. ANCA of IgA class (ANCA-IgA) has previously been described in crescentic GN with IgA deposition (22). Therefore, we performed an ANCA-IgA ELISA before and after the use of pembrolizumab. Both tests were negative in specific IgA anti-MPO and -PR3.

There is no strong recommendation for ICI-AKI management. ICI discontinuation and rapid introduction of oral corticosteroids are recommended in the case of ICI-AKI for grade 2 or more ATIN (2, 23). In the case of glomerular disease, immunosuppressive therapy could be considered. In our case, crescentic GN and the severity of AKI justified the initiation of immunosuppressive treatment with a high dose of corticosteroids and one pulse of cyclophosphamide. Cyclophosphamide was discontinued during treatment due to the progression of lung cancer requiring radiotherapy and hemorrhagic cystitis. Given the severity of renal damage, we did not attempt a rechallenge with ICIs. In the reviewed literature, 8/11 patients received corticosteroids without a consistent regimen; one patient also received mycophenolate mofetil and anti-TNF-a therapy in an inflammatory bowel disease context. Treatments for IgAN are currently undergoing a revolution, with many molecules showing significant results in both symptomatic (e.g., sparsentan or dapagliflozin) and specific treatment (e.g., Nefecon, a targeted-release formulation of budesonide) (24, 25). The use of these new treatments in the very specific context of immunotherapy remains to be explored.

In conclusion, we report a severe case of crescentic IgAN related to the use of pembrolizumab. IgAN related to ICIs is a much rarer complication than ATIN but could be underdiagnosed. All these cases call for a close collaboration between oncologists and nephrologists.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MC: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. ZL: Writing – original draft, Writing – review & editing. SL: Supervision, Writing – review & editing. JS: Writing – review & editing, Writing – original draft. GE: Supervision, Validation, Writing – review & editing, Writing – original draft. DD: Supervision, Validation, Writing – review & editing, Writing – original draft. CP: Writing – review & editing, Writing – original draft. MD: Investigation, Supervision, Writing – review & editing, Writing – original draft. MA: Supervision, Writing – review & editing, Writing – original draft. SF: Supervision, Writing – review & editing, Writing – original draft. TC: Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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# Case report: VEXAS syndrome: an atypical indolent presentation as sacroiliitis with molecular response to azacitidine

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VEXAS syndrome is a recently described autoinflammatory syndrome caused by the somatic acquisition of *UBA1* mutations in myeloid precursors and is frequently associated with hematologic malignancies, chiefly myelodysplastic syndromes. Disease presentation can mimic several rheumatologic disorders, delaying the diagnosis. We describe a case of atypical presentation resembling late-onset axial spondylarthritis, later progressing to a systemic inflammatory syndrome with chondritis, cutaneous vasculitis, and transfusion-dependent anemia, requiring high doses of steroids. Ruxolitinib was used as the first steroid-sparing strategy without response. However, azacitidine showed activity in controlling both inflammation and the mutant clone. This case raises the question of whether azacitidine's anti-inflammatory effects are dependent on or independent of clonal control. We discuss the potential relevance of molecular remission in VEXAS syndrome and highlight the importance of a multidisciplinary team for the care of such complex patients.

KEYWORDS

**VEXAS syndrome, autoinflammatory, ruxolitinib, azacitidine, case report**

## Introduction

VEXAS syndrome is a novel entity that was first described in 2020 by Beck et al. (1). The acronym stands for some of its most distinctive features: V—vacuoles in erythroid and myeloid precursors cells, E—low levels of E1 (a ubiquitin-activating enzyme), X—the mutated *UBA1* gene located on the X chromosome, A—autoinflammatory syndrome, and S—somatic mutations.

This acquired autoinflammatory disease is caused by inactivating mutations of the X-linked *UBA1* gene that lead to loss of ubiquitination, subsequent accumulation of misfolded proteins, and activation of multiple inflammatory pathways. Of note, the majority of VEXAS syndrome cases that have been described are associated with a somatic mutation at p.Met41 of UBA1. However, there have been multiple reports of other mutations at the *UBA1* gene and even UBA1-negative VEXAS-like presentation of systemic autoinflammatory diseases associated with myelodysplastic syndrome (MDS) (2–6). *UBA1* variants are estimated to be present in 1/4,000 men over 50 years (7), and different mutations are responsible for a wide variety of clinical presentations and disease severity (1, 8).

VEXAS syndrome can mimic multiple inflammatory disorders, most commonly relapsing polychondritis, vasculitis, and Sweet syndrome (7). It typically presents as a progressive systemic inflammatory condition in men over 50 years of age. The most frequently described manifestations are fever, cutaneous involvement, and hematological abnormalities (9, 10). The latter can range from mild macrocytic anemia to a formal diagnosis of MDS (present in 30%–63%), monoclonal gammopathy of undetermined significance (MGUS), or myeloma (10%–25% of cases, many with concomitant MDS). However, whether the hematologic neoplasms arise from the *UBA1* mutant clone or as a consequence of clonal selection promoted by the inflammatory state remains to be clarified (11).

The lack of awareness of the medical community and the unusual constellation of symptoms and signs both contribute to the misdiagnosis and underdiagnosis of VEXAS syndrome. The treatment of this hemato-inflammatory condition usually requires high doses of corticosteroids, as well as several steroid-sparing therapies, namely, JAK inhibitors, IL-6 inhibitors, hypomethylating agents, and allogeneic hematopoietic stem cell transplant. The prognosis is not yet fully established, with reported 5-year survival rates ranging from 63% to 83% (9).

We describe a challenging case of VEXAS syndrome with an indolent presentation as sacroiliitis, later progressing to a severe systemic inflammatory syndrome and transfusion-dependent anemia, who responded to azacitidine after prolonged steroid dependency and ruxolitinib failure (see Figure 1). We additionally provide evidence of molecular response to azacitidine, opening the door to residual disease monitoring by next-generation sequencing (NGS).

## Case description

A 74-year-old man of Caucasian ancestry presented to our Rheumatology Clinic in February 2022 with a 6-month history of fatigue, anorexia, nighttime lower back pain, and prolonged morning stiffness. He had a history of lower extremity deep vein thrombosis (DVT) in July 2021 but had no relevant medical history. Blood workup revealed macrocytic anemia (hemoglobin [Hb] 8.8 g/dL, mean corpuscular volume [MCV] 101.0 fL) and increased acute-phase reactants [C-reactive protein (CRP) 4.27 mg/dL, ferritin 994 ng/L, erythrocyte sedimentation rate (ESR) 113 mm/h]. There were no other cytopenias nor significant changes in renal, hepatic, or thyroid function. Hemolysis was not present and vitamin $B_{12}$, folate, copper, and zinc levels were normal.

The patient had been prescribed prednisolone 15 mg daily for 3 weeks by his general practitioner, with partial improvement of his

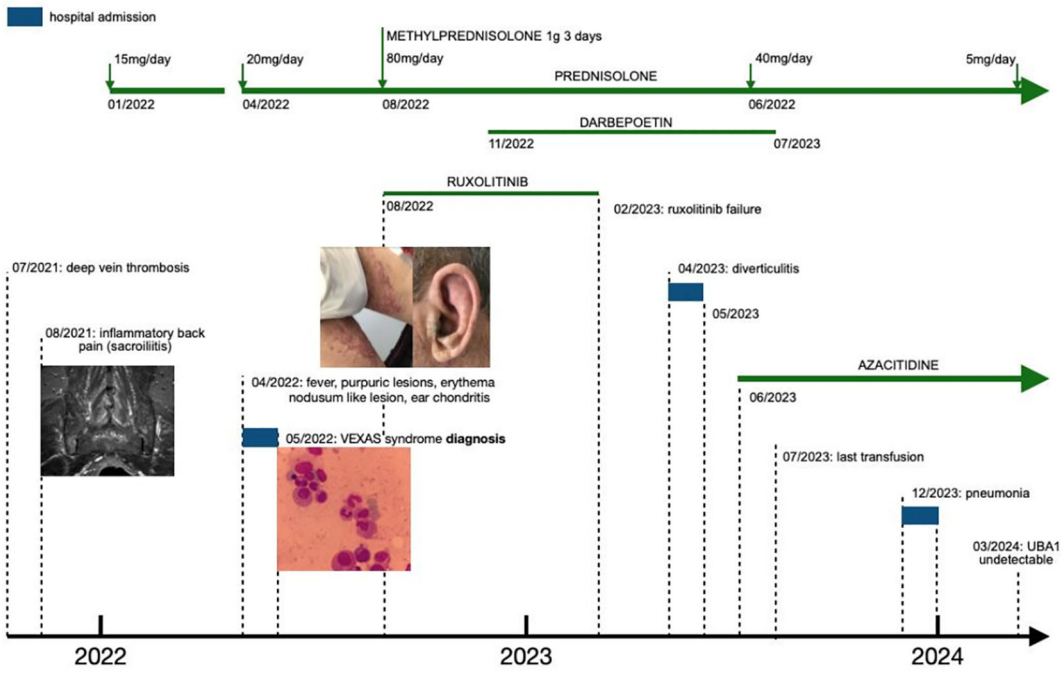



FIGURE 1
Timeline of symptoms and interventions. Refer to Figures 2, 3 for a more detailed view of the images.

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symptoms and laboratory tests (Hb 11.0 mg/dL, MCV 105.7 fL, CRP 0.58 mg/dL, ESR 115 mm/h). Magnetic resonance imaging (MRI) of the sacroiliac joints was obtained and showed bilateral sacroiliitis with moderate asymmetric inflammatory activity (see Figure 2). Additionally, a color Doppler ultrasound of the head, neck, and upper extremities and positron emission tomography (FDG-PET/CT) were performed, with no evidence of large vessel vasculitis. FDG-PET/CT was normal apart from a diffusely increased FDG uptake in the bone/bone marrow, suggestive of non-specific medullary stimulation.

After the hematology review, anemia was first labeled as anemia of chronic disease, possibly related to inflammation secondary to an undiagnosed inflammatory condition.

In April 2022, the patient was admitted to the Infectious Diseases Department due to a 10-day history of fever (1–2 spikes/day with a maximum temperature of 39.0°C) while on prednisolone 7.5 mg daily. On admission, he presented with inflammatory lower back pain, bilateral lower limb purpuric skin lesions (see Figure 2), worsening anemia (Hb 8.5 g/dL, MCV 100.0 fL), and raised CRP and ESR (10.5 mg/dL and 88 mm/h, respectively). Prednisolone was stopped and the patient was started on diclofenac 50–75 mg twice daily. A complete workup for fever of unknown origin was performed. Computed tomography (CT) of the neck, chest, abdomen, and pelvis and transesophageal echocardiogram were unremarkable. Blood cultures, serologic screening for infectious causes, and a comprehensive autoimmune panel were negative.

A skin biopsy was performed when the patient developed an erythematous nodular skin lesion on the dorsum of the foot with findings of non-specific neutrophilic vasculitis. Progressively worsening anemia with new transfusion dependency (minimum Hb 5.9g/dL) prompted a bone marrow aspiration and biopsy. The initial report noted a hypercellular marrow with erythroid hypoplasia, an increased myeloid to erythroid ratio (M:E 7:1), and no significant morphological changes nor left shift.

On the third week of hospital admission with persistent fever, slightly improved inflammatory lower back pain, and persistently elevated acute-phase reactants, the patient developed auricular chondritis (see Figure 2). Hence, a diagnosis of relapsing polychondritis was assumed. Prednisolone 20 mg daily was started with the resolution of the fever, chondritis, and skin lesions. Due to the persistence of disproportionate macrocytic anemia after discharge, a review of the bone marrow aspirate was requested, showing extensive vacuolization of myeloid and erythroid precursors, without features of MDS (see Figure 3). No cytogenetic abnormalities were identified in FISH or karyotyping, and a 30-gene NGS panel was negative for the most common MDS-related gene mutations.

Therefore, a diagnosis of VEXAS syndrome was suspected and subsequently confirmed through the identification of the *UBA1* p.Met41Thr variant by NGS, with a variant allele fraction (VAF) of 71.25%.

Soon after discharge, while on prednisolone 12.5 mg daily, the patient was readmitted due to recrudescence of fever, back pain, severe anemia, and a rise in acute-phase reactants. He received intravenous methylprednisolone pulse therapy (1 g daily for 3 days) followed by prednisolone 1 mg/kg/day (80 mg) and ruxolitinib (starting at 15 mg twice daily). After an initial response, symptomatic relapse occurred upon prednisolone reduction below 30 mg. Despite titrating ruxolitinib dose up to 25 mg twice daily and starting darbepoetin alfa support (maximum 300 µg weekly), tapering below 30 mg of prednisolone was not possible.

A bone marrow aspirate was repeated and confirmed persistent vacuolization but no progression to MDS or acute myeloid leukemia (AML). Given the severe inflammatory behavior and absence of progression to MDS, a switch to tocilizumab was decided. However, before starting tocilizumab, the patient was admitted for diverticulitis with a local abscess, further increasing the risk of bowel perforation reported with this drug (12). A decision was then made to start azacitidine at the standard dose of 75 mg/day/$m^2$ administered for 5 + 2 days (28-day cycles). Azacitidine was started in June 2023, allowing progressive steroid tapering, from an initial dose of 40 mg of prednisolone daily to a minimum dose of 5 mg daily as of March 2024. No significant adverse events were noticed. The patient has received 9 cycles of azacitidine and is currently in clinical remission, with CRP <0.5 mg/dL, ESR <50 mm/h, and Hb >12g/dL, and has been transfusion-free for 8 months. Importantly, after 9 months of therapy, bone marrow reassessment was consistent with a significant decrease in precursor

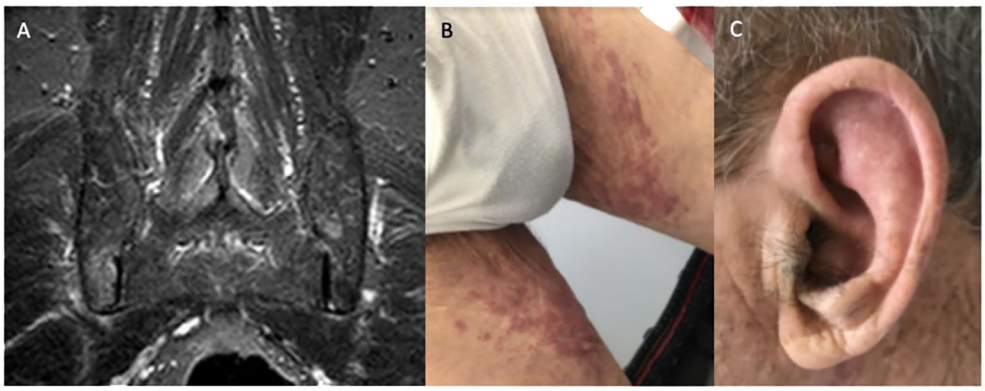



FIGURE 2
**(A)** Magnetic resonance imaging documenting active sacroiliitis; **(B)** lower limb purpuric lesions; **(C)** ear chondritis.

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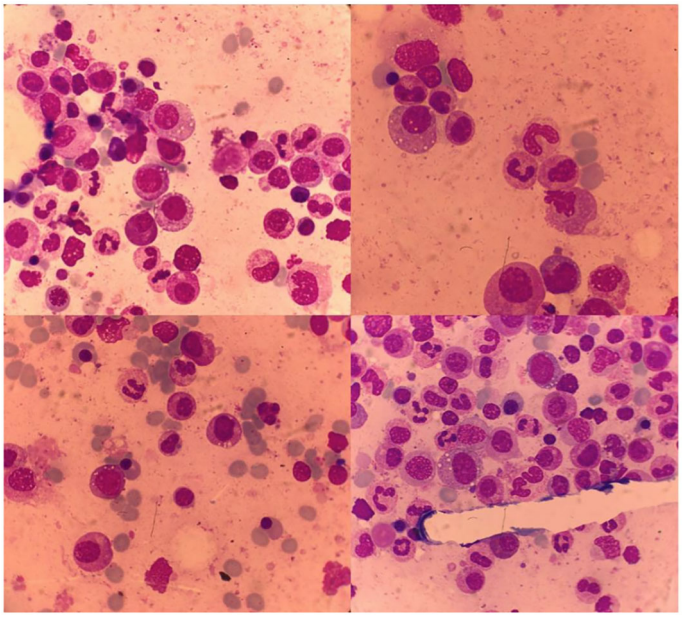


FIGURE 3
Bone marrow with vacuolization of myeloid and erythroid precursor cells.

cell vacuolization with no additional signs of dysplasia, and the *UBA1* p.Met41Thr VAF decreased from 71.25% to being undetectable, suggesting a deep molecular response.

During the entire follow-up, the existence of a multidisciplinary team allowed for the assessment of different comorbidities. The patient received prophylaxis with acyclovir 200 mg twice daily and trimethoprim–sulfamethoxazole 960 mg thrice weekly while on prednisolone >20 mg/day. Immunizations against SARS-CoV-2, influenza, *Streptococcus pneumoniae*, and herpes zoster were also administered. Despite this, the patient experienced several infectious complications, including a dental abscess, two viral upper respiratory tract infections (one caused by respiratory syncytial virus), an oral candidiasis, and two admissions for acute diverticulitis and severe bilateral pneumonia requiring high-flow oxygen therapy (presumably bacterial). He also suffered two osteoporotic vertebral fractures, despite early institution of antiresorptive treatment with zoledronic acid and calcium carbonate and cholecalciferol supplementation. Given the history of DVT and the thrombotic risk associated with VEXAS syndrome, secondary thromboprophylaxis with rivaroxaban was kept during the entire treatment course.

## Patient perspective

Throughout the whole process of the disease, the patient was supported by his wife and family. The novelty of the disease that contributed to a delayed diagnosis affected both the patient and his caregivers. A joint statement by the patient and his wife (main caregiver) was collected: "*The initial phase of the disease was very complicated as the symptoms were so pronounced that they prevented my husband from having an active lifestyle as before. This disease has had an enormous impact on the autonomy of my husband. That and the high number of hospital visits limited the activities we had planned for our retirement years. We felt that the final diagnosis was only possible with the dedication and collaboration of a multidisciplinary team. Getting to know the disease's name and what limited information there is about it was essential to start to understand what was happening. We are grateful to all the staff and for having the chance to do this treatment, that allowed us to regain some independence.*"

## Discussion

The case presented here illustrates the difficulty in diagnosing and managing VEXAS syndrome. Indolent symptom onset with mild non-specific findings can be misleading. We present a difficult-to-diagnose case of a 74-year-old man with symptoms spanning a 9-month period before diagnosis. The first manifestation was likely the unprovoked DVT. Patients with VEXAS syndrome are at a high risk of venous thromboembolic events, with a reported prevalence of 41% and a recurrence rate of 41% (13). Obiorah et al. have reported two episodes of deep vein thrombosis as an initial manifestation in a cohort of 16 VEXAS syndrome patients (14). Of interest, Khider et al. demonstrated that systematically screening for the UBA1 mutation among 97 male patients aged over 50 years after a first thromboembolic event did not yield discernible benefit. This sheds light on the limited utility of such screening in this specific cohort, highlighting the overall high prevalence of thromboembolic events in older patients without an underlying autoinflammatory disease (15).

The DVT was followed by inflammatory lower back pain with evidence of sacroiliitis on MRI over half a year later. At this time,

the clinical presentation resembled late-onset axial spondylarthritis; however, the marked inflammatory syndrome and macrocytic anemia remained to be clarified. In fact, many of the described VEXAS syndrome cases in the literature were first classified as an inflammatory rheumatic disease (7). Initial symptoms suggesting an axial spondylarthritis are quite atypical. Magnol et al. described a case of a patient with axial and peripheral spondylarthritis who, after a sustained clinical response over 2 years under TNF inhibitor therapy, developed anterior uveitis, ear and nose chondritis, neutrophilic dermatosis, medium vessel vasculitis, and macrocytic anemia. After the first description of VEXAS syndrome, the authors revisited the case and were able to confirm the molecular diagnosis (16).

In the presented case, the development of fever, severe anemia, skin findings, chondritis, and a marked inflammatory syndrome widened the differential diagnosis. At this point, symptoms seemed to be consistent with steroid-dependent relapsing polychondritis, but the transfusion-dependent macrocytic anemia was yet to be explained. Only a second review of the marrow aspirate identified vacuolization of erythroid and myeloid precursors as a prominent feature. These previously overlooked marrow changes were very important clues to the final diagnosis, highlighting the importance for hematopathologists to be familiar with this entity and the need for physicians across various specialties to communicate and collaborate throughout the diagnostic process.

After overcoming the diagnostic challenge, physicians had to face another challenge: treatment. While awaiting the results of the first clinical trials dedicated to VEXAS syndrome, the management of these patients has been informed by case reports and case series. A significant part of the treatment options discussed in the literature are chosen based on the symptoms of the patient and the rheumatological/hematological disease that most closely aligns with their condition. A rational approach has been targeting the dominant phenotype of the disease, either 1) using MDS-directed therapies such as azacitidine, lenalidomide, or allogeneic stem cell transplant for those with features consistent with a hematologic neoplasm or 2) targeting inflammatory hyperactivation, both unspecifically (steroids, JAK inhibitors, cyclosporine) or by blocking specific cytokines (anti-IL1, anti-IL6, anti-TNF) in those whose clinical behavior resembles classical autoinflammatory diseases (17).

This line of thought was followed to select the first line of treatment for this patient. In the absence of an overt hematologic neoplasm, ruxolitinib was chosen as frontline therapy based on the results published by Heiblig et al. suggesting the superiority of ruxolitinib over other JAK inhibitors, as well as higher response rates when compared with tocilizumab (18).

After ruxolitinib failure, taking into account the predominantly inflammatory behavior, the absence of dysplasia or increased marrow blasts, the high number of hospital visits required for azacitidine treatment, and azacitidine's higher myelotoxicity, tocilizumab was chosen as second-line therapy. However, upon the moment of treatment decision, the patient had severe diverticulitis, thus increasing the already known risk of tocilizumab for bowel perforation. This prompted the switch to azacitidine, which was associated with a remarkable clinical recovery and sustained transfusion independence, allowing for steroid tapering to low doses. The control of systemic inflammation with azacitidine raises the question of whether azacitidine has direct anti-inflammatory properties in VEXAS syndrome patients or whether reducing the clonal burden in the marrow is the primary driver of inflammation control. Indeed, there is evidence suggesting that azacitidine can modulate the number and function of regulatory T cells in MDS, as well as clinical evidence of immunomodulatory effects (19). Perhaps this strategy circumvents the need to determine the "dominant phenotype" by acting both on inflammation and on the clonal component.

In this case, we demonstrated both success in controlling inflammation and in attaining clonal suppression, as seen by a significant decrease in *UBA1* VAF in marrow samples over time. Sockel et al. presented two cases of molecular response to azacitidine in newly diagnosed VEXAS syndrome patients (20). Raajimakers et al. have described three cases of retrospectively diagnosed VEXAS syndrome. In their report, two patients, after failed attempts of treatment with azathioprine, mycophenolic acid, intravenous immunoglobulin, and anakinra, had a complete clinical response and almost eradication of the mutated clone while on treatment with azacitidine. One of these patients has been with no disease-directed treatment for 4.5 years with persistent remission and suppression of the mutant UBA1 clone (21). We hereby present a case of molecular response to azacitidine after ruxolitinib failure, confirming the potential for disease modification with azacitidine in VEXAS syndrome, even in a refractory setting. Nonetheless, a better understanding of the precise mechanisms of inflammation and clonal dynamics in VEXAS and of azacitidine's multiple modes of action should be given priority for better management of the disease.

As a much less genetically heterogeneous entity than MDS or AML, longitudinal monitoring of *UBA1* burden in VEXAS patients may have a role in guiding therapeutic decisions. Attainment of molecular responses (especially if sustained over time) may open the door to discuss time-limited therapy and treatment-free intervals in selected cases. However, these observations need to be replicated in prospective multicentric cohorts to validate the prognostic value of molecular clearance and define the thresholds of clinical significance. Until further data emerge, it is unclear whether stopping azacitidine will be possible in our patient.

Lastly, we emphasize that the management of VEXAS syndrome requires a dedicated multidisciplinary team and a special focus on supportive care. We believe that most adverse events (including numerous infections) experienced by this patient were attributable to prolonged steroid exposure. Therefore, steroid-sparing strategies to mitigate these risks should be a research priority.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

## Author contributions

RP: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Investigation, Methodology. GS: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. MB: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. JI: Conceptualization, Investigation, Writing – review & editing. TM: Conceptualization, Investigation, Writing – review & editing. CS: Conceptualization, Investigation, Writing – review & editing. JL: Conceptualization, Supervision, Writing – review & editing. JF: Conceptualization, Supervision, Writing – review & editing. JR: Conceptualization, Investigation, Supervision, Writing – review & editing.

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# Anti-NMDAR encephalitis in a child with long impaired consciousness and persistent antibodies: a case report and mini review

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We described a challenging case of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in a young girl. Despite enduring months of reduced consciousness with ongoing antibody presence, she ultimately exhibited remarkable improvement within a 5-year follow-up period. Additionally, we conducted a concise review of relevant literature on anti-NMDAR encephalitis, with a specific focus on anti-NMDAR antibodies. Our findings enhance the clinical comprehension of anti-NMDAR encephalitis and offer valuable insights to clinicians for its management.

KEYWORDS

**anti-NMDAR encephalitis, anti-NMDAR antibody, autoimmune encephalitis, case report, prognosis**

## Introduction

Since its initial description in 2007, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has gained increasing recognition. It primarily affects women and has a median age of onset of 21 years (1). The typical course of anti-NMDAR encephalitis includes five stages: a prodromal phase, a psychotic and/or seizure phase, an unresponsive and/or catatonic phase, a hyperkinetic phase, and a gradual recovery phase (2). However, in children, particularly those under 13 years old, their presentations and progression often differ from those seen in young adults. Notably, the pediatric group exhibits a more balanced sex ratio and a weaker association with cancer (3). Children commonly present with seizures, abnormal movements, insomnia, and irritability. They are also more prone to progressing to multifocal neuropsychiatric symptoms rather than maintaining a single clinical syndrome (4). While still considered rare, anti-NMDAR encephalitis has emerged as a significant cause of pediatric encephalitis in certain regions, potentially attributed to

increased awareness and accessibility of testing technology (5). This report describes a patient suffering from long impaired consciousness with persistent antibodies in her serum, but still achieve an impressive outcome.

## Case presentation

An 8-year-old previously healthy girl was admitted to our hospital due to altered mental status persisting for the previous 4 days, along with recurrent and relentless seizures. Upon arrival at the emergency department, despite receiving phenobarbitone and diazepam, her seizures persisted for nearly 2 h. Lumbar puncture revealed normal cerebrospinal fluid (CSF) pressure, along with 45 nucleated cells (90% lymphocytes), a protein level of 24 mg/dL, and a glucose level of 2.3 mmol/L. Initially, viral encephalitis was suspected based on the CSF findings. However, her seizures worsened after treatment initiation, and she became completely unresponsive with increased involuntary movements. Autoimmune encephalitis (AE) was then considered, and on the fifth day of hospitalization, serum testing using an NMDA-positive cell-based assay confirmed the presence of anti-NMDAR antibodies with a titer of 1:100. Unfortunately, CSF testing for anti-NMDAR antibodies was not performed. Subsequent routine electroencephalography (EEG) revealed abnormal slow wave and delta brush patterns, leading to a diagnosis of anti-NMDAR encephalitis. Brain magnetic resonance imaging (MRI) throughout her illness showed no abnormalities, and no evidence of tumor was detected. Herpes simplex virus (HSV) IgM antibodies were negative. Treatment with high-dose intravenous methylprednisolone (IVMP, 15 mg/kg/day for 3–5 days) and intravenous immunoglobulin (IVIG, 2 g/kg over 3–5 days) was initiated. Despite two courses of IVMP and IVIG within the first month, the patient showed no improvement, and serum antibody titer increased to 1:1,000. Meanwhile anti-NMDAR antibody titer in CSF was 1:100, but routine CSF analysis turned normal. Rituximab (375 mg/m$^2$ weekly in 4 weeks) was then administered weekly in addition to prolonged IVIG and IVMP. Within a month, CD19 B-cell levels decreased to less than 0.1%, CSF antibody titer decreased to 1:32, and the frequency of seizures and involuntary movements noticeably decreased, but serum antibody titer increased to 1:1,000 and mental status improvement was negligible. Throughout her hospitalization, she experienced recurrent low fever with increased sputum production. Initially, her respiratory function appeared unaffected, but she later developed paroxysmal hypoxemia, with both frequency and severity gradually increasing. On the 50th day of hospitalization, her respiratory condition worsened, necessitating transfer to the pediatric intensive care unit (PICU) for assisted ventilation. Chest computed tomography scan revealed collapse of the right upper lobe and scattered infiltration. Sputum culture revealed the presence of *Pseudomonas aeruginosa*, for which imipenem/cilastatin was administered, along with oxygen delivered at a rate of 10 L/min via a simple mask for approximately 10 days. Significantly, stabilization of oxygenation coincided with a decline in seizures and involuntary movements.

Despite receiving multiple immunotherapies, the patient remained unconscious, with a Glasgow Coma Scale (GCS) score of E4V2M4 (she could open eyes spontaneously and only make incomprehensible sounds with withdrawal from painful stimuli). After 3 months in our hospital, her parents opted to transfer her to the Children's Hospital of Shanghai. There, she underwent additional rounds of immunotherapy including IVMP, IVIG, plasma exchange, and cyclophosphamide. By the sixth month of her illness (late April 2019), her eyes could follow objects and she could say certain words (for example, she said "dinosaur" when her mother showed her a dinosaur toy). However, her symptoms fluctuated in the subsequent month, prompting another round of immunotherapy, including IVMP, IVIG, and rituximab, which marked the conclusion of her immunotherapy regimen (all immunotherapies that the patient received are shown in Figure 1). Following this (June 2019), her overall condition slowly but steadily improved, and she commenced rehabilitation to restore her motor and cognitive function. Despite entering a phase of clinical recovery, her serum antibody titer continued to fluctuate between 1:1,000 and 1:3,200.

After her discharge in August 2019, she rechecked serum anti-NMDAR antibody titers every half a year, as well as gynecological ultrasound and chest x-ray annually. No sign of tumor was found during her follow-up. In the spring of 2020, even though she could not walk independently or speak fluently with a serum antibody titer of 1:1,000, she had returned to school and could get average scores on exams. By the spring of 2021, she could walk without assistance and engage in long conversation. The serum antibody titer decreased to 1:320 at that time. The titer further declined to 1:32 in November 2022, and remained until the latest test (31 January 2024). Immature behaviors were the main complaints of her parents in later years. However, she became more mature year by year in their eyes. Now, she has attended a key junior high school and exhibited behavior consistent with her pre-illness state, demonstrating good academic performance (the course of clinical status and antibody titers was exhibited in Figure 2).

## Discussion

While the anti-NMDAR antibody is among the most extensively researched and understood neuronal surface antibodies, its production and pathogenic mechanisms remain incompletely understood. Tumors and viral encephalitis are two confirmed triggers. Ovarian teratomas exhibit a notable association with anti-NMDAR encephalitis, although to a lesser extent in children. The presence of nervous tissues within ovarian teratomas may contribute to pathogenesis. Teratomas associated with anti-NMDAR encephalitis are significantly more likely to contain nervous tissues and exhibit greater inflammatory infiltrates of immune cells in tumor tissue (7). It is hypothesized that nervous tissues within teratomas may harbor NMDARs or similar structures exposed to infiltrating antigen-presenting cells such as B cells and tumor-associated dendritic cells. Regarding infection, the relationship between HSV encephalitis (HSE) and anti-NMDAR encephalitis has been extensively discussed, particularly in children (8). One prevailing theory suggests that HSV has a high affinity for limbic structures, leading to the release

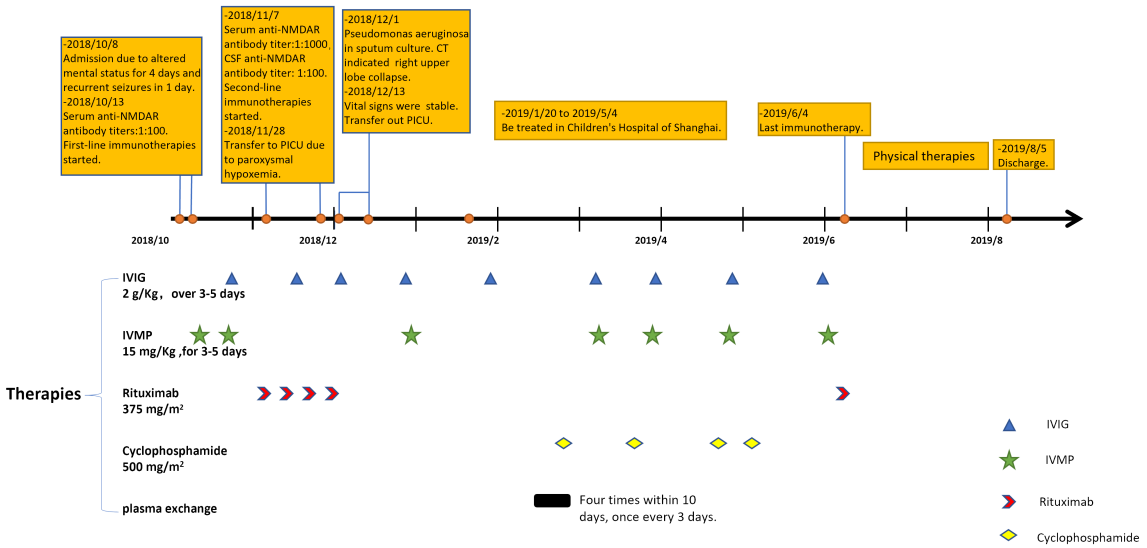



FIGURE 1
The timeline of our patient in 1 year after disease onset and her immunotherapies. IVIG, intravenous immunoglobulins; IVMP, intravenous methylprednisolone.

of neuronal antigens (9). There are also rare reports of other pathogens found in the CSF of anti-NMDAR encephalitis patients, including other types of herpesvirus, enterovirus, and adenovirus (8, 10). Anti-NMDAR antibodies could be present after HSE without corresponding symptoms (11). While infection may not directly induce antibody production, it likely plays a significant auxiliary role in facilitating antibody penetration across the blood–brain barrier (BBB) by increasing its permeability. Recently, studies on genetic predisposition in AE have yielded promising findings, with certain human leukocyte antigen (HLA) genes strongly associated with other forms of AE (12). Although no established HLAs have been linked to anti-NMDAR encephalitis, associations with HLA-A and HLA-DRB1 have been reported (13).

NMDAR antibodies typically induce cross-linking, internalization, and lysosomal degradation of NMDARs, resulting in the attenuation of NMDAR function. This effect is not complement-mediated and is generally reversible. Activation of the ephrin type B2 receptor can prevent this process (12, 14). Lynch et al. proposed that the antibody effect is dependent on NMDAR subtypes, where antibodies cause hyperfunction or hypofunction at extrasynaptic or synaptic NMDARs, respectively (14).

Rapid identification of anti-NMDAR encephalitis remains challenging, particularly due to atypical symptomatology in children. While psychiatric manifestations are often considered a red flag, they may hold less significance in children. This could be attributed to biological factors or technical limitations (15, 16). The psychopathological features of anti-NMDAR encephalitis are intricate, with some overlapping with neurological symptoms, particularly challenging in pediatric evaluations. Moreover, many pediatric practitioners may lack sufficient training in psychiatry, leading to potential misidentification of psychiatric phenotypes.

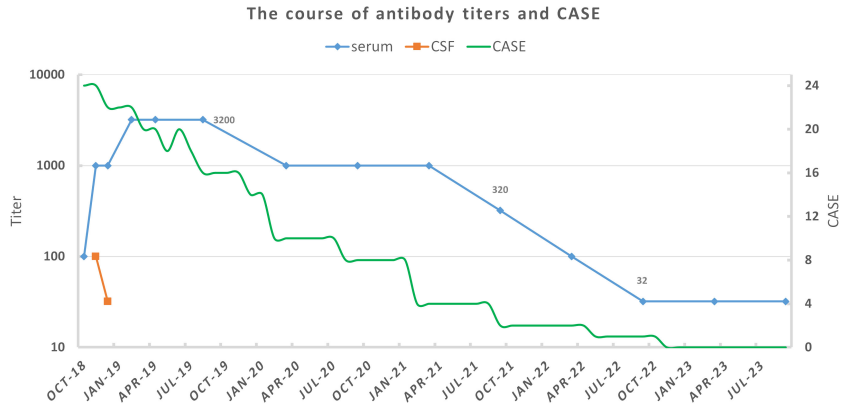



FIGURE 2
The course of antibody titers and clinical status for our patient. Antibody titers were tested by cell-based assay with HEK293 cells. Clinical status was assessed by Clinical Assessment Scale for Autoimmune Encephalitis (CASE) according to medical records and follow-up (6).

Consequently, the incidence and phenotypes of anti-NMDAR encephalitis may vary significantly across studies. Catatonia is among the most frequently reported psychiatric syndromes in both adults and children, exhibiting a broad spectrum of symptoms. Chronic psychiatric and behavioral issues persist in approximately one-third of children for months to years following the onset of AE (17). However, the use of antipsychotic medications to manage psychiatric symptoms in AE should be approached cautiously, as these medications may exacerbate AE symptoms and increase the risk of neuroleptic malignant syndrome due to intolerance. Furthermore, antipsychotic medications often fail to alleviate symptoms (18, 19).

Seizures are among the major symptoms of anti-NMDAR encephalitis, and some individuals may progress to status epilepticus and require intensive care unit (ICU) admission, which are often predictive of a poor outcome (20). It is uncommon in children for seizures to occur as the sole manifestation. Generalized and focal seizures are nearly evenly distributed, with approximately half of all children presenting with both types of seizures (21). Seizures typically respond well to immunotherapy, particularly when compared to antibody-negative AE, which is associated with a lower rate of seizure freedom and a higher risk of postencephalitic seizures (22). The International League Against Epilepsy (ILAE) has proposed the term "acute symptomatic seizures secondary to autoimmune encephalitis" for seizures that resolve following immunotherapy, and "autoimmune-associated epilepsy" for seizures that persist (23). Levetiracetam and valproic acid are commonly used antiseizure medications in AE. Notably, dyskinesia is also a frequent presentation, posing challenges in differential diagnosis, especially in comatose patients. Comorbid catatonia–delirium, tonic–clonic seizures, and orolingual dyskinesia may serve as clinical hallmarks of anti-NMDAR encephalitis (24). In our patient's case, significant paroxysmal orofacial automatisms were observed with no EEG correlations, and she consistently bit her buccal mucosa.

While the presence of antibodies is crucial for diagnosis, the testing process takes time and does not guarantee accuracy. Additionally, the existence of antibody-negative AE should not be overlooked. Diagnosis at onset is challenging, with epileptic seizures and sleep disturbances being two distinct features. EEG findings are often nonspecific, with extreme delta brush being a characteristic abnormality observed mainly in severely affected patients (25, 26). MRI has low sensitivity (less than 50%), and abnormal CSF findings are common but non-discriminatory compared to viral encephalitis. Detection of IgG intrathecal synthesis can enhance CSF sensitivity, with positive results more frequently seen in anti-NMDAR encephalitis than other types of AE (27, 28). Early identification heavily relies on recognizing initial symptoms. Although antibody detection is critical for diagnosis, commercial cell-based assays may yield false-negative results, necessitating brain immunohistochemistry if clinical suspicion remains high despite negative commercial assay results (29).

NMDAR antibodies are more readily detected in CSF than in serum, making it advisable to test for antibodies in both fluid compartments. Even with the use of three different techniques, Mar Guasp et al. found that 15% of patients with anti-NMDAR encephalitis did not exhibit antibodies in the serum but only in the CSF, a proportion that may be even higher in clinical practice. This discrepancy could be explained by activated T and B cells crossing the BBB and exclusively orchestrating the synthesis of NMDAR antibodies in the brain. Interestingly, patients with antibodies exclusively in the CSF appeared to have a milder form of the disease, although outcomes and relapse frequencies were similar to those with positive antibodies in both CSF and serum (30). As widely acknowledged, anti-NMDAR antibodies play a pivotal role in disease progression by reducing cell-surface and synaptic NMDAR levels, thus impairing memory and behavioral function (31). However, the ongoing controversy revolves around whether and how antibody titers correlate with clinical severity and prognosis. It is generally believed that CSF antibody titers hold more clinical significance than serum antibody titers (32). Observational studies have indicated that CSF antibody titers are positively correlated with ICU admission, ventilator use, and the presence of tumors (33). However, a study on hippocampal damage secondary to anti-NMDAR encephalitis found that neither CSF nor serum antibody titers corresponded with memory or cognitive performance (34). According to Cai et al., CSF antibody titers only exhibited a weak correlation with the modified Rankin scale (mRS) ($r$ = 0.243) (35). A previous study by Xiaoting Zhang et al. demonstrated that CSF or serum antibody titers did not influence the response to first-line treatments (36). It is not uncommon for antibodies to persist in both serum and CSF, as evidenced by a retrospective study conducted by Gresa-Arribas et al., where 24 out of 28 CSF and 17 out of 23 serum samples from recovered patients remained antibody-positive (32). The prognostic value of persistent antibodies remains uncertain. A recent study found that patients with persistent CSF NMDAR antibodies at 12 months of follow-up experienced relapses more frequently and earlier. These patients also exhibited higher CSF antibody titers at diagnosis, longer ICU admissions, and received more extensive treatment. However, the same study did not find a significant difference in long-term outcomes between patients with persistent CSF antibodies and those without (37).

In our patient's case, continuous monitoring of CSF antibodies was not feasible due to disagreement of her custodian. Before initiation of second-line immunotherapies, her CSF routine examination had turned normal. After using rituximab 375 mg/$m^2$ weekly over a month, CSF antibody titers decreased from 1:100 to 1:32. Mitigation of seizures and dyskinesias was observed, especially after she was transferred from the PICU. It may be regarded as partial improvement, but also that could just result from the natural course of the disease (38). In contrast to CSF antibody titer, serum antibody titer significantly increased to 1:1,000 and then 1:3,200. Serum titers remained high even at the turning point, where she became responsive. They declined slowly and remained 1:32 after 5 years. That may indicate a sustained immune response. Refractory anti-NMDAR receptor encephalitis with high serum antibody titers had been reported in some cases. We list characteristics of some cases as well as ours in Table 1. All of them were female. Three had found teratomas and underwent teratoma resections. In a 14-year-old female patient, teratoma was found during follow-up (39). Existence of tumors is the most

TABLE 1 Characteristics of patients with refractory anti-NMDAR encephalitis and high antibody titers.

| Author | Thomas et al. | Tuhina et al. | Wang et al. | Serena et al. | Our case |
|---|---|---|---|---|---|
| **Age, sex** | Late 30s, F | 14 years, F | 27 years, F | 29 years, F | 8 years, F |
| **Onset** | Psychosis, headaches | Headaches, hallucinations, psychosis, seizures | Psychosis, seizures, loss of consciousness | Seizures, headaches | Altered mental status, seizures |
| **Tumor** | Teratoma | Teratoma | Teratoma | No | No |
| **MRI findings** | Normal | Abnormal | Abnormal | Abnormal | Normal |
| **Initial serum titer** | 1:102,400 | 1:640 | 1:1,000 | 1:800 | 1:100 |
| **Peak serum titer** | 1:102,400 | 1:2,560 | 1:1,000 | 1:800 | 1:3,200 |
| **Last serum titer** | 1:25,600 | 1:160 | 1:300 | 1:800 | 1:32 |
| **Follow-up period (since disease onset) (months)** | 25 | 12 | 18 | 6 | 66 |
| **Treatment** | Teratoma resection, IVMP, IVIG, RTX, CYC, MTX | IVMP, RTX, plasma exchange, bortezomib, teratoma resection | Teratoma resection, plasma exchange, RTX, IVMP, IVIG, CYC, intrathecal DXM and MTX | IVMP, IVIG, plasma exchange, RTX, CYC, bortezomib | IVMP, IVIG, plasma exchange, RTX, CYC |
| **Prognosis** | Bad | Good | Good | Good | Good |

IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; CTX, cyclophosphamide; RTX, rituximab; DXM, dexamethasone; MTX, methotrexate.

suspected reason for high serum antibody titers and treatment failure. One case underwent bilateral salpingo-oophorectomy due to consideration of non-visible teratomas, though she had tumor removal 1 year before (40). However, repeat abdominal and pelvic ultrasounds of our patient showed no abnormalities, which differed from those cases. We observed that no immediate titer drop happened after tumor resection. In the case of Serena et al., serum antibody titers rebounded during recovery with a titer of 1:800 (41). Unfortunately, they did not explain it. However, the report indicated that clinical status did not fluctuate. Moreover, it has been reported that infants born to mothers with anti-NMDAR encephalitis during pregnancy, and subsequently tested positive for the antibody, can exhibit normal growth and neuronal development (42). Our patient retained a high antibody titer of 1:3,200 when her general recovery began. Probably, serum anti-NMDAR antibodies alone would not cause symptoms or hinder recovery.

We were not certain what led to the recovery of our patient. Her recovery may be a result of previous treatments. Perhaps the effect of treatments may not be observed immediately. International consensus recommendations defined poorest responders as those who fail to make substantial and functionally useful improvements in the first 3 months after treatment commencement, but they also proposed that 18 months was the median overall duration of immunotherapy for the poorest responders (43). Still, no recommendations were given about cessation of immunotherapies. It was particularly challenging in severe patients like our case. Remarkably, our patient did not manifest any neuropsychological sequelae despite undergoing extensive treatment. A recent study on neuropsychological outcomes revealed common deficits such as lower sustained attention, worse verbal memory, and self-reported fatigue, none of which were observed in our patient after 5 years (44). Numerous studies have investigated predictors of outcomes, with early treatment initiation and avoidance of ICU admission identified as predictors of favorable outcomes in a systematic review (45). The One-Year Functional Status score (NEOS) has been proposed as a predictive tool for outcome at 1 year post-disease onset, with indicators including ICU admission, treatment delay exceeding 4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI findings, and CSF white blood cell count exceeding 20 cells/μL (46). While these methods can aid in outcome prediction, they should be used cautiously to guide treatment decisions, along with consideration of persistent antibodies. To date, no significant biomarker has been identified to reliably guide treatment decisions (47). Therefore, as demonstrated by our case, clinical status remains paramount in treatment decisions.

Approximately one in five patients with anti-NMDAR encephalitis are refractory to standard first-line and second-line treatments. Recent reports suggest the efficacy of bortezomib in both adult and pediatric patients (48). Other agents such as mycophenolate mofetil, azathioprine, methotrexate, and tocilizumab have also been mentioned in previous years, but their use remains limited in scale with uncertain safety and efficacy (49, 50). Francesco Mannara et al. proposed allosteric modulation of NMDARs as a potential additional treatment. Their work demonstrated that SGE-301, a potent and selective positive allosteric modulator of NMDAR, prevented NMDAR dysfunction in a mouse model (51). Krienke et al. designed a noninflammatory messenger RNA vaccine delivering autoantigens into lymphoid dendritic cells in an experimental autoimmune encephalomyelitis model, resulting in antigen-specific tolerization and reduced disease severity (52).

In conclusion, pediatric anti-NMDAR encephalitis differs from the adult form in terms of pathophysiology and clinical manifestations. Early recognition and prompt initiation of immunotherapy are crucial for achieving a better prognosis. This case may instill confidence in clinicians, as despite prolonged impaired consciousness, lack of immediate response to first-line and second-line immunotherapies, and persistent serum antibodies

after 5 years, the patient still experienced an unexpectedly positive outcome. We suggested that long-term prognosis and outcomes are generally favorable, even in cases where patients do not respond immediately to standard treatments and long-time unawareness occurs. Therefore, decisions regarding continuing immunotherapy should be based on clinical status rather than antibody titers, especially in serum. However, further studies with larger sample sizes are needed to thoroughly investigate the relationship between antibody titers, clinical severity, and prognosis.

## Patient's perspective

The patient could not recall her illness properly, but she did not have any discomfort. Her parents described the event as "a long nightmare", but was glad that they did not give up. At first, they were anxious about persistent antibodies in their daughter's serum and the long-term prognosis of their daughter. However, their concerns had been alleviated since the patient recovered well. They hope to share their daughter's experiences to inspire and help others suffering from the same disease.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

WZ: Writing – original draft, Writing – review & editing. WC: Writing – review & editing. WT: Writing – review & editing. YW: Writing – review & editing. CT: Writing – review & editing. QS: Writing – review & editing. XS: Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Efficacy of steroid therapy in the acute stage of anti-NMDAR and anti-MOG antibody overlapping encephalitis: a case report and literature review

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**Background:** Recently, cases of overlapping encephalitis caused by anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been reported, and their clinical characteristics are gradually becoming clear. Acute-phase treatment typically involves the use of steroids, and although some studies have suggested that steroids can be effective, the extent of their efficacy has not yet been fully explored.

**Case presentation:** We present the case of a 25-year-old man with anti-NMDAR and anti-MOG antibody overlapping encephalitis who showed considerable improvement after steroid treatment. To gain a deeper understanding of the efficacy of steroids in managing this condition, we conducted a literature review of cases of anti-NMDAR and anti-MOG antibody double-positive encephalitis that were treated with steroids during the acute phase. Thirteen cases were analyzed, including a new case diagnosed at our hospital. All patients showed improvement after receiving steroid treatment in the acute phase. Ten patients did not have any sequelae, and nine of them showed a rapid or major response during the acute phase. In contrast, three patients experienced sequelae (mild cognitive decline, visual impairment, and memory impairment, respectively), with their response to steroids in the acute phase being slow or limited. Relapses occurred in five patients, in one patient during steroid tapering, and in another two patients after cessation of steroids.

**Conclusion:** Steroid therapy can be effective in the acute stage of anti-NMDAR and anti-MOG antibody overlapping encephalitis. A positive prognosis may be expected in patients who experience substantial improvement with steroid therapy during the acute phase.

KEYWORDS

**anti-NMDAR encephalitis, autoimmune encephalitis, myelin oligodendrocyte glycoprotein (MOG), N-methyl-D-aspartate receptor (NMDAR), overlapping encephalitis, steroid**

# 1 Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder that causes brain inflammation. The initial report of anti-NMDAR encephalitis involved 12 young women, of whom 11 (91.7%) had ovarian teratomas (1). However, a subsequent multicenter study found that 35.9% of patients had ovarian teratomas, and it is now recognized that the disease can occur in individuals of any age, regardless of sex or the presence of tumors (2). The primary symptoms of anti-NMDAR encephalitis include psychiatric disorders, seizures, impaired consciousness, and involuntary movements (3). Brain imaging often reveals no obvious abnormalities. The treatment of anti-NMDAR encephalitis typically involves intravenous methylprednisolone (IVMP), intravenous immunoglobulins (IVIG), and plasma exchange (PE); however, only half of these cases show improvement with treatment (2). The acute stage of the disease often requires a prolonged hospital stay of 3–4 months, followed by rehabilitation (4). The condition generally follows a monophasic course with a 2-year relapse rate of approximately 12% (2).

Myelin oligodendrocyte glycoprotein (MOG) is a component of the myelin sheath of the central nervous system. MOG antibody-associated disease (MOGAD) is a newly recognized clinical condition that results in the inflammation and destruction of myelin in the central nervous system (5). Most patients with MOGAD respond well to steroid treatment (6); however, approximately 45% of these patients experience recurrence of symptoms within 2 years after disease onset (7).

Over the past few years, anti-NMDAR encephalitis has been reported to be associated with MOG antibodies. Some researchers have considered this condition as another type of autoimmune encephalitis, distinct from anti-NMDAR encephalitis or MOGAD alone. Since Titulaer et al. first reported an overlapping syndrome of anti-NMDAR and anti-MOG antibodies (8), a growing number of cases have been documented, and their clinical characteristics have become more apparent. Previous reviews have identified several features of this condition, including its higher prevalence in young men (9–13); symptoms similar to anti-NMDAR encephalitis, such as psychiatric symptoms and seizures (10, 12, 13); complex imaging findings with features of both anti-NMDAR encephalitis and MOGAD (10, 12, 13); and a generally favorable functional prognosis (9–13), despite the tendency for recurrence (9–12). Initial treatment often involves steroids. Although some studies have pointed out their effectiveness, previous studies have not thoroughly examined the response to steroid therapy.

This study aimed to report about a patient with encephalitis showing both anti-NMDAR and anti-MOG antibodies who responded favorably to steroids and to review and discuss existing literature on the effectiveness of steroid therapy during the early stages of this condition.

# 2 Case presentation

A previously healthy 25-year-old right-handed man complained of fever and left-sided headache that worsened over time. Seven days later, he was found walking around the room and talking to himself, followed by generalized tonic–clonic seizures that lasted approximately 1–2 minutes, with loss of consciousness. The patient denied any history of trauma, infection, alcoholism, or drug abuse. The patient's family genetic history was unremarkable. During the neurological examination, he was found to have mild impairment of consciousness (Glasgow Coma Scale score: E4V4M5), aphasia, acalculia, oral dyskinesia, myoclonus of the right upper extremity, and right-hand clumsiness. On further examination, no notable cranial nerve, sensory testing, tendon reflex, or meningeal sign abnormalities were detected. Brain magnetic resonance imaging (MRI) findings were normal; however, brain single-photon emission computed tomography revealed increased technetium-99m ethyl cysteinate dimer (99mTc-ECD) uptake in the left frontotemporal region (Figure 1). Electroencephalography showed intermittent frontal rhythmic delta activity, which was more prominent in the left hemisphere. The pressure of the cerebrospinal fluid (CSF) was 130 $mmH_2O$. CSF examination revealed leukocytosis (165/μL; 80% mononuclear), mildly increased protein (48 mg/dL, normal range < 40 mg/dL), and normal glucose (67 mg/dL). The immunoglobulin G (IgG) index was 0.65, and 10 CSF restricted oligoclonal bands were detected. Myelin basic protein was negative. Cytology results were negative for tumor cells, and blood tests for tumor markers were negative. Computed tomography (CT) scans of the chest, abdomen and pelvis did not reveal any tumors. All tests for bacteria, fungi, acid-fast bacilli, viral infections, and systemic autoimmune markers were negative.

Initially, the patient was suspected of having nonconvulsive status epilepticus associated with viral encephalitis and was administered intravenous acyclovir and antiseizure drugs. Despite receiving this treatment, his level of consciousness continued to decline, and his involuntary movements and abnormal behaviors worsened. On the ninth day after admission, he was barely able to speak. Since the patient did not respond to acyclovir and antiseizure medications, autoimmune encephalitis was suspected. The patient's CSF and serum, which had been cryopreserved at the time of admission, were sent to the Department of Animal Model Development, Brain Research Institute, Niigata University, Japan. On the tenth day after admission, the patient was administered IVMP at 1000 mg/day for 5 days empirically prior to the results. The day after administration, his level of consciousness improved significantly, allowing him to engage in simple conversations and recover from right-hand clumsiness and psychobehavioral abnormalities. After 3–4 days of treatment, he underwent cognitive function tests and scored 24/30 on the Mini-Mental State Examination and 14/18 on the Frontal Assessment Battery. After the administration of a second IVMP regimen (1000 mg/day for 3 days), his involuntary movements and mild cognitive decline were relieved, resulting in the full resolution of his symptoms. The patient was discharged on the 35th day and returned to work.

A fixed cell-based assay returned positive results for anti-NMDAR antibodies in the CSF, whereas the serum was negative. He also tested positive for anti-MOG antibodies in both the CSF and serum. Test results were negative for antibodies against contactin-associated protein-like 2 (CASPR2), amino-3-hydroxy-

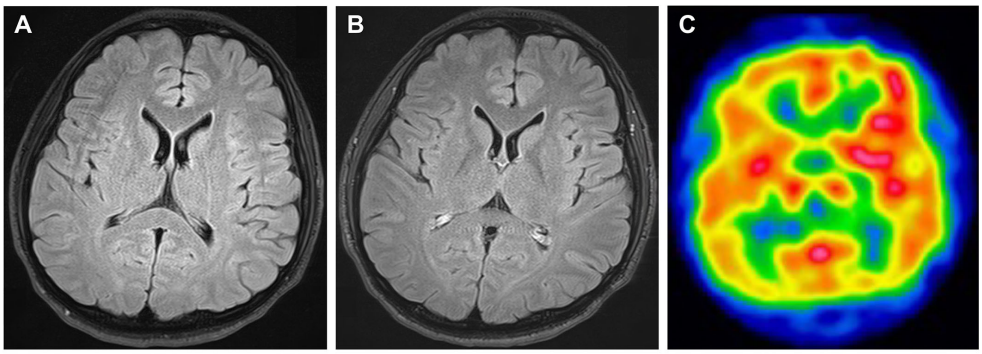



FIGURE 1
Brain images taken prior to immunotherapy. No abnormalities are obvious in fluid-attenuation inversion recovery (FLAIR) magnetic resonance imaging **(A)** or contrast-enhanced FLAIR imaging **(B)**. Brain single-photon emission computed tomography displayed increased 99mTc-ECD uptake in the left frontotemporal region **(C)**.

5-methyl-isoxazolepropionic acid receptor (AMPAR), leucine-rich glioma-inactivated 1 (LGI1), dipeptidyl-peptidase-like protein 6 (DPPX), and gamma-aminobutyric acid B (GABAB) receptor. Stored serum samples collected on admission tested negative for anti-aquaporin-4 (AQP4) antibodies by enzyme-linked immunosorbent assay using commercially available kits (RSR Limited, Cardiff, UK). Additional tests performed by a commercially available fixed cell-based assay indirect immune-fluorescence method (Euroimmun, Lübeck, Germany) revealed that the patient had a CSF anti-NMDAR antibody titer of 1:20 (positivity ≥1:1). The patient's CSF and serum anti-MOG antibodies were measured at the Department of Neurology, Tohoku University, Japan, using a cell-based assay with full-length human MOG-transfected human embryonic kidney cells 293 using goat anti-human Fc-specific IgG as a secondary antibody (Pierce Biotechnology, Rockford, USA), revealing both titers of 1:1024 (positivity ≥1:128 in serum, ≥1:1 in CSF). The cryopreserved CSF sample obtained after the first course of IVMP (on the 17th day after admission) showed a decreased anti-MOG antibody titer of 1:8.

A follow-up examination 2 months later revealed that anti-MOG antibody titer in his CSF had decreased to 1:1, whereas anti-MOG antibody levels in his serum remained high (titer 1:512). Therefore, oral prednisolone (PSL) was initiated at a dose of 10 mg/day to prevent recurrence. However, due to the development of depressive symptoms, which was suspected to be a side effect of PSL, the dose was subsequently reduced to 5 mg, and the symptoms resolved. The patient achieved complete remission with no neurological defects, side effects, relapses, or infectious events at the seven-month follow-up and continued to receive oral PSL. The timeline of the patient's clinical presentation, examination findings, and interventions is shown in Figure 2.

## 3 Literature search

The literature search strategy followed the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search was conducted in the PubMed database up to December 4, 2023, using the terms "NMDAR" and "MOG," and the reference lists of the retrieved papers were also screened to include all previously reported cases. To provide a comprehensive overview of patient characteristics, patients with incomplete information on demographic, clinical, and imaging/serological findings and treatment were excluded. The following cases and episodes were also excluded: (i) episodes without encephalitis; (ii) cases with positive tests for antibodies other than anti-NMDAR and anti-MOG antibodies; (iii) episodes in which pretreatment specimens were not simultaneously positive for anti-NMDAR and anti-MOG antibodies; (iv) episodes in which steroids were not used in the acute phase; and (v) episodes lacking information on response to acute-phase treatment and follow-up. One newly diagnosed patient at our hospital was also included in this study. The flowchart of the study is shown in Figure 3.

The search in PubMed identified 109 patients. After further assessment, 13 patients (13 episodes), including the present patient, were selected for further review. Information on enrolled patients is presented in Table 1 (9, 14–24). Among the 13 patients, 10 were male (76.9%). The age of onset ranged from 6 to 54 years, with a median of 25 years. The main clinical manifestations of this overlapping encephalitis were headache and psychiatric symptoms (53.8%); cognitive impairment, seizure, and paralysis (46.2%); fever (38.5%); impaired consciousness and sensory disturbance (30.8%); and involuntary movement and sleep disorder (23.1%). Only one patient had a complication of optic neuritis. MRI was performed for all episodes before starting acute-stage immunotherapy. MRI revealed abnormalities in the cerebral cortex (46.2%), subcortical white matter, meninges, and pons (23.1%), and thalamus and midbrain (15.4%). Three (23.1%) patients had no obvious brain lesions. One patient with optic neuritis demonstrated contrasting effects in bilateral optic nerves. Only one case was associated with ovarian teratomas, and surgical ovarian removal was performed during the acute phase; the remaining cases showed no signs of tumors.

The presence of anti-NMDAR antibodies in the CSF was confirmed in all cases, with 12 positive results and titers ranging

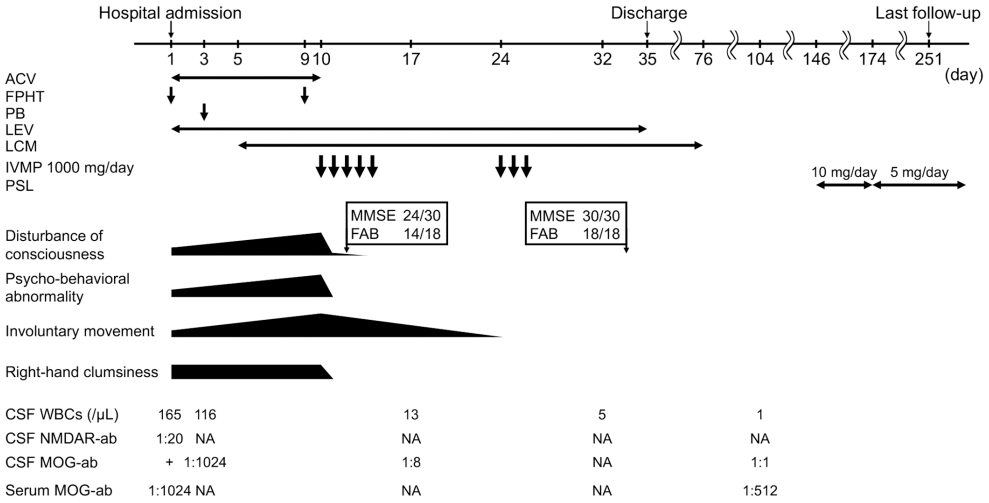



FIGURE 2
Timeline of clinical manifestations, treatment, and CSF and serum findings in our patient. ACV, acyclovir; FPHT, fosphenytoin; PB, phenobarbital; LEV, levetiracetam; LCM, lacosamide; IVMP, intravenous methylprednisolone; PSL, prednisolone; CSF, cerebrospinal fluid; WBC, white blood cell; NMDAR-ab, anti-N-methyl-D-aspartate receptor antibody; MOG-ab, anti-Myelin oligodendrocyte glycoprotein antibody; NA, not available; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.

from 1:10 to 1:32. Serum anti-NMDAR antibodies were tested in nine cases, returning positive results in five cases, with a titer of 1:10. The presence of anti-MOG antibodies was tested in the CSF of eight cases, with six returning positive results (titers ranging from very weak to 1:1024). In all cases, serum anti-MOG antibodies were tested, and all results were positive (titers ranging from very weak to 1:1024).

In the identified literature, all data were available for acute-phase immunotherapy, treatment responses, and long-term immunotherapy. Follow-up data were also available for all episodes for a median period of 6 months (ranging from 1 to 24 months). Steroids were used in all episodes during the acute stage. The most common first-line therapy was IVMP, which was administered to 11 patients. Dexamethasone and PSL were used in one episode each. All patients showed improvement during the acute stage, and 10 cases did not have sequelae. Of these 10 cases, nine exhibited a significant response to steroids during the acute stage, with five relying solely on steroids and four using a combination of steroids and other immunosuppressive medications. For follow-up treatment, six cases were treated with steroids alone, while three received no further treatment. In contrast, three patients demonstrated residual sequelae during follow-up. During the acute phase, one of these patients was treated with steroids alone, while the remaining two were treated with a combination of steroids and other immunosuppressive

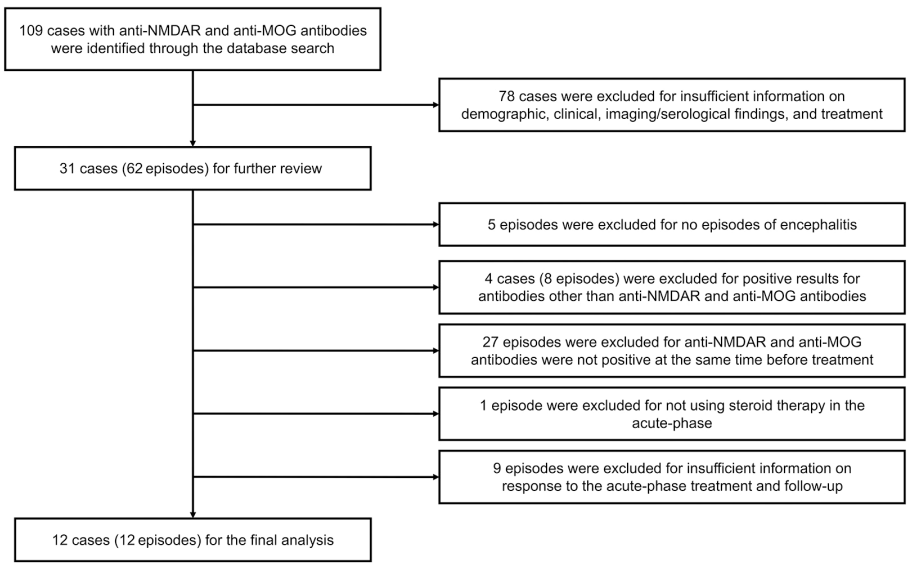



FIGURE 3
Study flowchart.

TABLE 1 Overview of cases included in this study.

| Case (Ref) | Age (years)/ Sex | Symptoms | MRI lesions | Tumor | NMDAR-ab | | MOG-ab | | Acute-phase immunotherapy (timing) | Treatment response | Long-term immunotherapy | Relapse | Sequelae | Interval to the last F/U or relapse (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CSF | Serum | CSF | Serum | | | | | | |
| 1 (14) | 9/F | Fever, impaired consciousness, cognitive impairment, paralysis, dysphagia | Cerebral cortex | No | + | + | NA | + | IVMP, IVIG (NA) | Symptom free at discharge | PSL | Yes | No | 5 |
| 2 (15) | 54/M | Impaired consciousness, psycho-behavioral symptoms, sleep disorder, ataxia, dizziness | Parenchyma surrounding the third ventricle, midbrain, cerebellum | No | 1:32 | NA | NA | 1:320 | IVMP, IVIG, RTX (NA) | Discharged home on the 21st day, with mild gait disturbance | PSL | No | No | 2 |
| 3 (16) | 6/M | Psycho-behavioral symptoms, sleep disorder, speech disorder, gait disturbance | Normal | NA | + | NA | NA | 1:320 | IVMP (NA) | Improved on the third day of the treatment, discharged with full recovery | No | No | No | 3 |
| 4 (17) | 22/F | Headache, fever, seizure, cognitive impairment, psychiatric symptoms, sensory disturbance | Cerebral cortex, meninges | Yes | + | − | Very weak | Very weak | IVMP, IVIG, PE (NA) | Resolved completely, discharged on the 23rd day | No | Yes | No | 3 |
| 5 (18) | 31/M | Headache, cognitive impairment, psychiatric symptoms, involuntary movement, paralysis, sensory disturbance, weight loss | Deep white matter, internal capsule, thalamus, pons | No | + | − | NA | + | IVMP, PE (third day of admission) | Some of the symptoms improved after treatment | RTX | No | Mild cognitive impairment | 6 |
| 6 (19) | 37/M | Headache, seizure, paralysis | Cerebral cortex, meninges | NA | 1:10 | 1:10 | 1:10 | 1:10 | PSL (NA) | Resolved completely during treatment | No | No | No | 24 |
| 7 (9) | 19/M | Impaired consciousness, paralysis, sensory disturbance | Subcortical white matter, basal ganglia, thalamus, pons | NA | + | − | − | + | IVMP, IVIG (NA) | Recovered quickly from lethargy | PSL | Yes | No | 2 |

*(Continued)*





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TABLE 1 Continued

| Case (Ref) | Age (years)/ Sex | Symptoms | MRI lesions | Tumor | NMDAR-ab | | MOG-ab | | Acute-phase immunotherapy (timing) | Treatment response | Long-term immunotherapy | Relapse | Sequelae | Interval to the last F/U or relapse (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CSF | Serum | CSF | Serum | | | | | | |
| 8 (20) | 36/M | Headache, speech disorder, sensory disturbance | Midbrain, pons | NA | – | 1:10 | + | + | DEX (NA) | Relieved quickly, discharged on the 17th day without any sequela | PSL | Yes | No | 14 |
| 9 (21) | 28/M | Headache, fever, seizure, visual impairment, dizziness | Cerebral cortex, subcortical white matter, optic nerve | No | 1:10 | NA | 1:32 | 1:10 | IVMP (59th day after onset) | Some of the symptoms disappeared two months after discharge | PSL, MMF | No | Visual impairment | 6 |
| 10 (22) | 30/M | Headache, fever, seizure, cognitive impairment, psycho-behavioral symptoms | Cerebral cortex, meninges | NA | 1:10 | 1:10 | 1:100 | 1:1000 | IVMP, IVIG (NA) | Improved gradually | PSL, CPA | No | No | 24 |
| 11 (23) | 16/M | Cognitive impairment, psychiatric symptoms, involuntary movement, paralysis | Normal | NA | 1:10 | 1:10 | – | 1:32 | IVMP, IVIG, CPA (NA) | Mild remission, relieved gradually | PSL | Yes | Memory impairment | 1 |
| 12 (24) | 20/F | Seizure, sleep disorder | Cerebral cortex, subcortical white matter | No | 1:10 | NA | NA | 1:32 | IVMP (NA) | Resolved after a month | PSL | No | No | 6 |
| 13 (Our case) | 25/M | Headache, fever, seizure, impaired consciousness, cognitive impairment, psycho-behavioral symptoms, involuntary movement, paralysis | Normal | No | 1:20 | – | 1:1024 | 1:1024 | IVMP (10th day of admission) | Improved significantly, some of the symptoms disappeared the day after treatment | PSL | No | No | 7 |

Ref, reference; M, male; F, female; NA, not available; NMDAR-ab, anti-N-methyl-D-aspartate receptor antibody; MOG-ab, anti-myelin oligodendrocyte glycoprotein antibody; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulins; RTX, rituximab; PE, plasma exchange; PSL, prednisolone; DEX, dexamethasone; CPA, cyclophosphamide; MMF, mycophenolate mofetil; F/U, follow-up; mo, months. –, + mean negative, positive.





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agents. The response to the acute-phase treatment was either slow or partial in all three cases. Relapses occurred in five cases, one of which (Case 7) occurred during steroid tapering and after the discontinuation of steroid use in another two (Cases 1 and 11).

# 4 Discussion

We identified a case of encephalitis that tested positive for both anti-NMDAR and anti-MOG antibodies and that responded well to steroid therapy during the acute stage. At the time of IVMP initiation, we suspected autoimmune encephalitis, specifically anti-NMDAR encephalitis, due to the presence of psychiatric symptoms and the absence of obvious lesions on imaging. Contrary to our expectations, the patient responded rapidly and well to steroid-only treatment, with some of his symptoms resolving by the next day. He was discharged a month later without any lasting effects after having received two IVMP courses. It was later discovered that the patient was positive not only for anti-NMDAR antibodies but also for anti-MOG antibodies.

Previous studies have suggested that both antibodies contribute to the development of overlapping encephalitis (10, 11). However, another report suggested that one of the antibodies might be a bystander in the process (19). We propose that the co-occurrence of anti-NMDAR and anti-MOG antibodies in autoimmune encephalitis represents a novel form of the condition that diverges from anti-NMDAR encephalitis or MOGAD alone and that each antibody has its own unique pathological implications, as discussed below. Anti-NMDAR IgG antibodies exhibit a pathogenic nature (25). Given that patients with overlapping encephalitis frequently exhibit symptoms similar to anti-NMDAR encephalitis, including psychiatric symptoms and seizures (10, 12, 13), we believe that anti-NMDAR antibodies also have pathological significance in overlapping encephalitis. Furthermore, our study revealed that psychiatric symptoms and seizures were common. According to the recent diagnostic criteria for MOGAD, antibody titers are believed to be important for the pathological significance of anti-MOG antibodies (5). Although anti-MOG antibody titers can vary among patients with overlapping encephalitis, the response to steroid treatment and high relapse rates in this condition are challenging to attribute to the clinical phenotype exhibited by anti-NMDAR antibodies and are similar to the clinical features of MOGAD (10, 20, 26). Thus, we believe that the pathological significance of anti-MOG antibodies in overlapping encephalitis is substantial.

Previous studies have presented potential mechanisms for the co-occurrence of anti-NMDAR and anti-MOG antibodies; however, the underlying reasons for their coexistence remain unclear. One key observation that may provide insight into the presence of these antibodies is that oligodendrocytes display functional NMDARs on their surfaces (27, 28). Damage to oligodendrocytes can potentially expose the antigens of both NMDAR and MOG proteins, leading to production of both antibodies (26, 29). Additionally, viral infections may play a role in the co-occurrence of these antibodies (19, 21, 30). Immune reconstitution during immunotherapy has also been suggested as a possible reason for the presence of both types of antibodies (31).

Several case reports on overlapping syndromes have demonstrated significant improvements after steroid treatment. However, studies exploring the effects of steroid therapy across multiple cases are lacking. In a study of five patients with overlapping syndromes, by Fan et al., high-dose steroids and IVIG were used as treatment during the acute phase, which resulted in a significant improvement in the modified Rankin Scale (mRS) score after a median of 18 months (32). Hou et al. used methylprednisolone and IVIG as treatment during the acute phase in seven children with this overlapping syndrome, and in a follow-up study of these patients approximately 1–2 years later, all patients had an mRS score of less than 1 (33).

In this study, we reviewed the efficacy of steroid therapy in 13 patients with encephalitis with coexisting anti-NMDAR and anti-MOG antibodies. Notably, all patients showed improvement during the acute-phase steroid treatment. Furthermore, 76.9% of the patients had favorable outcomes, with no long-term effects, and most experienced rapid or major recovery during the acute stage. Some patients showed improvement within a few days after treatment, whereas others who were discharged recovered within a month or were asymptomatic at the time of discharge. These results suggest that patients with overlapping encephalitis who respond well to steroid treatment during the acute stage may have a positive prognosis. In contrast, three patients remained symptomatic. Interestingly, their improvement after the initial steroid treatment was slow or limited. Despite the fact that their sequelae were generally mild, and the observation periods were short, it is possible that patients who do not show significant early improvement with steroid treatment may have long-term consequences. However, further studies are required to confirm this hypothesis.

The reason for the response of patients with anti-NMDAR and anti-MOG antibody overlapping encephalitis to steroid therapy is not yet completely understood; however, it may be explained by the involvement of anti-MOG antibodies in the pathogenesis of the disease. MOGAD has been reported to exhibit features of responding to steroids during acute phase treatment and relapse upon tapering or discontinuing steroid treatment (6, 34). In this study, many patients responded well to steroid treatment during the acute phase, while three of the five relapse episodes occurred during tapering or after discontinuation of steroid treatment. Another hypothesis for the high treatment response to steroids in overlapping syndromes is the low titers of anti-NMDAR antibodies. All cases in which anti-NMDAR antibody titers were measured in this study had low titers. A literature review of FLAIR hyperintense lesions in MOG-associated encephalitis with seizures with anti-NMDAR antibodies, reported by Yang et al., also found low levels of anti-NMDAR antibodies in the CSF, with titers ranging from 1:1 to 1:32 (22). Other studies have demonstrated that anti-NMDAR antibody titers are associated with symptom severity and prognosis and that patients with low levels of these antibodies typically exhibit milder symptoms and more favorable outcomes (35–38).

Our study has several limitations. First, the sample size was too small to provide a clear picture of the response to steroid treatment, due to the rarity of the coexistence of anti-NMDAR and anti-MOG antibodies and the limited number of cases with coexisting antibodies prior to treatment. Second, the information available on treatment response varied between episodes, with the speed and magnitude of recovery being difficult to quantify in some cases. Moreover, the duration of follow-up differed, with some papers describing follow-up periods of less than 6 months. Finally, there were episodes in which

immunotherapy was used in combination with steroids, making it difficult to determine the pure effect of steroid therapy because the combination may have altered the therapeutic response.

In conclusion, our patient was diagnosed with anti-NMDAR and anti-MOG antibody overlapping encephalitis due to the presence of anti-NMDAR antibodies and high levels of anti-MOG antibodies, along with symptoms indicative of anti-NMDAR encephalitis and significant improvement after steroid treatment, which suggests that both antibodies are involved in the disease process. Our study suggest that steroid therapy is beneficial for acute phase treatment of anti-NMDAR and anti-MOG antibody overlapping encephalitis. Patients who showed rapid or significant improvements with steroid therapy tended to have a good prognosis. This approach may help avoid additional immunotherapy and ensure careful follow-up. Therefore, based on their history and symptoms, we recommend measuring anti-MOG antibodies in patients who respond well to steroids, even if anti-NMDAR encephalitis is suspected. Further prospective studies with a large number of cases and detailed documentation are needed to provide proper guidance for acute phase and follow-up treatments of overlapping encephalitis.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

HK: Writing – original draft, Writing – review & editing, Methodology, Validation. YT: Writing – review & editing. JN: Writing – review & editing. KY: Writing – review & editing. NT: Writing – review & editing. SH: Data curation, Writing – review & editing. TK: Writing – review & editing. KK: Investigation, Writing – review & editing. NM: Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: "Fur stole and turtleneck" and "halter-back" signs: an expanded wardrobe for dermatomyositis

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A diagnosis of dermatomyositis requires recognition of distinct patterns of skin disease in combination with, and sometimes without, muscle weakness. Often, a striking contrast between involved and uninvolved areas is observed. Familiar patterns include eyelid and midfacial eruptions, Gottron papules/sign, and upper back (shawl sign), central chest (V/open collar sign), and lateral thigh (holster sign) involvement. More recently, new specific antibody/phenotype-associated patterns have been reported. We describe a case series of two distinct patterns of skin involvement in six adult patients with both classical and amyopathic dermatomyositis. Three had paraneoplastic disease. All had intermediate to richly pigmented skin; five were of Afro-Caribbean and one was of Asian-Caribbean descent. Four were men, and two were women. Ages ranged from 41 to 89 years. All patients had concomitant hallmark signs (facial, hand, and/or trunk signs). Three were amyopathic. The first pattern involved a sharply demarcated, horizontally oriented hyperpigmented patch/thin plaque across the shoulders and upper chest, extending up the anterior neck. The second was the combination of the classical upper back shawl distribution with distinct mid-back sparing and diffuse involvement of the lower back. Named patterns help with the recognition of skin rashes in dermatomyositis. Based on the current lexicon describing items of apparel, we liken the first pattern to a "fur stole and turtleneck" sign and the latter to a "halter-back" or "reflected-shawl" sign. Biopsies revealed hyperkeratosis and interface dermatitis, often with epidermal atrophy, compatible with dermatomyositis. These patterns perhaps represent the coalescence of already well-described signs, photo-exacerbation, koebnerization, mechanical stretch, and other currently unclear factors contributing to patterning in dermatomyositis. Pattern distribution recognition is particularly valuable in individuals with richly pigmented skin who may lack typical violaceous erythema. The distinct

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demarcation led to the initial misdiagnosis of allergic contact dermatitis or other exogenous dermatitis in most of our patients. Further work involves evaluation of antibody phenotype and internal involvement associations. Limitations include lack of specific antibody panels and longitudinal follow-up data.

KEYWORDS

dermatomyositis, autoimmune connective tissue disease, shawl sign, cutaneous, dermatologic, skin of color, bullous dermatomyositis

## Introduction

Dermatomyositis (DM) is characterized by a combination of distinctly patterned cutaneous signs with or without associated muscle disease. Classical (hallmark) patterning includes Gottron papules/sign, heliotrope, V-neck, shawl, sleeve, and holster signs (1). More recently, specific antibody-associated reproducible non-hallmark phenotypes have expanded the spectrum of patterned skin disease. Psoriasiform lesions, verrucous palmar papules, red-on-white lesions, and ovoid palatal patches have been described with anti-TIF1-γ antibodies while ulcerating, and inverse Gottron papules are seen in patients with antibodies against MDA5 (2–5). Although skin biopsies reveal characteristic interface dermatitis (ID), the light microscopic findings are indistinguishable from acute/subacute and occasionally chronic cutaneous lupus erythematosus (6). Recognition of the typical and expanding patterns of skin involvement is therefore crucial to arrive at the correct diagnosis, particularly in individuals with richly pigmented skin and amyopathic disease, cases where non-hallmark features predominate, or in resource-poor settings with limited access to ancillary antibody testing. We describe a series of two distinct patterns of skin involvement in six adult patients with both classical and amyopathic DM. Based on the current apparel-based lexicon describing trunk/proximal limb signs, we designate these signs "fur stole and turtleneck" sign (FSTNS) and "halter-back" sign (HBS).

## Case descriptions

### Case 1

An 80-year-old Afro-Caribbean woman presented to the dermatology clinic for evaluation of a hyperpigmented and pruritic eruption on the chest, present for 3 years. She had a history of Hashimoto thyroiditis, hypertension, and gastroesophageal reflux disease maintained on levothyroxine, nifedipine, and lansoprazole. Recent blood work revealed a low-titer positive ANA (1:40) and positive anti-centromere and anti-U1RNP antibodies. Anti-Ro/La/Jo-1/Sm/Scl-70 and ds-DNA were negative. She denied features of Raynaud phenomenon or skin tightening. She denied muscle weakness. She had been referred to exclude systemic sclerosis (SSc) or allergic contact dermatitis. The patient was unsure if her rash was photo-exacerbated. Physical examination revealed dark brown, scalded-appearing hyperpigmentation involving the eyelids, malar cheeks, external ear, and lateral thighs. Hyperpigmented patches and plaques overlying the joints and extending along the interarticular surface (Gottron papules with ray sign) were noted (Figure 1A). A hyperpigmented and hyperkeratotic patch with subtle background erythema on the upper back consistent with a shawl sign was present. Although pruritic, she denied pre-existing erythema. Dermoscopy revealed nail fold telangiectasia with drop-out capillary loops. The skin, while hyperpigmented and hyperkeratotic, was not sclerotic. No sclerodactyly, facial telangiectasia, or facial skin tightening was identified. The cutaneous findings were compatible with DM. Strikingly, sharply demarcated horizontally oriented hyperpigmentation with prominent skin markings and focal hypopigmentation was present across the anterior shoulders and upper chest and extending up the anterior neck (Figure 2A). There was distinct sparing of the lower chest. The pattern across the chest was reminiscent of a fur stole, while the confluent involvement of the neck resembled a turtleneck sweater. A skin biopsy of the anterior shoulder revealed hyperkeratosis, epidermal atrophy, basal layer vacuolation, squamatization of the basal layer, and melanophages consistent with an ID of autoimmune connective tissue disease (AICTD). Alcian blue revealed mildly increased dermal mucin (Figure 3A). No significant perivascular lymphocytic inflammation was present. Homogenization and sclerosis compatible with scleroderma were not present. Musculoskeletal examination revealed normal power. Creatinine kinase (CK) levels were normal (117 U/L). The patient was started on hydroxychloroquine sulfate 200 mg daily, prednisone 15 mg daily (tapered to 7.5 mg), mycophenolate mofetil 500 mg twice daily, and 0.05% clobetasol propionate ointment. Investigations including pulmonary function tests, CT-CAP, upper/lower gastrointestinal endoscopy, mammography, serum protein electrophoresis, serum CA-125, and CEA were recommended. Myositis antibody panel was also suggested but declined due to financial constraints. CT-CAP revealed changes compatible with interstitial lung disease. At the time of writing (1 year after diagnosis), no cancer has been detected and the skin disease is controlled.

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FIGURE 1
Select cutaneous manifestations of dermatomyositis in reported patients. Note Gottron sign/papules **(A)**, "ragged" cuticular hypertrophy in Case 2 **(B)**, and typical violaceous erythema, scale and "sleeve" sign in Case 3 **(C)**. Cases 1–3 also had a fur stole and turtleneck sign. Those with a halter-back/reflected shawl sign demonstrate Gottron papules (Cases 4 and 5, **D**, **E**) and V-sign (Case 6, **F**). Case 6 also had erosion and blisters (not shown).

## Case 2

A 73-year-old Afro-Caribbean man admitted for aspiration pneumonia with a history of hypertension (maintained on telmisartan and nifedipine) and dysphagia was referred to the dermatology in-patient service for evaluation of a hyperpigmented rash present for 3 months. The patient had concomitant proximal muscle weakness with a recent inability to ambulate. He also reported an 8-month history of generalized joint pain. He had a history of positive rheumatoid factor [RF, 106 IU/L (normal <40 IU/L)], anti-cyclic citrullinated peptide, and ANA (no titer available). Anti-Ro/La/Jo-1/Sm/Scl-70 and ds-DNA were negative. The patient was unsure if his rash was photo-exacerbated. Dermatologic examination revealed dark brown scalded-appearing hyperpigmentation involving the central face, eyelids, and external ear. A hyperkeratotic papule was seen overlying the right second metacarpal joint. Cuticular hypertrophy with intra-cuticular hemorrhage was present (Figure 1B). The features were consistent with DM. A sharply demarcated, horizontally oriented macular hyperpigmentation involving the upper chest, anterior shoulders, and anterior neck (fur stole and turtleneck sign) was noted (Figure 2B). He denied a pre-existing erythematous phase. A skin biopsy (anterior shoulder) revealed epidermal atrophy, subtle basal layer vacuolation apoptotic keratinocytes, little inflammation, and scattered heavily pigmented melanophages consistent with an ID (Figure 3B). Alcian blue was negative for dermal mucin. Musculoskeletal examination revealed reduced power (3/5) of the bilateral hip flexors. CK levels were elevated (1,575 U/L). Anti-Ro/La/Jo-1/Sm/Scl-70 and ds-DNA were negative. Additional investigations including muscle biopsy, malignancy screens, myositis antibodies, and pulmonary function tests were recommended but not performed due to financial constraints. The patient defaulted from follow-up.

## Case 3

A 60-year-old Afro-Caribbean man presented to the dermatology clinic for evaluation of a >1-year history of a pruritic rash, previously diagnosed as a contact/eczematous dermatitis. He had a history of schizophrenia but was not maintained on any medications. He denied muscle weakness but endorsed a history of recent decreased appetite and weight loss. The patient was unsure if his rash was photo-exacerbated. Dermatologic examination revealed violaceous erythema involving the malar cheeks and eyelids. Poikiloderma and scaly hyperpigmented plaques with background violaceous erythema were also seen in a shawl and sleeve-sign pattern (Figure 1C) and on the lateral abdomen. Similar




FIGURE 2
"Fur stole and turtle neck" and "Halter-back/reflected shawl" signs. Note the horizontally oriented sharply demarcated involvement of the upper chest and anterior shoulders (fur stole pattern) with diffuse involvement of the anterior neck (turtleneck pattern) in Cases 1–3 **(A–C)**. Observe the varied primary morphologies including atrophic hyperpigmentation with focal depigmentation **(A)**, macular hyperpigmentation (Case 2, **B**), and thin hyperkeratotic, hyperpigmented, and violaceous plaques (Case 3, **C**). Halter-back/reflected shawl sign (Cases 4–6, **D–F**) exhibits upper and lower back involvement with distinct sparing of the mid-back. Again, note the variable primary morphologies including psoriasiform plaques (Case 4, **D**), macular hyperpigmentation/red-brown erythema (Case 5, **E**), and macular diffuse and flagellate erythema (Case 6, **F**). This latter patient has antibodies against NXP-2 and SSA 52 kd.

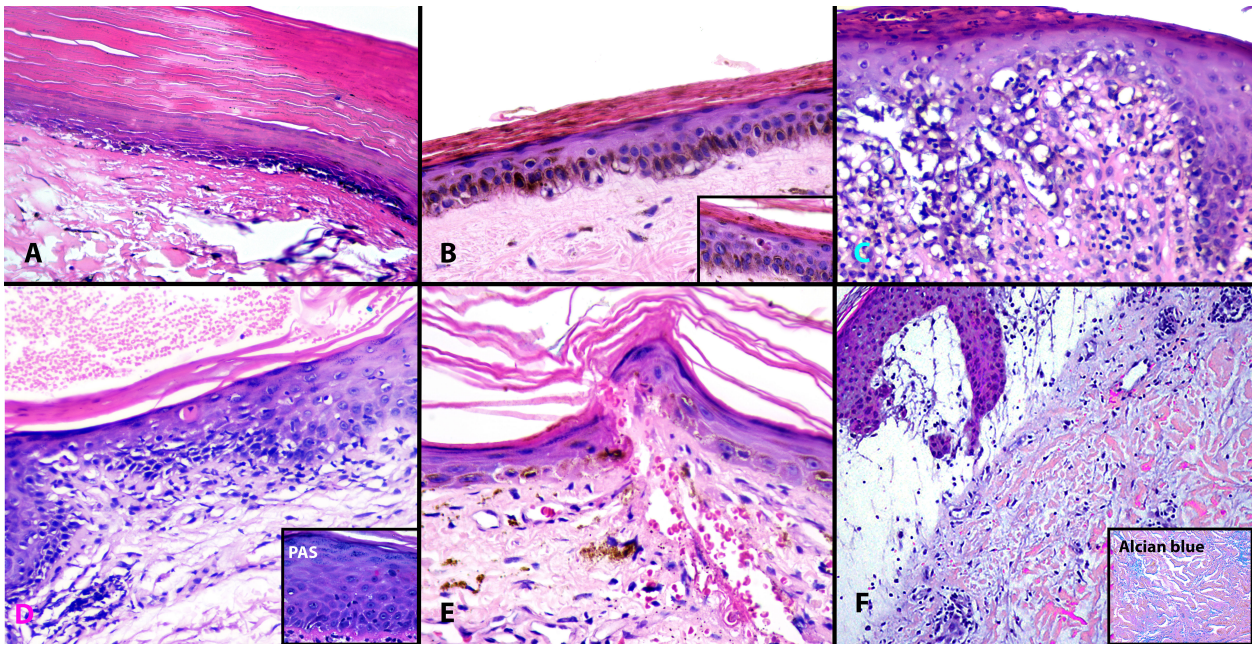



FIGURE 3
Histopathologic findings in "Fur stole and turtle neck" and "Halter-back/reflected shawl" signs. All cases demonstrated interface dermatitis. Note the hyperkeratosis, epidermal atrophy, and basal vacuolar change in biopsies from Cases 1, 2, and 4 (**A, B**, **D**). Apoptotic keratinocytes are visualized (**B** inset, **D**, **E**). Case 3 **(C)** has mild epidermal hyperplasia and a more prominent lymphocytic infiltrate while Case 6 **(F)** demonstrates massive papillary dermal edema and increased dermal mucin, highlighted by Alcian blue (**F**, inset). **(A–E)**, Hematoxylin and eosin (H&E) ×200; D inset, Periodic acid Schiff (PAS) ×400; F, H&E ×100; F inset, Alcian Blue ×200.

lesions were also present in a sharply demarcated distribution involving the upper chest, anterior shoulders, and anterior neck (fur stole and turtle neck pattern, Figure 2C). Skin biopsy (chest) revealed hyperkeratosis, mild epidermal hyperplasia, basal layer vacuolation, apoptotic keratinocytes, a superficial perivascular and focally band-like lymphocytic infiltrate, and scattered melanophages consistent with an ID (Figure 3C). Alcian blue revealed increased dermal mucin. Shortly after biopsy, the patient developed erythematous plaques overlying the metacarpal and interphalangeal joints consistent with Gottron papules. The features were consistent with DM. Musculoskeletal examination revealed normal power and CK levels were normal (31 U/L). The patient was commenced on prednisone 60 mg daily, hydroxychloroquine sulfate 400 mg daily, and 0.05% clobetasol propionate ointment twice daily. ANA/Anti-Ro/La/Jo-1/Sm/Scl-70 and ds-DNA were negative. Myositis-antibody panel was not performed due to financial constraints. A computed tomography (CT) scan of the chest revealed a large necrotic mediastinal mass suspicious for malignancy. At the time of writing, the patient is awaiting biopsy of the mass.

## Case 4

An 89-year-old Asian-Caribbean man presented for evaluation of a pruritic rash present for 4 years and managed as chronic eczematous dermatitis. Dermatologic examination revealed violaceous erythema and hypopigmented patches involving the eyelids, photodistributed malar cheeks, forehead, anterolateral arms, and the V of the neck. Erythematous papules were present over the metacarpal and interphalangeal joints consistent with Gottron papules (Figure 1D). The findings were characteristic of DM. In addition, well-defined erythematous and psoriasiform plaques involving the upper (shawl sign) and lower back with distinct sparing of the mid-back was noted (Figure 2D). The distribution was reminiscent of a halter-back blouse or, given its mirror image, a "reflection" shawl sign. The spared skin was not limited to the inferior margin of the scapula. A biopsy (shoulder) revealed hyperkeratosis, epidermal atrophy, apoptotic keratinocytes, a sparse superficial perivascular lymphocytic infiltrate, increased dermal mucin, and a PAS-positive thickened basement membrane zone consistent with ID of AICTD (Figure 3D). He endorsed difficulty getting up from a seated position and muscle examination revealed decreased power at the hip flexors. While muscle enzymes were requested, the patient declined any bloodwork. He commenced 0.05% clobetasol propionate ointment, mycophenolate mofetil 1 g twice daily, and hydroxychloroquine sulfate 200 mg daily. CT scan of the pelvis revealed a bladder mass. Biopsy confirmed papillary urothelial carcinoma. Transurethral resection of bladder tumor resulted in marked improvement of skin disease.

## Case 5

A 54-year-old man presented with a 6-month history of a pruritic rash involving the trunk, scalp, and hands. He had a history of hypertension and dyslipidemia, maintained on nifedipine and simvastatin for >5 years. He also had a 3-year history of Stage IIIA erythrodermic mycosis fungoides, in remission and controlled on methotrexate 20 mg weekly and folic acid. He was previously maintained with narrow-band ultraviolet light therapy but had recently noted increased pruritus and redness after treatment and phototherapy was discontinued. Although initially interpreted as recurrent erythrodermic mycosis fungoides, the eruption evolved to violaceous erythema involving the scalp, erythematous lichenoid papules and plaques overlying the metacarpal and interphalangeal joints with interarticular extension (Gottron papules with Ray sign, Figure 1E), and mid-facial hyperpigmentation compatible with DM. Violaceous erythema was seen involving the upper and lower back, with striking sparing of the mid-back (halter-back/reflection shawl pattern, Figure 2E). The sparing was not limited to the inferior border of the scapula. Biopsies of the new rash (back and thigh) revealed hyperkeratosis, epidermal atrophy, apoptotic keratinocytes, a sparse superficial perivascular lymphocytic infiltrate, and prominent melanophages consistent with an ID (Figure 3E). No Pautrier microabscesses or lymphocytic atypia were seen to suggest mycosis fungoides. Dermal mucin was not increased. The patient had no weakness and a musculoskeletal examination revealed normal power. CK level was normal (134 U/L). Upper and lower GI endoscopy, scrotal ultrasound, CT-CAP, PSA levels, and serum protein electrophoresis were normal. Within 6 months, the patient developed night sweats, weight loss, and enlarged lymph nodes. Inguinal lymph node biopsy revealed an atypical lymphoid infiltrate with Reed–Sternberg cells. The infiltrate expressed CD30, CD15, and PAX-5 consistent with the nodal Hodgkin disease. Chemotherapy was commenced (adriamycin, bleomycin, vinblastine sulfate, and dacarbazine) with resolution of his DM-type rash.

## Case 6

A 51-year-old Afro-Caribbean woman with no history of chronic illness presented to the emergency room with a 2-month history of a pruritic skin rash diagnosed as an "allergic reaction" and prescribed antihistamines. She subsequently developed shoulder and thigh pain with progressive muscle weakness. Four days before presentation, she became unable to stand. Skin examination revealed diffuse erythema involving the upper chest (V-neck, Figure 1F), outer arms (sleeve sign), outer thighs (holster sign), and abdomen. Areas of detachment and both flaccid and tense bullae were noted. Striking flagellate and diffuse erythema were noted to involve the upper back and lower back with sparing of the mid-back (HBS/RSS, Figure 2F). Musculoskeletal examination revealed decreased power at the hips, elbows, and knees. Skin biopsy (arm) revealed basal layer vacuolar change, massive papillary dermal edema with subepidermal clefting, a sparse superficial perivascular lymphocytic infiltrate, and Alcian blue-positive increased dermal mucin (Figure 3F). The findings were consistent with DM. CK levels were elevated (3,866 U/L). A myositis antibody panel revealed positive anti-NXP-2 and anti-SSA 52 kd antibodies. The patient was commenced on prednisone 1 mg/kg and

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TABLE 1 Clinical and laboratory findings in patients with fur-stole, turtleneck, and halter-back/reflected shawl signs.

| Details | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| **Demographics** | 80 years old<br>F | 73 years old<br>M | 60 years old<br>M | 89 years old<br>M | 54 years old<br>M | 41 years old<br>F |
| **Referral diagnosis** | Scleroderma<br>Pellagra<br>ACD | Dermatomyositis<br>Scleroderma | Eczematous dermatitis<br>Contact dermatitis | Pruritus<br>Eczematous dermatitis | MF flare | ICD<br>Allergic reaction |
| **Comorbidities** | Hashimoto thyroiditis<br>HTN | None | Schizophrenia | HTN, DMII | MF<br>HTN<br>DM | None |
| **DM features** | Malar and eyelid pigmentation, GP, Ray sign, shawl/sleeve/holster signs, poikiloderma | Malar and eyelid pigmentation, GP, cuticular dystrophy, sleeve sign | Malar and eyelid erythema<br>Shawl/sleeve signs, poikiloderma | Malar and eyelid erythema, GP, shawl, sleeve, V-sign | Mid-facial pigmentation, GP, Ray sign<br>Shawl sign<br>Violaceous scalp erythema | V-sign, sleeve sign<br>Flagellate erythema<br>Bullae |
| **Specific pattern** | FSTNS | FSTNS | FSTNS | HBS/RSS | HBS/RSS | HBS/RSS |
| **Biopsy** | Yes<br>ID + EA | Yes<br>ID + EA | Yes<br>ID + PSEH | Yes<br>ID + EA | Yes<br>ID + EA | Yes<br>ID + papillary dermal edema |
| **Autoantibody status** | ANA+, U1RNP+, centromere+ | ANA+, RF+, CCP+ | ANA–<br>ENA– | NP | ANA–<br>ENA– | Anti-NXP-2 and anti-SSA 52 kd |
| **Muscle status** | Amyopathic<br>CK 117 | Myopathic<br>CK 1575 | Amyopathic<br>CK 31 | Clinically myopathic<br>CK NP | Amyopathic<br>CK 134 | Myopathic<br>CK 3866 |
| **Cancer associated** | Not at time of writing | Defaulted from care | Likely (large necrotic paratracheal mass, awaiting biopsy) | Yes (bladder papillary urothelial carcinoma | Yes<br>Hodgkin lymphoma | Not at time of writing |

ACD, allergic contact dermatitis; ANA, antinuclear antibody; CK, creatine kinase; CCP, cyclic citrullinated peptide; DMII, Type II diabetes mellitus; EA, epidermal atrophy; ENA, extractable nuclear antigens; FSTNS, fur stole and turtle neck sign; GP/S, Gottron papules; HBS, halter-back sign; HTN, hypertension; ID, interface dermatitis; ICD, irritant contact dermatitis; PSEH, psoriasiform epidermal hyperplasia; MF, mycosis fungoides; NP, not performed; RSS, reflected shawl sign.

mycophenolate mofetil 1 g twice daily. Malignancy screens were recommended but none were performed. At the time of writing (20 months after diagnosis), the patient's disease is well-controlled without known malignancy or internal disease.

Clinical/laboratory findings for Cases 1–6 are summarized in Table 1.

## Discussion

We describe two striking and repeatedly encountered patterns of skin involvement in six adult patients with DM. We define FSTNS as a horizontally oriented eruption across the anterior shoulders and chest, extending up the anterior neck with sharp inferior demarcation from the lower chest and abdomen. It differs from the shawl sign (eruption over the upper back, neck, and posterior shoulders) and the V/open collar sign describing V-shaped erythema corresponding to the central chest (7). The HBS or "reflected-shawl" sign (RSS) is defined as upper (classical shawl) and mirror-image lower back involvement with distinct, horizontally oriented mid-back sparing. All forms, regardless of their primary morphology (see below), demonstrated characteristic ID, albeit with varying degrees of epidermal change and inflammation.

Regarding the clinical features of those with an FSTNS, all were Afro-Caribbean and had hallmark DM features. Case 1 had background autoimmunity (Hashimoto thyroiditis) and positive anti-U1RNP/centromere antibodies. Specifically, given her antibody status, we considered an overlap syndrome/MCTD with some features of SSc. We also note focal admixed hypopigmentation involving the chest. While admixed "salt-and-pepper" pigmentation of SSc cannot be entirely excluded, we consider most of her eruption a manifestation of DM for the following reasons: (1) While the patient is older and may have background age-related skin laxity, at the time of presentation, she continued to be symptomatic (pruritus) and therefore a "burnt-out" AICTD is unlikely. (2) Even in burnt-out SSc, biopsy findings should not have overlying ID, atrophy, or squamatization of the basal layer. (3) The patient's malar, eyelid, sleeve-sign, articular, and shawl-sign pigmentation together with her chest eruption is highly patterned and sharply demarcated, features/distribution unusual in SSc. (4) While mixed hyper/hypopigmentation is most commonly seen in SSc, we recognize that it is not specific for this entity and similar findings have been reported in DM (8). The combination of epidermal atrophy and dyspigmentation favors poikiloderma of DM over SSc. Other entities presenting histologically with ID and post-

inflammatory pigmentation, particularly lichen planus pigmentosus (LPP), could be entertained but distinct clinical features including often asymptomatic circular/oval patches on the trunk, diffuse (but non-patterned) pigmented patches with distinct blue-gray color, and predilection for the temporal and preauricular rather than malar face easily distinguish this condition (9). Case 2 had rheumatoid arthritis overlap. Two were amyopathic and one had muscle involvement. Case 1 has radiographic features suggestive of interstitial lung disease and Case 3 is likely malignancy-associated, although a definitive cancer diagnosis is pending. Importantly, as all are within 5 years of diagnosis, an associated malignancy/systemic disease may yet emerge in the remainder. Interestingly, while the distribution pattern was reproducible, the primary morphology varied. One patient had atrophic but hyperkeratotic and hyperpigmented skin, another had primarily macular hyperpigmentation, and the third had scale, background classical violaceous erythema, and admixed hyperpigmentation. None of the patients were suspected to have medication-induced disease.

Two of our patients with HBS/RSS were Afro-Caribbean and one was Asian-Caribbean. Two had muscle involvement and one was amyopathic. Similar to those with FSTNS, while the pattern of involvement was strikingly similar, the primary morphology was variable, including psoriasiform plaques, violaceous macular erythema, and diffuse and flagellate red macular erythema. Case 6 had the additional unique finding of vesiculobullous disease. While rare, bullous DM is well described and included as compatible in Sontheimer's diagnostic criteria for ADM (10). Bullae are due to marked subepidermal edema as seen in our case (11). Very recently, like our patient, bullous DM has been described in a patent with anti-NXP2 antibodies (12).

Recognition of described patterns of cutaneous disease is crucial for early and accurate diagnosis of DM, highlighted by the initial misclassification in five of our six patients, three of whom had likely paraneoplastic disease. In particular, eczematous dermatitis was frequently considered, presumably because patterned itchy skin disease often generates a differential diagnosis of allergic contact dermatitis (13). Identification of distribution patterns is particularly important in individuals with richly pigmented skin where DM is often misclassified due to the frequent absence of morphologically typical violaceous erythema and predominance of pigmentary alteration (14). This is underscored in Cases 1 and 3 where pigmentation was the primary aberration and both patients denied noticeable precursor erythema. Although most dermatologists and rheumatologists are familiar with classical hallmark features, less familiar non-hallmark and atypical eruptions are increasingly described. Some of these have reproducible associations with specific antibodies including ovoid palatal patch/verrucous palmar papules/red-on-white patches with anti-TIF1-γ antibodies, calcinosis/edema with anti-NXP-2 antibodies, and inverse/ulcerated Gottron papules and anti-MDA5 antibodies (2–5, 15). Other non-classical/novel presentations without definitive/repeated antibody associations include whip-like or flagellate erythema (described in some individuals with anti-TIF1-γ antibodies but also in Case 6 with anti-NXP-2 disease), pityriasis rubra pilaris-like (Wong-type) DM, and perinasal swelling (16–18). We add FSTNS and HBS/SS to the recognizable patterns of skin disease in DM. Unfortunately, apart from Case 6, we are currently unable to link these patterns to specific autoantibodies.

What initiates patterned skin disease in DM? While sun exposure is the presumed culprit for some signs (malar erythema, sleeve sign, and V-sign), for lesions over bony prominences, trauma is a likely contributor. The development of unilateral Gottron papules on the functional hand of a patient with hemiparesis and inverse Gottron papules after participating in tug-of-war support a role for trauma (19, 20). Additionally, compared with photodistributed signs, Gottron papules exhibit mechanical stretch-related expression of CD44v7. Proposedly, in combination with abnormal amounts of osteopontin, there is a resulting increased inflammatory cell influx, raising the possibility that areas of increased physiologic skin stretch may induce cutaneous lesions of DM (21). While FSTNS could simply represent the coalescing of V and sleeve signs, unique characteristics include involvement of the anterior neck and the sharp inferior horizontal demarcation rather than the rounded apex of the V-sign. Perhaps a combination of photoexposure and well-established high skin tension of the anterior chest (22) contributes to this pattern, although involvement of the anterior neck remains unexplained by these and other proposed triggers having low skin tension, relative sun protection by the mandibular overhang, and not being particularly prone to trauma. For HBS/RSS, sparing of the mid-back is suggestive of the role of scratching contributing to this morphology. The pattern of central back sparing is strikingly similar to the "butterfly sign" seen in pruritic disorders, due to the inability to effectively reach, and thus pick/scratch, the central back, leading to post-inflammatory pigmentation or excoriations involving the upper and lower back but with uninvolved mid-back skin (23). As DM is not an exogenous or artifactual disease, scratching likely induces an isomorphic (koebnerized) response, inducing new disease in areas of induced trauma (24). In support, pruritus was reported in all our patients with this pattern. Like FSTNS, the posterior shoulders and upper back have increased skin tension (25). Skin tension compounded by physiologic movement around the shoulder joint and with bending could potentially contribute to this pattern. While these proposed mechanisms are plausible, we should also recall that certain variants of DM have unusual sparing/involvement patterns, unassociated with any of the factors described above, and we cannot exclude an unexplained predilection for our reported patterns. In particular, Wong-type DM, like its morphologic comparator disease, pityriasis rubra pilaris, has seemingly random islands of normal skin in a background of erythroderma (18). Additionally, an "angel-wing" pattern described as involvement of the upper and lower back, but with unusual sparing in an arched wing-like pattern along the inferior scapular border, has been described in a subset of Japanese patients with anti-SAE antibodies (26). While similar (and perhaps mechanistically related) to HBS/RSS, the sparing pattern was distinctly arched along the inferior border of the scapular rather than broad sparing of the mid-back. Although, based on the countries of origin of rare presentations, certain DM patterns may favor particular ethnic groups/geographic locations, at this time we are unable to determine if this is true for FSTNS and HBS/RSS. Nevertheless, these morphologic variants further highlight the tendency for distinct patterning of skin disease in DM and the need for clinician familiarity with the progressively protean presentations of this disease.

## Conclusion

In summary, we present two recognizable patterns of patterned skin disease in adult DM. Recognition should prompt early diagnosis and appropriate investigations. A sharply demarcated disease should not be viewed as unusual in DM. Although the distribution is strikingly similar, the primary morphology of the eruption varies. Biopsy demonstrates classical ID and will easily exclude exogenous causes of dermatitis including allergic contact etiologies. At this time, patients with FSTNS and HBS/RSS do not have a specific risk profile and should therefore be carefully evaluated for muscle disease, internal involvement, and associated malignancies. Further work includes evaluating for antibody–phenotypic associations. Limitations include a lack of confirmed myositis antibodies in the majority of patients and outstanding results, primarily due to patient financial constraints.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the studies involving humans because case reports at our institution do not require IRB approval. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

JH: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. AB: Data curation, Methodology, Resources, Writing – original draft, Writing – review & editing. TM: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. CB: Data curation, Methodology, Resources, Writing – original draft, Writing – review & editing, Investigation. AS: Data curation, Resources, Writing – original draft, Writing – review & editing. SS: Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. KF: Data curation, Investigation, Resources, Writing – original draft, Writing – review & editing. AA: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Sequential therapy with dupilumab and baricitinib for severe alopecia areata with atopic dermatitis in children

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An 8-year-old female child presented with patchy hair loss for 1 year, accompanied by eyebrow loss for 6 months. Microscopic examination of the hair confirmed the features of active stage alopecia areata, with a Severity of Alopecia Tool (SALT) score of 70%. The diagnosis was severe alopecia areata. The patient had a history of atopic dermatitis since infancy, with recurrent episodes of scattered papules and pruritus for 8 years. Initial treatment involved subcutaneous injections of dupilumab 300mg every 2 weeks for 6 months, resulting in a reduction of SALT score to 20% and improvement of atopic dermatitis symptoms. Discontinuation of Dupilumab and initiation of daily oral Baricitinib at a dose of 2mg for a duration of 5 months. According to the SALT score evaluation, the severity of hair loss was less than 10% and there was significant regrowth of hair. No significant adverse reactions were observed during the treatment period.

KEYWORDS

**alopecia areata, atopic dermatitis, autoimmunity, baricitinib, dupilumab**

## Introduction

Alopecia areata (AA) is a common immune-mediated, inflammatory, non-scarring hair loss condition, with a slightly higher incidence in children compared to adults. The exact pathogenesis of AA is not fully understood, but histopathologically, lymphocytic T-cell infiltration around the hair follicles can be observed. Studies have indicated that childhood AA often has a familial predisposition, and severe cases in children can pose challenges in treatment, with possible resistance to conventional therapies (1). Immune-mediated inflammatory skin diseases encompass a group of commonly associated conditions, including atopic dermatitis (AD), vitiligo, and AA, with clinical overlap in some cases, and the severity of the diseases showing correlation, making treatment more complex (2). In this article, we present a case study involving an 8-year-old patient who had both severe

alopecia areata and atopic dermatitis. The patient underwent a 6-month treatment involving Dupilumab subcutaneous injections, followed by a 5-month treatment with Baricitinib oral medication. The therapeutic outcomes were highly satisfactory, as evidenced by significant improvement in AD symptoms and substantial regrowth of hair in most of the affected areas of alopecia. The study has received approval from the Institutional Ethics Committee of China-Japan Friendship Hospital, with the assigned approval number of 2020-127-K80.

## Case report

An 8-year-old female patient, with a height of 135cm and weight of 26.5 kilograms, presented with coin-sized patches of hair loss on the scalp. The onset occurred one year ago without any known precipitating factors. The patient had previously been diagnosed with alopecia areata and received treatment with minoxidil solution and topical clobetasol, but with no significant improvement. The patient also had a history of atopic dermatitis, which worsened during the hair loss period and was accompanied by noticeable itching. The patient's father had a personal history of alopecia areata, but there was no significant family history of the condition. Dermatological examination showed patchy hair loss on the scalp without eyebrow or eyelash involvement (Figure 1). The Severity of Alopecia Tool (SALT) score was 70%. During the initial visit, the examination revealed dark red patches and pinpoint-sized papules on the buttocks, groin, and limbs. These areas exhibited lichenification, scratch marks, erosion, crusting, dryness, scaling, and significant pruritus. The Eczema Area and Severity Index (EASI) score was 50.3, the Scoring Atopic Dermatitis (SCORAD) score was 72.1, and the Children's Dermatology Life Quality Index (CDLQI) score was 27. Laboratory findings indicated elevated levels of total immunoglobulin E (IgE) and an increased proportion of double-negative T cells (CD3+CD4-CD8-). Allergen testing revealed sensitivities to various substances, including egg white and wheat. Other laboratory tests were within normal limits. Dermoscopy revealed characteristic features such as black dots, broken hairs, and exclamation mark hairs in the affected areas. Some areas showed reduced hair follicle openings or absence of hair, with only minimal vellus hairs. Nail abnormalities were also observed (Figure 2). The diagnosis is severe alopecia areata. The patient received subcutaneous injections of 300mg of dupilumab every two weeks for a duration of six months. Following a six-month course of treatment with dupilumab, there was a significant improvement in the atopic dermatitis, characterized by the absence of new skin lesions and subjective itching symptoms. Importantly, during the most recent follow-up, there has been no recurrence of atopic dermatitis. After this treatment, most of the affected areas showed hair regrowth, although some of the regenerated hair was white in color. The SALT score decreased to 20%. However, the patient experienced eyebrow loss during the treatment period (Figure 3). Discontinuation of Dupilumab and initiation of oral Baricitinib at a dose of 2mg once daily resulted in further improvement in hair regrowth after 5 months, the eyebrows and hair have essentially fully recovered. The patient is advised to gradually reduce the dosage (Figure 4).During the treatment, regular blood tests and tests assessing liver and kidney function were performed. The pre-treatment laboratory investigations revealed the following results: alanine aminotransferase (ALT) of 5 IU/L (reference range: 0-40 IU/L), aspartate aminotransferase (AST) of 21 IU/L (reference range: 0-42 IU/L), total bilirubin of 7.34 μmol/L (reference range: ≤23 μmol/L), direct bilirubin of 0.87 μmol/L (reference range: ≤8 μmol/L), serum total bile acids of 6.3 μmol/L (reference range: 0-10 μmol/L), uric acid of 277 μmol/L (reference range: 150-420 μmol/L), and creatinine of 48 μmol/L (reference range: 35-106 μmol/L). Following oral administration of baricitinib, the reevaluation of the aforementioned parameters showed the following results: ALT of 6 IU/L, AST of 26 IU/L, total bilirubin of 7.09 μmol/L direct bilirubin of 2.24 μmol/L, serum total bile acids of 4.9 μmol/L, uric acid of 274 μmol/L, and creatinine of 45 μmol/L. The pre-treatment hematological examination revealed the following results: total white blood cell count of 9.1 x 10^9/L (reference range: 3.5-9.5 x 10^9/L); neutrophil percentage of 44.6% (reference range: 40%-75%); lymphocyte percentage of 45.7% (reference range: 20%-50%); red blood cell count of 5.02 x 10^9/L (reference range: 3.8-5.1 x 10^9/L); hemoglobin level of 137 g/L (reference range: 115-150 g/L); and platelet count of 261 x 10^9/L (reference range: 125-350 x 10^9/L). Upon reevaluation after treatment, the white blood cell count remained unchanged at 9.1 x 10^9/L; neutrophil percentage was 44.6%, lymphocyte percentage was 45.7%; red blood cell count was



FIGURE 1
During the patient's first visit, we noticed a significant amount of hair loss, while there were no observable changes in the eyebrows and eyelashes.

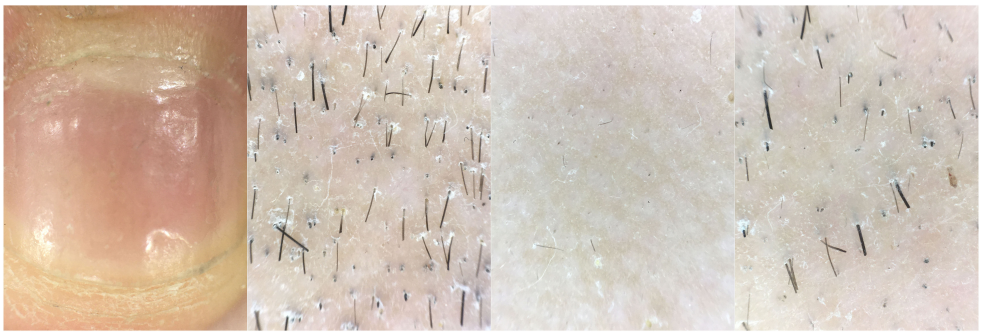


FIGURE 2
Clinical photographs reveal nail damage, while dermatoscopic examination shows the presence of black dot sign, exclamation mark hairs, and broken hairs at the site of skin lesions.

5.02 x 10^9/L, hemoglobin level was 137 g/L, and platelet count was 261 x 10^9/L. Immunoglobulin E (IgE) levels decreased. The IgE level before treatment was measured at 323 IU/mL(reference range: 5-161 IU/mL). After 3 months of treatment with Dupilumab, the IgE levels decreased to 277 IU/mL, and after 6 months of treatment, they further decreased to 140 IU/mL, within the normal range. Both dupilumab and baricitinib were prescribed off-label for this patient. After a thorough assessment of the patient's condition and treatment requirements, and extensive communication with the patient's caregivers, we implemented the treatment plan mentioned above with explicit informed consent. This approach yielded satisfactory therapeutic outcomes. No adverse drug reactions were observed during the course of treatment.

In clinical practice, relapse of alopecia areata has been observed in some patients after discontinuing oral baricitinib. Therefore, it is crucial for patients to adhere to medical advice and either continue their medication or gradually taper the dosage to ensure the efficacy of JAK inhibitors. Discontinuing medication without medical guidance should be avoided to prevent relapse. During follow-up, close monitoring of the child's condition and potential adverse drug reactions will be conducted. We will provide guidance on gradually tapering the medication or transitioning to safer topical or systemic therapies to maintain treatment efficacy.

## Discussion

Alopecia Areata (AA) is a prevalent autoimmune disorder characterized by non-scarring alopecia, which can range from localized patches on the scalp to total hair loss on the entire body. In the US population, the lifetime incidence of alopecia areata (AA) is estimated to be 2%. A nationwide cohort study of US employer-sponsored insurance found that the prevalence of AA ranged from 0.199% to 0.222% between 2016 and 2019, with an incidence rate of 91.46 to 92.90 cases per 100,000 patient-years (3, 4). Partial alopecia areata can spontaneously resolve in some patients, but it is often characterized by a high risk of relapse. In certain cases, the condition can progress to severe forms such as alopecia totalis. AA often coexists with atopic dermatitis (AD), and the severity and susceptibility of the diseases are correlated. Treatment of AA can be challenging and significantly impacts the physical and mental well-being of patients. The prevalence of AA is higher in children than in adults, and children commonly experience psychological issues related to hair loss. Moreover, treatment options for pediatric AA are more limited compared to adults. Therefore, seeking safe and effective treatments for pediatric AA is crucial (5). A cohort study conducted in the UK suggests that patients with Alopecia Areata are at a higher risk of developing



FIGURE 3
Partial hair regrowth and the presence of white hairs were observed during the second visit, but there was partial eyebrow loss.



FIGURE 4
After 11 months of sequential treatment, the patient's hair has almost completely regrown.

autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and atopic dermatitis, among others. In particular, the prevalence of atopic dermatitis in the Alopecia Areata group was found to be 15.7%, while it was only 7.8% in the control group (6).The pathogenesis of AA is not fully understood, and it may involve heterogeneity. Some studies suggest that interferon-gamma (IFN-γ)-mediated Th1 response induces AA, while others indicate that Th2-mediated immune response and Treg cell deficiency play a major role in AA development (7, 8). The JAK/STAT signaling pathway is involved in various important biological processes, including cell proliferation, differentiation, apoptosis, and immune regulation, through the signaling of multiple cytokines and growth factors. Several cytokine pathways implicated in AA pathogenesis, such as IFN-γ and the common gamma chain cytokine family, can participate in AA development via the JAK/STAT pathway. Research also suggests that certain cytokines, such as IL-4, enhance Th2 cell differentiation through the JAK pathway and contribute to the inflammatory immune response in AD (9, 10).

Baricitinib, a selective JAK1/JAK2 inhibitor, is the first targeted therapy approved by the FDA for systemic treatment of alopecia areata (AA). Clinical trials in phase II and III have confirmed the effectiveness and safety of baricitinib in treating severe AA in adults (11–13). Currently, literature data on the use of JAK inhibitors for treating pediatric AA are based on individual case reports and case series. However, previous studies have indicated that the JAK/STAT signaling pathway is a key target for treating AA and AD. There have been relevant case reports demonstrating the effectiveness and safety of JAK inhibitors in these patients. Therefore, for children with both conditions, baricitinib is one of the available treatment options (14).

Atopic dermatitis is a chronic, non-infectious inflammatory skin disease characterized by persistent itching. It commonly presents with eczematous skin lesions, including erythema and papules. This condition is more prevalent in children (15). A meta-analysis has confirmed that alopecia areata significantly raises the risk of atopic dermatitis, particularly in cases of early-onset alopecia areata (before 10-13 years of age) and severe alopecia areata (16). Alopecia areata is considered a type 1 inflammatory disease, where activated NKG2D+CD8+ cells produce the Th1 cytokine interferon-gamma. This disrupts immune tolerance of hair follicles and exposes self-antigens, resulting in dense infiltration of inflammatory cells and apoptosis around the hair follicles, ultimately leading to hair loss (7). It is widely accepted that atopic dermatitis (AD) is primarily driven by Th2 immune responses. A meta-analysis has indicated a potential correlation between the severity of alopecia areata (AA) and AD, with worse outcomes observed in patients with concurrent onset of both conditions. While both AD and AA are classified as inflammatory disorders, the clinical association between the two may not be fully explained by the traditional Th1/Th2 paradigm. Nevertheless, recent research has demonstrated a Th2 cytokine bias in AA. Elevated levels of Th2 cytokines (such as IL-4, IL-5, IL-6), IgE, and eosinophils have been observed in the serum of AA patients, suggesting that Th2 bias may play a significant role in the pathogenesis of AA (17–19).

Dupilumab has been approved for the treatment of moderate to severe atopic dermatitis (AD) in children, as well as in adults. Theoretically, downregulating the Th2 pathway through treatment with dupilumab may enhance the Th1 pathway, which could potentially induce or exacerbate alopecia areata (AA). There have been clinical reports documenting similar cases in which AA was observed or worsened after treatment (20) (19). It is interesting to note that in clinical practice, patients with both alopecia areata (AA) and atopic dermatitis (AD) have shown improvements in symptoms of both conditions after receiving treatment with dupilumab. The child described in this report experienced a reduction in AA and achieved hair regrowth in certain areas affected by hair loss following dupilumab treatment (21). In a clinical study, patients with alopecia areata (AA) with or without atopic dermatitis (AD) were randomly assigned in a 2:1 ratio to receive treatment with dupilumab injections or placebo. After 24 weeks of treatment, it was observed that the placebo group experienced further progression of the disease, while the dupilumab group showed improvement in SALT scores. Furthermore, in patients with IgE levels ≥200IU/mL, the rate of remission further increased after 48 weeks of treatment, suggesting the involvement of Th2-mediated inflammatory response in the pathogenesis of AA. Additionally, baseline IgE levels may be considered as one of the predictive indicators of dupilumab efficacy (22). It is worth noting that in this particular case, the initial IgE levels of the patient were elevated. After treatment, there was an improvement in both hair loss and skin itching symptoms, along with a decrease in serum IgE levels. This further confirms the previously mentioned conclusion.

In this report, the patient also experienced hair regrowth in some areas of alopecia after treatment with Dupilumab, which may indicate that Dupilumab has some potential for treating AA. However, there was eyebrow loss. In the case of this patient, it is important to recognize that she had severe alopecia areata (AA) with extensive hair loss and a prolonged duration of the disease. The effectiveness of using Dupilumab as a standalone treatment for severe alopecia areata is limited. The patient's eyebrow hair loss further indicates that Dupilumab alone has not fully stopped the immune system-mediated damage to the hair follicles. Therefore, it is necessary to consider altering the treatment plan. After an additional 5 months of oral treatment with baricitinib, the SALT score decreased to less than 10%.

The patient in this case was diagnosed with severe AA in combination with AD, with a long disease duration and poor response to local treatment. However, with the sequentially therapy, the patient showed significant improvement, suggesting that the sequential treatment of dupilumab and baricitinib may hold potential for severe AA combined with AD. Long-term follow-up of this patient is necessary, and a large number of multicenter, double-blind, randomized controlled trials are needed to demonstrate the long-term efficacy and safety of dupilumab and baricitinib treatment. This will greatly facilitate the application of sequentially therapy in patients with alopecia areata and atopic dermatitis, benefiting a large number of patients.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. The studies involving human/animal participants were reviewed and approved by Chinese-Japanese Friendship Hospital Clinical Research Ethics Committee.

## Author contributions

HF: Writing – original draft, Conceptualization, Investigation, Writing – review & editing. FZ: Conceptualization, Writing – original draft. WL: Investigation, Writing – original draft. YJ: Data curation, Writing – original draft. QL: Investigation, Writing – original draft. DY: Writing – review & editing, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Paraneoplastic neuromyelitis optica spectrum disorder associated with ovarian dysgerminoma: a case report and literature review

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Neuromyelitis optica spectrum disorder (NMOSD) is a clinical syndrome characterized by attacks of acute optic neuritis and transverse myelitis. We report a case with paraneoplastic NMOSD that improved after immunosuppressive therapy, surgical resection, and chemotherapy. A 48-year-old woman initially presented with gradual binocular visual loss over the course of one week. The patient was evaluated using magnetic resonance imaging (MRI), computed tomography (CT), visual evoked potential (VEP), pathological biopsy, immunohistochemistry, and autoimmune antibody testing. The brain MRI findings were normal. The VEP revealed prolonged P100 latencies in the right eye and an absence of significant waves in the left eye. Positive serum AQP4-IgG antibodies were found. The patient was diagnosed as NMOSD. Then the patient responded well to treatment with methylprednisolone. An ovarian tumor was found in the patient using abdominal MRI and CT. The tumor was surgically resected, and a pathological biopsy revealed that it was ovarian dysgerminoma. The patient received four rounds of chemotherapy after surgery. One month after the final chemotherapy treatment, a positron emission tomography (PET) scan revealed no tumor. The vision of the patient gradually recovered and serum AQP4 was negative. Furthermore, we summarized the characteristics of patients diagnosed with paraneoplastic NMOSD associated with ovarian neoplasms in previous studies. This is a characteristic case of overlapping NMOSD and ovarian dysgerminoma, demonstrating the importance of tumor therapy in cases of paraneoplastic NMOSD.

KEYWORDS

paraneoplastic NMOSD, AQP4, ovarian dysgerminoma, immunosuppression, IVMP

# 1 Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing inflammatory nervous system disease characterized by simultaneous or consecutive attacks of acute optic neuritis (ON) and transverse myelitis (TM) (1). IgG autoantibodies to aquaporin 4 (AQP4-IgG), the most abundant water channel protein in the central nervous system (CNS) (2), are currently the serological and pathophysiological marker of NMOSD (3). Ovarian dysgerminoma is a rare malignant tumor that originates from ovarian primordial germ cells, with an incidence of 0.109 per 100,000 women-years (4). Some studies have found an association between NMOSD and cancer, such as lung cancer, breast cancer, ovarian teratomas, etc. (5). To our knowledge, paraneoplastic NMOSD complicated with ovarian dysgerminoma is rare. Herein, we report a case with NMOSD overlapping ovarian dysgerminoma with an excellent prognosis.

# 2 Case report

A 48-year-old Chinese woman initially visited the Department of Ophthalmology at the Central Hospital of Shaoyang on February 15, 2022, due to a one-week history of visual impairment. She had a history of uterine fibroids and had a total hysterectomy 11 years ago. Upon physical examination, it was noted that she had no light perception in both eyes, and bilateral pupillary light reflexes were absent. Other ophthalmic tests conducted by ophthalmologists showed normal results. Consequently, the visual deterioration of the patient was considered as optic nerve or visual cortex damage.

Then the patient was referred to the Department of Neurology in our hospital for neurologic evaluation. A systemic neurological examination was conducted, revealing that muscle strength, muscle tension, tendon reflexes, sensory nervous system, cerebellar functions, Babinski signs, and meningeal irritation signs were all within normal limits. She underwent visual evoked potential (VEP) test, which showed prolonged P100 latencies in the right eye and no detectable P100 waves in the left eye. Magnetic resonance imaging (MRI) of eyes, optic nerves, orbits, brain, and spinal cord showed normal findings. A lumbar puncture was performed, which revealed normal intracranial pressure, white cell counts, glucose, and chloride levels in the cerebrospinal fluid (CSF). Then we completed the investigation with serum and CSF demyelinating antibodies (AQP4, MOG, GFAP, and MBP) screening by the cell-based assay (CBA) method (Kingmed Diagnostics Co., Ltd., which is the largest College of American Pathologists-certified laboratory in China) (6). The AQP4-IgG (antibody titer: 1:10, assessed by CBA method) was detected positive in the serum (Figure 1A), while no abnormalities were found in the CSF AQP4-IgG (Figure 1B). Additionally, we searched for IgG-oligoclonal bands (OCBs) in the CSF and serum using isoelectric focusing electrophoresis analysis. The patient's serum and CSF contained identical IgG-OCBs. (Figure 1D). Therefore, according to IPND Criteria 2015, the patient was diagnosed as NMOSD by the clinical feature and the positive antibody.

The patient then underwent a course of treatment of methylprednisolone. The patient was on IVMP for 5 days (1,000 mg/day) (the dosage was decreased every 3 days), followed by oral prednisone (60 mg/day) and mycophenolate mofetil (1 g/day). The vision of patient gradually recovered after immunosuppressive

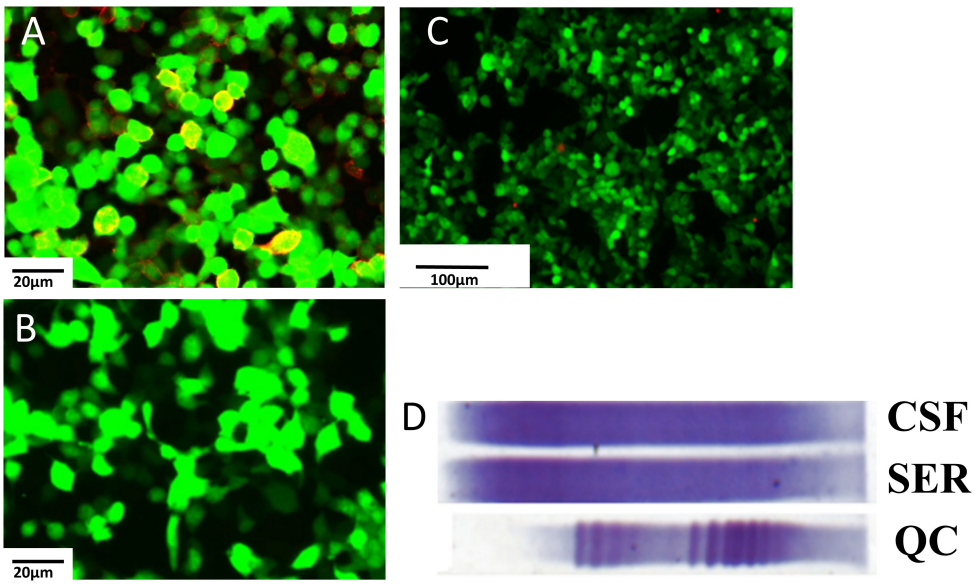



FIGURE 1
Demyelinating antibody of central nervous system. **(A)** AQP4 antibodies (1:10) are detected in the serum in the first test (scale bar 20μm). **(B)** AQP4 antibodies are found negative in the CSF (scale bar 20μm). **(C)** AQP4 antibodies are found negative in the serum in the second detect (scale bar 20μm). **(D)** OCBs are found in both serum and CSF, and the locations are identical. AQP4, aquaporin 4; CSF, cerebrospinal fluid; OCBs, oligoclonal bands.

therapy. She was continued on immunosuppressive treatment with prednisone (60 mg/day) (the dosage was decreased to 10mg/day) and mycophenolate mofetil (1 g/day) after discharge.

The patient experienced discomfort in the lower abdomen while undergoing methylprednisolone treatment. Abdominal palpation revealed a round, hard mass in the left lower abdomen with poor mobility, but without any tenderness or rebound pain. Abdominal magnetic resonance imaging (MRI) and computed tomography (CT) showed a tumor in the left ovarian. An equal-density mass was seen on the abdominal CT (Figure 2A). Additionally, a T2 hyperintense (Figure 2B) and a T1 hypointense (Figure 2C) lesion in the left lower abdomen was discovered by abdominal MRI. Moreover, the cancer biomarkers [alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA-125), and CA-199] were detected, but the tumor markers were negative. After undergoing a pathologic biopsy and surgical resection, the neoplasm was diagnosed as an ovarian dysgerminoma (Figure 3A). Immunohistochemistry of tumor tissues showed positive results for cluster of differentiation 117 (CD117), spalt-like transcription factor 4 (SALL4), and octamer-binding transcription factor 3/4 (OCT3/4), while negative for epithelial membrane antigen (EMA), CD3, CD20, CD30, pair box gene 8 (PAX-8), human melanoma black 45 (HMB-45), anaplastic lymphoma kinase (ALK), and placental alkaline phosphatase (PLAP) (Figures 3B-D). The ovarian mass was confirmed as a malignant tumor after the pathological biopsy. As a result, the patient had four rounds of chemotherapy and stopped using immunosuppressive medication.

The patient underwent a positron emission tomography (PET) scan one month after the final chemotherapy treatment. The PET-CT scan, used to assess the course of treatment after the most recent round of chemotherapy, showed no indications of the tumor (Figure 2D). Moreover, the patient's vision returned to normal. We rechecked that AQP4-IgG in the serum of the patient was negative (Figure 1C). Throughout the following two years of follow-up, the patient remained free from any abnormal symptoms.

## 3 Diagnostic assessment

The initial clinical features were similar to the presentation of ophthalmic diseases. However, ophthalmic examinations, MRI

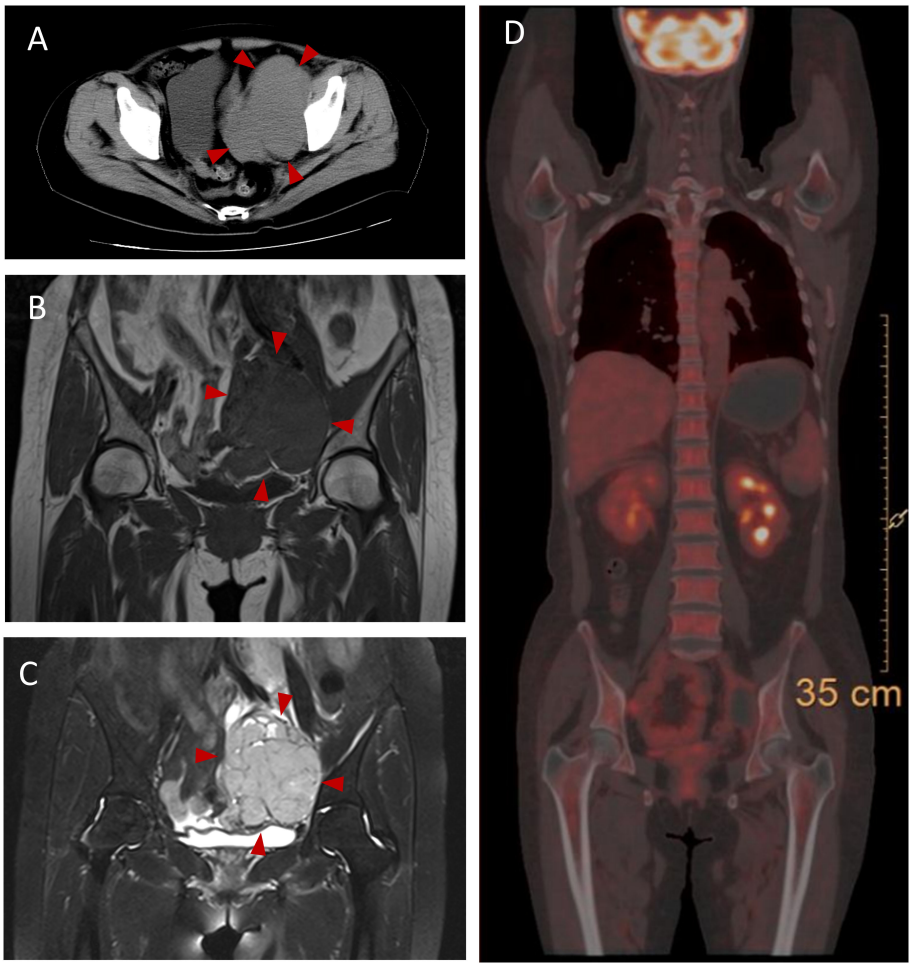



FIGURE 2
Abdominal CT and MRI and PET-CT findings in this case. **(A)** Abdominal CT shows an equal-denstiy mass pointed by the red arrowheads in the left lower abdomen. **(B)** T1-weighted image shows a hypointense mass pointed by the red arrowheads in the left lower abdomen. **(C)** T2-weighted image shows a hyperintense mass pointed by the red arrowheads in the left lower abdomen. **(D)** PET-CT shows no neoplasm indications. CT, computer tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

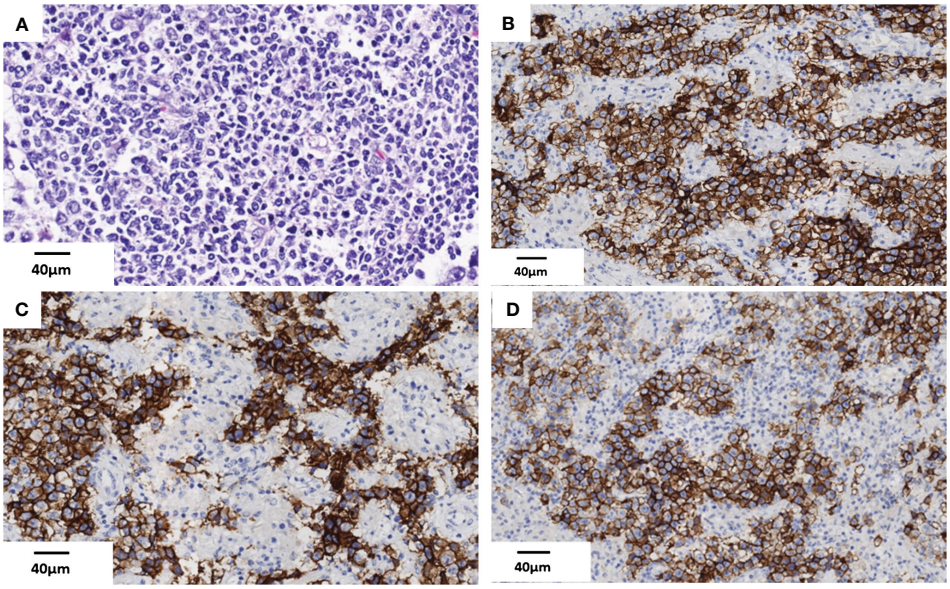



FIGURE 3
Histopathologic findings of the ovarian dysgerminoma in this case. **(A)** Tumor cell nests are located in the ovarian parenchyma (HE) (scale bar 40μm). **(B–D)** Immunohistochemistry of tumor tissues show CD117 (+), SALL4 (+), and OCT3/4 (+) in this case (scale bar 40μm). HE, hematoxylin and eosin.

results, and VEP findings revealed optic nerve damage without any lesions in the eyes. Therefore, we suspected that the patient had NMOSD. Subsequent testing found that the antibodies for NMOSD were positive in the serum, confirming the diagnosis of NMOSD. The patient responded well to immunosuppressive treatment. The combination of abdominal symptoms, physical signs, and findings from both CT and MRI scans strongly indicated the presence of a left ovarian tumor in the patient. Then the pathologic biopsy and immunohistochemistry of tumor tissues confirmed the diagnosis of ovarian dysgerminoma. Thus, the patient was diagnosed as paraneoplastic NMOSD overlapping with ovarian dysgerminoma.

## 4 Literature review

A literature search was performed using the PubMed and Web of Science database. The following combinations of search terms were used: "neuromyelitis optica spectrum disorder and ovarian neoplasms", and "NMOSD and ovarian neoplasms". The search was limited to articles in English. A review was done of the information that was available in full-text or abstract form, along with any relevant citations and references. We summarized the clinical manifestations of all nine cases with paraneoplastic NMOSD associated with ovarian neoplasms are presented in Table 1.

## 5 Discussion

We described a unique clinical case of NMOSD associated with ovarian dysgerminoma for the first time. NMOSD is a rare autoimmune disease causing multifocal central nervous system (CNS) inflammation (13). AQP4-IgG was detected in more than 80% of patients with NMOSD (3). Approximately 5% of NMOSD with malignancies (such as breast and ovarian cancer) were considered as paraneoplastic NMOSD (14). However, the mechanisms of the paraneoplastic NMOSD are still unclear.

Intratumorally neural tissue that expresses AQP4 may be a mediating factor in paraneoplastic NMOSD linked to malignancy (15). Previous studies reported that a part of patients with ovarian teratoma expressed N-methyl-D-aspartate receptor (NMDAR) and AQP4-IgG (12, 16). Moreover, in addition to GFAPα-IgG, the coexistence of AQP4-IgG and/or anti-NMDAR was detected in most of the autoimmune GFAP astrocytopathy patients with teratomas (16). These investigations revealed a common pathogenesis between CNS autoimmune disorders and ovarian teratomas (12). In this case, the AQP4-IgG was detected positive in the serum using CBA method. Furthermore, both ovarian dysgerminoma and ovarian teratoma are malignant ovarian tumors derived from germ cell. Therefore, we hypothesize that ovarian dysgerminoma can develop into paraneoplastic NMOSD induced by malignancy-associated autoimmune mechanisms, similar ovarian teratoma. However, to our knowledge, up to now, there is no research on the relationship between ovarian dysgerminoma and neurologic demyelinating diseases. Thus, the assumption of AQP4 mediating ovarian dysgerminoma needs further study to identify.

The reports presented in Table 1 summarize on all nine patients with NMOSD associated with ovarian neoplasms. In the presented case, all nine female patients with positive AQP4-IgG. The age at onset of this case of paraneoplastic NMOSD, typically around 50 years old, was consistent with the clinical characteristic of paraneoplastic NMOSD with ovarian neoplasms. Most ovarian tumors linked to paraneoplastic NMOSD were teratomas, with this study uniquely reporting a singular case of NMOSD in

TABLE 1 Characteristics of patients with overlapping NMOSD and ovarian neoplasms.

| Country | Publication date | Sex | Age (years) | Types of neoplasms | NMOSD phenotypes | MRI findings | Auto-antibodies | Tumor pathology | Duration of follow-up | Treatment of NMOSD | Treatment of neoplasms | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Spina (7) | 2013 | F | 43 | Ovarian teratoma | APS, LETM | Demyelinating lesions in the brainstem | AQP4 (+) | AQP4, CD20, CD4, CD3, and CD138 | 1 year | IVMP + TPE + IVIg | Surgery | Good |
| Canada (8) | 2018 | F | 54 | Ovarian serous adenocarcinoma | APS | Demyelinating lesions from the medulla to spinal cord | AQP4 (+) | AQP4 | 2 years | IVMP + TPE + mitoxantrone | Surgery + chemotherapy | Good |
| Italy (9) | 2013 | F | 50 | Ovarian teratoma | LETM, BS | Demyelinating lesions in the pons, hypothalamus, medulla oblongata, and cervical spine | AQP4 (+) | NA | 17 months | IVMP + TPE + AZA | Surgery | Good |
| France (10) | 2019 | F | 15 | Ovarian teratoma | APS, LETM | Demyelinating lesions in the brainstem, and a cervical spinal cord | AQP4 (+) | AQP4, CD3, CD20, and CD8 | 2 years | IVMP + Rituximab | Surgery | Good |
| | | F | 21 | Ovarian teratoma | APS, LETM | Demyelinating lesions in the hypothalamus, temporal lobes, area postrema, and spinal cord | AQP4 (+) | AQP4, CD3, CD20, and CD8 | 9 months | IVMP + TPE + Rituximab | Surgery | Important visual sequelae |
| | | F | 41 | Ovarian teratoma | APS, LETM | Demyelinating lesions in the spinal cord | AQP4 (+), GFAP (+) | AQP4, CD3, CD20, and CD8 | 2 years | IVMP + MMF | Surgery | Mild sensory abnormalities |
| India (11) | 2019 | F | 46 | Ovarian adenocarcinoma | ON, LETM | Demyelinating lesions in the cervical cord | AQP4 (+) | NA | 6 months | IVMP + AZA | Chemotherapy + surgery | Limb weakness |
| Japan (12) | 2021 | F | 27 | Ovarian teratoma | APS, LETM, ON | Demyelinating lesions in spinal cord and pons | AQP4 (+) | AQP4, CD8, CD45, CD20, and CD138 | 16 months | IVMP + tacrolimus | Surgery | Good |
| China (our case) | 2024 | F | 48 | Ovarian dysgerminoma | ON | Normal | AQP4 (+) | CD117, SALL4, and OCT3/4 | 2 years | IVMP + MMF | Surgery + chemotherapy | Good |

APS, area postrema syndrome; AQP4, aquaporin 4; AZA, azathioprine; CD, cluster of differentiation; F, female; IVMP, intravenous methylprednisolone; GFAP, glial fibrillary acidic protein; IVIg, intravenous immunoglobulin; LETM, longitudinally extensive transverse myelitis; MMF, mycophenolate mofetil; NA, not available; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TPE, therapeutic plasma exchange; BS, brainstem; (+), positive.





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conjunction with an ovarian dysgerminoma. The patient only had the clinical symptoms of optic neuritis without myelitis or brainstem lesion, which is inconsistent with the clinical features of NMOSD overlapping with ovarian teratomas. Most case with paraneoplastic NMOSD associated with ovarian neoplasms revealed demyelinating lesions in the central nervous system. However, the MRI of this case did not detect any demyelinating lesions. The clinical manifestations of NMOSD overlapping with ovarian dysgerminoma requires more studies to summarize.

Overall, patients with paraneoplastic NMOSD associated with ovarian neoplasms had a favorable prognosis after immunosuppressive therapy. However, no unified guideline on the treatment of paraneoplastic NMOSD was reported in the literature. Intravenous methylprednisolone (IVMP) is the most commonly used treatment for paraneoplastic NMOSD and has demonstrated excellent therapeutic efficacy (5). Regarding primary tumor treatments, surgical resection and chemoradiotherapy may improve neurological symptoms (10, 12). In this case, the serum AQP4-IgG was negative after immunosuppressive therapy and tumor surgery. Previous studies have found that the clinical symptoms of patients with ovarian teratoma were significantly improved after resection, and the titer of AQP4 antibody in serum decreased or became negative (12). However, it is not clear whether this phenomenon is caused by immunosuppressive therapy or tumor removal. Moreover, it is unclear if patients with paraneoplastic NMOSD require ongoing immunosuppressive medication following surgery. On the one hand, immunosuppressive therapy is useful in avoiding NMOSD recurrence; on the other hand, several immunosuppressive drugs, such as azathioprine and mitoxantrone, have been linked to cancer recurrence and metastasis (8). In our study, the patient terminated immunosuppressive therapy prior to tumor surgery, and after a half-year follow-up, the tumor and NMOSD did not recur. The result suggests that ovarian dysgerminoma may trigger paraneoplastic NMOSD. When the primary tumor was removal, NMOSD caused by autoimmune abnormalities also improved.

Our case report has some limitations. First, the result of AQP4 expression in this case of the ovarian dysgerminoma was missed. Previous studies have uncovered AQP4 expression in ovarian neoplasm tissues (7, 8, 10, 12). This evidence indicates that ovarian neoplasms might mediate paraneoplastic NMOSD through AQP4 expression. Regrettably, we did not check for AQP4 expression in the tumor slices in our case, leaving the relationship between the ovarian dysgerminoma and paraneoplastic NMOSD unclear. Second, we did not find any abnormal MRI findings. Enhanced MRI of the optic nerve or optical coherence tomography (OCT) may have revealed optic nerve damage to support the diagnosis.

In summary, we reported a case with ovarian dysgerminoma overlapping NMOSD for the first time. It is crucial to detect ovarian tumor for patients with NMOSD. The clinical features of patients with ovarian dysgerminoma overlapping NMOSD requires more studies to summarize. Moreover, our study suggests that the treatment of primary tumors is crucial, and long-term immunosuppressive therapy may not be necessary for paraneoplastic NMOSD.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving humans were approved by The Ethics Committee and the Expert Committee of The Central Hospital of Shaoyang. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

PL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SW: Data curation, Writing – review & editing. CZ: Formal analysis, Methodology, Writing – review & editing. YL: Conceptualization, Data curation, Methodology, Writing – review & editing.

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## Conflict of interest

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# Unveiling early stage autoimmune gastritis: novel endoscopic insights from two case reports

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The predominant characteristic of autoimmune gastritis (AIG) is corpus-dominant advanced atrophy, which is mostly observed in the middle to late stages. More reports are needed on the endoscopic features of the early stage. In this report, we present two cases of early-stage AIG in which endoscopic examinations showed no atrophy of the gastric mucosa but displayed a transition of collecting venules from a regular to an irregular arrangement. In addition, yellowish-white cobblestone-like elevations were observed in the fundic gland region. Histologically, the observed manifestations included pseudohypertrophy and protrusion of parietal cells into the lumen, possibly along with hyperplasia of G cells, lymphocytic infiltration and potentially pseudopyloric gland metaplasia. Serologically, the anti-parietal cell antibody returned positive results, whereas the anti-intrinsic factor antibody yielded negative results. In this study, we summarized some endoscopic features of two patients, aiming to provide clues for endoscopists to detect early-stage AIG.

KEYWORDS

**autoimmune gastritis, early-stage, endoscopy, collecting venules, yellowish-white cobblestone-like elevations**

## 1 Introduction

Autoimmune gastritis (AIG) is a type of atrophic gastritis associated with autoimmunity (1, 2) and is associated with an increased risk of gastric neuroendocrine tumors and pernicious anemia (3–5). Early identification and management of AIG are particularly important ways to improve patient prognosis. Nonetheless, patients with AIG often exhibit atypical clinical symptoms (6, 7), necessitating a reliance on endoscopic imaging, serological markers, and other diagnostic tools for accurate identification (8–10). Among these, endoscopic imaging is the most critical opportunity for detection, determining the necessity for further biopsy and serving as an important criterion for diagnosing AIG (11,

12). The characteristic endoscopic manifestation of AIG is the homogeneous atrophy of the gastric body with antral sparing. Simultaneously, other features include remnant oxyntic mucosa, sticky adherent dense mucus, and hyperplastic polyps (13). These characteristic endoscopic manifestations play a key role in diagnosing AIG, but are more commonly observed in the middle to late stages than in the early stage (14). This challenge complicates the endoscopists' ability to identify early-stage AIG during diagnosis, leading to missed opportunities for comprehensive evaluation and a low rate of confirmed early-stage AIG diagnoses.

This study reported two cases of suspected early-stage AIG based on endoscopic manifestations that were confirmed by further serological and histopathological examinations. In this study, we summarize the endoscopic characteristics observed in early-stage AIG cases: non-atrophic gastric mucosa, irregular arrangement of localized collecting venules (CVs) in the fundic gland region, yellowish-white cobblestone-like elevations, and mild gastric mucosal swelling or non-swelling. We aimed to provide insights for enhancing the endoscopic diagnosis of early-stage AIG, thereby increasing the rate of clinical confirmation.

## 2 Case 1

A 41-year-old Chinese man underwent an upper gastrointestinal endoscopy because of a burning sensation in the upper abdomen. He had never undergone eradication therapy for *Helicobacter pylori* (*H. pylori*) infection and was not taking any medications, including proton pump inhibitors or antibiotics. Both his grandfather and uncle had rheumatoid arthritis.

Endoscopic examination revealed a normal antral mucosa (Figure 1A). The greater curvature of the corpus exhibited an irregular distribution of folds with deep fissure-like structures and a localized yellowish-white color (Figure 1B). Yellowish-white cobblestone-like elevations were observed in the upper part of the lesser curvature of the corpus. Closer examination of the surface revealed an irregular distribution of localized CVs (Figures 1C, D). In addition, the lesser curvature of the corpus displayed localized whitish areas with elongated and widened CVs on the surface. Magnifying endoscopy with narrowband imaging did not reveal any significant mucosal swelling (Figures 1E, F).

(Figures 2A–D) shows the HE staining results of corpus; (Figures 2E, F) shows the H+/K+ ATPase staining results of corpus; (Figures 2G, H) shows the CgA staining results of corpus; (Figures 2I, J) shows the PGI staining results of corpus; (Figures 2K, L) shows the MUC6 staining results of corpus; (Figures 2M, N) shows the CD3 staining results of corpus; (Figures 2O, P) shows the H. pylori staining results of corpus; (Figures 2Q–T) shows the HE staining results of antrum; (Figures 2U, V) shows the Gastrin staining results of antrum; (Figures 2W, X) shows the CD3 staining results of antrum; (Figures 2Y, Z) shows the H. pylori staining results of antrum. Among them, histopathological examination of tissue obtained from the gastric corpus showed no significant atrophy of the gastric glandular cells; however, the arrangement of the parietal cells began to exhibit irregularities characterized by hyperplasia and protrusions into the lumen (Figures 2A, B). $H^+/K^+$ ATPase staining revealed no significant detachment of the parietal cells (Figure 2E). Chromogranin A staining revealed no significant proliferation of enterochromaffin-like cells (Figure 2G). Pepsinogen I and MUC6 staining showed that

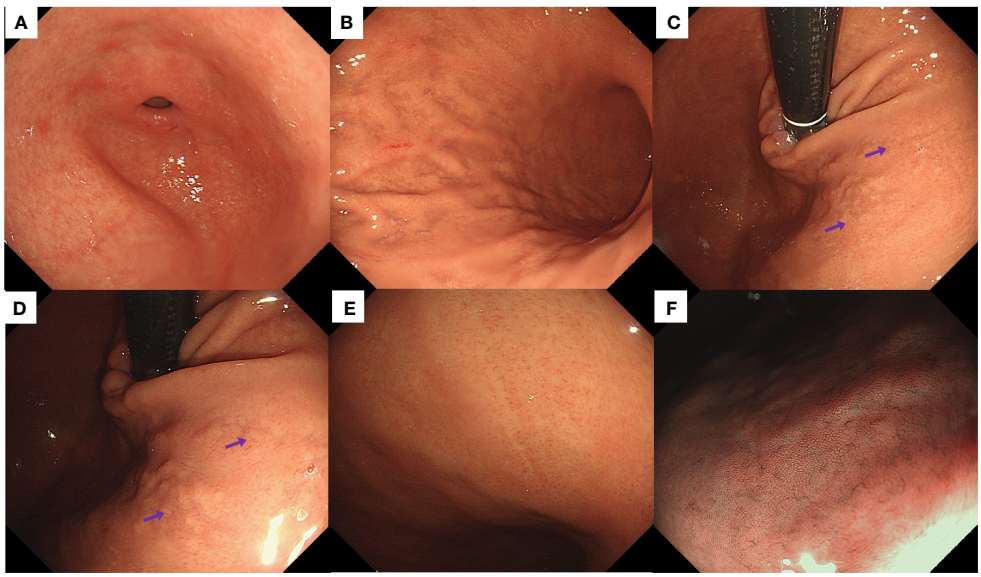



FIGURE 1
Endoscopic findings of the patient in Case 1. **(A)** Normal antrum. **(B)** The greater curvature of the corpus displayed an irregular distribution of folds, with deep fissure-like structures and localized yellowish-white discoloration. **(C, D)** Yellowish-white cobblestone-like elevations were noted in the lesser curvature of the corpus, accompanied by irregular distribution of CVs (purple arrows) on the surface. **(E)** Whitish areas with elongated and widened CVs were detected in the lesser curvature of the corpus. **(F)** Magnifying endoscopy with narrow-band imaging did not reveal significant mucosal swelling.

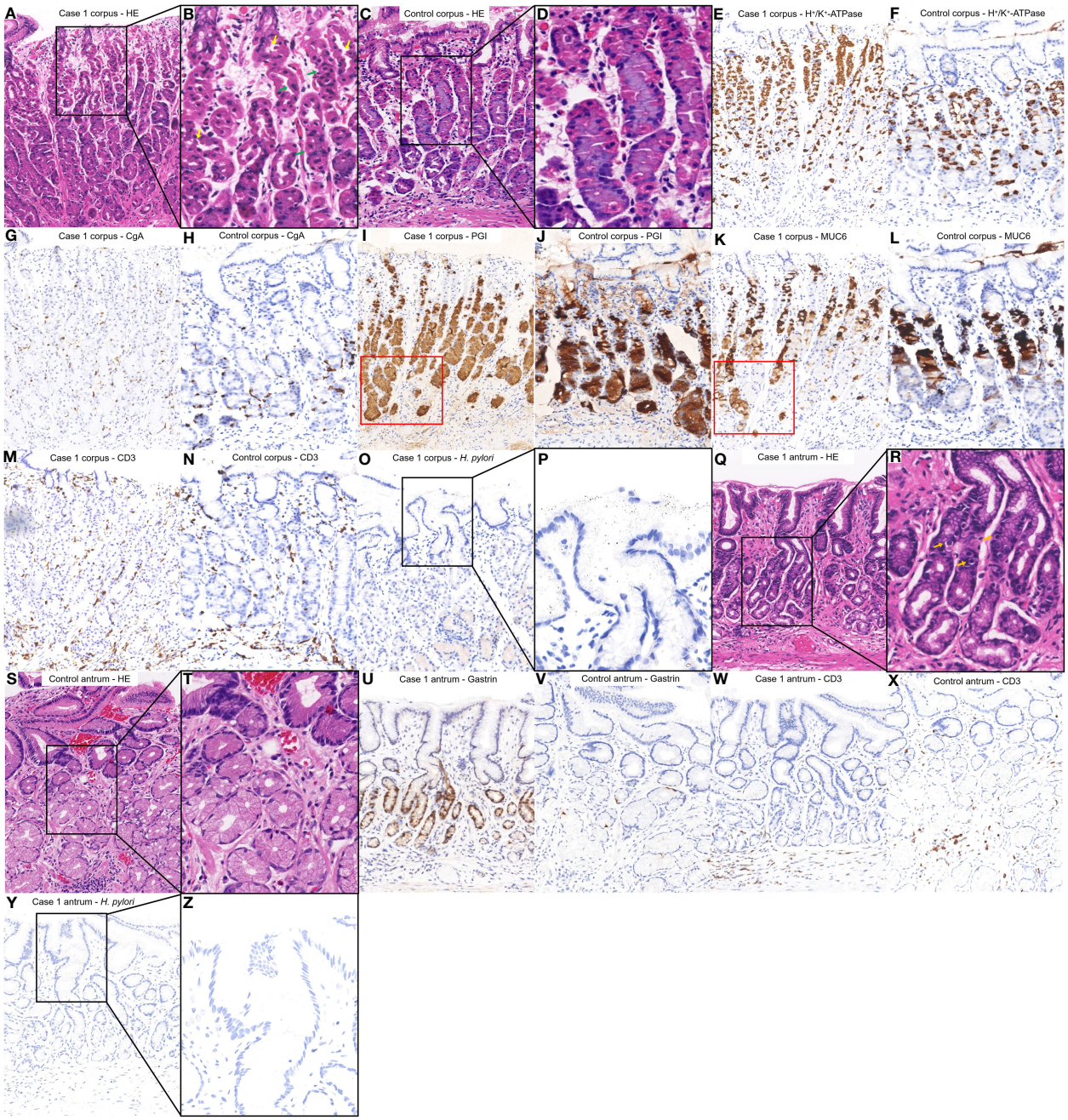



FIGURE 2
Histopathological findings from different regions of the patient's stomach in Case 1 and a healthy control case. **(A, B)** Tissue obtained from the corpus of the patient in Case 1 revealed the arrangement of the parietal cells exhibiting irregularities, characterized by pseudohypertrophy (green arrows) and protrusions into the lumen (yellow arrows). **(C, D)** Normal corpus. **(E, G, I, K, M, O, P)** were comparisons of differential staining in the same region of **(A, F, H, J, L, N)** were comparisons of differential staining in the same region of **(C)**. **(E)** H+/K+ATPase staining revealed areas where the parietal cells remained. **(F)** Normal $H^+/K^+$ATPase staining. **(G)** Chromogranin A staining exhibited no significant proliferation of enterochromaffin-like cells. **(H)** Normal Chromogranin A staining. **(I, K)** Pepsinogen I and MUC6 staining revealed that mucous neck cells appeared at the base of corpus glands (red square). **(J)** Normal Pepsinogen I staining. **(L)** Normal MUC6 staining. **(M)** CD3 staining revealed a small amount of lymphocytic infiltration. **(N)** Normal CD3 staining. **(O, P)** *H. pylori* staining revealed absence of *H. pylori*. **(Q, R)** The tissue obtained from the antrum of the patient in Case 1 revealed an absence of inflammation or atrophy but G cell hyperplasia (Orange arrows). **(S, T)** Normal antrum. **(U, W, Y, Z)** were a comparison of differential staining in the same region of **(Q, V, X)** were a comparison of differential staining in the same region of **(S)**. **(U)** Gastrin staining indicated the proliferation of G cells hyperplasia. **(V)** Normal Gastrin staining. **(W)** CD3 staining revealed a lack of significant lymphocytic infiltration. **(X)** Normal CD3 staining. **(Y, Z)** *H. pylori* staining revealed absence of *H. pylori*.

the mucous neck cells appeared at the base of corpus glands (Figures 2I, K). CD3 staining revealed a small amount of lymphocytic infiltration (Figure 2M). *H. pylori* staining did not reveal the presence of *H. pylori* (Figures 2O, P).

Histopathological examination of biopsy specimens from the antrum revealed no atrophy or inflammation but G cell hyperplasia (Figures 2Q, R). Gastrin staining indicated the proliferation of G cells (Figure 2U). CD3 staining revealed no significant lymphocytic infiltration (Figure 2W). *H. pylori* staining did not reveal the presence of *H. pylori* (Figures 2Y, Z).

Serological testing revealed a positive outcome for the anti-parietal cell antibody and negative results for anti-intrinsic factor antibody and *H. pylori* antibody. Additionally, the anti-thyroid peroxidase antibody level was significantly elevated at 90.12 IU/ml (normal range: 0–5.61 IU/ml). The other test results were within normal limits. The left column of Supplementary Table S1 shows the patients' laboratory data.

In summary, the patient was diagnosed with early-stage AIG through the following features: (i) Medical history: family history of autoimmune disease and no history of PPI administration and *H. pylori* infection. (ii) Serology: PCA positive. (iii) Histopathology: A major histopathologic change of pseudohypertrophy and protrusion of parietal cells into the lumen is present with G cell hyperplasia, lymphocytic infiltration and possibly pseudopyloric gland metaplasia.

## 3 Case 2

A 70-year-old man underwent upper gastrointestinal endoscopy in July 2023 due to complaints of "postprandial fullness." Prior to this assessment, he had not been prescribed medications, such as proton pump inhibitors. A positive urea breath test indicated the presence of *H. pylori* infection. Surprisingly, 2 weeks later, the serum *H. pylori* antibody test yielded negative results. Importantly, the patient had never undergone eradication therapy for *H. pylori*. His medical history revealed the presence of thyroid nodules, with normal thyroid function and antibody levels. Notably, the patient's brother had a history of thyroid cancer.

Endoscopic examination revealed no inflammation or atrophy of the antral mucosa (Figure 3A). Smooth mucosa with consistently thick folds was observed in the greater curvature of the corpus (Figure 3B). The fundus mucosa displayed no signs of atrophy and exhibited a distinct and orderly arrangement of CVs (Figure 3C). Yellowish-white cobblestone-like elevations were noted on the lesser curvature of the corpus, indicating an irregular morphology and distribution of CVs upon closer examination (Figure 3D). Magnifying endoscopy with narrow-band imaging revealed distinct CVs on the surface of the swollen mucosa (Figure 3E). Indigo carmine staining revealed gastric area swelling (Figure 3F).

(Figures 4A–D) shows the HE staining results of corpus; (Figures 4E, F) shows the H+/K+ ATPase staining results of corpus; (Figures 4G, H) shows the CgA staining results of corpus; (Figures 4I, J) shows the PGI staining results of corpus; (Figures 4K, L) shows the MUC6 staining results of corpus; (Figures 4M, N) shows the CD3 staining results of corpus; (Figures 4O, P) shows the H. pylori staining results of corpus; (Figures 4Q, R) shows the HE staining results of antrum; (Figures 4S, T) shows the Gastrin staining results of antrum; (Figures 4U, V) shows the CD3 staining results of antrum; (Figures 4W, X) shows the H. pylori staining results of antrum. Among them, histopathological examination of the tissue obtained from the gastric

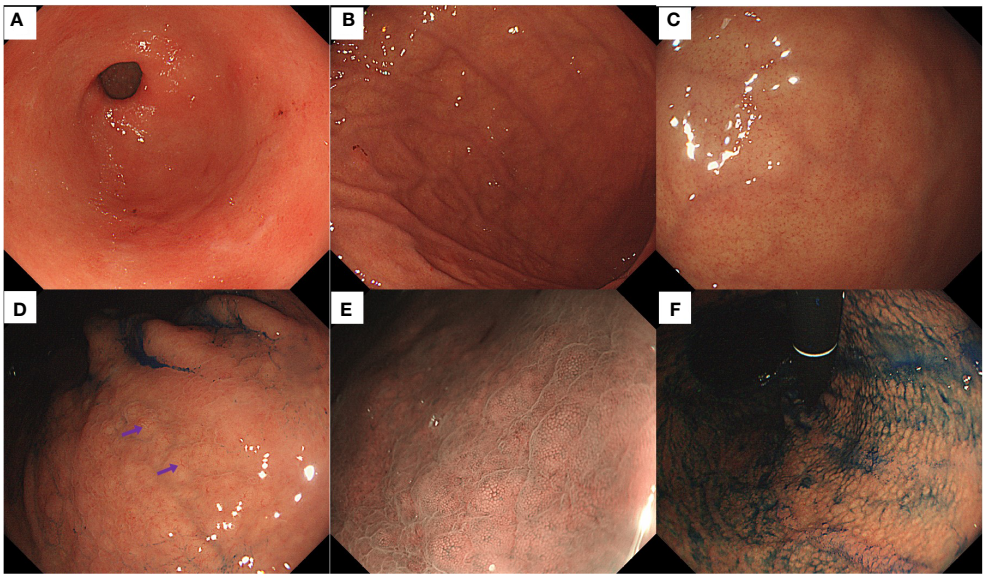



FIGURE 3
Endoscopic findings of the patient in Case 2. **(A)** Normal antrum. **(B)** Smooth mucosa with consistently thick folds were present in the greater curvature of the corpus. **(C)** Regular arrangement of CVs was visible on the mucosal surface of the fundus. **(D)** Some yellowish-white cobblestone-like elevations were present in the lesser curvature of the corpus, and an irregular distribution of CVs (purple arrows) on the surface was observed. **(E)** Magnifying endoscopy with narrow-band imaging revealed distinct CVs on the surface of the swollen mucosa. **(F)** The indigo carmine staining highlighted the gastric-area swelling.

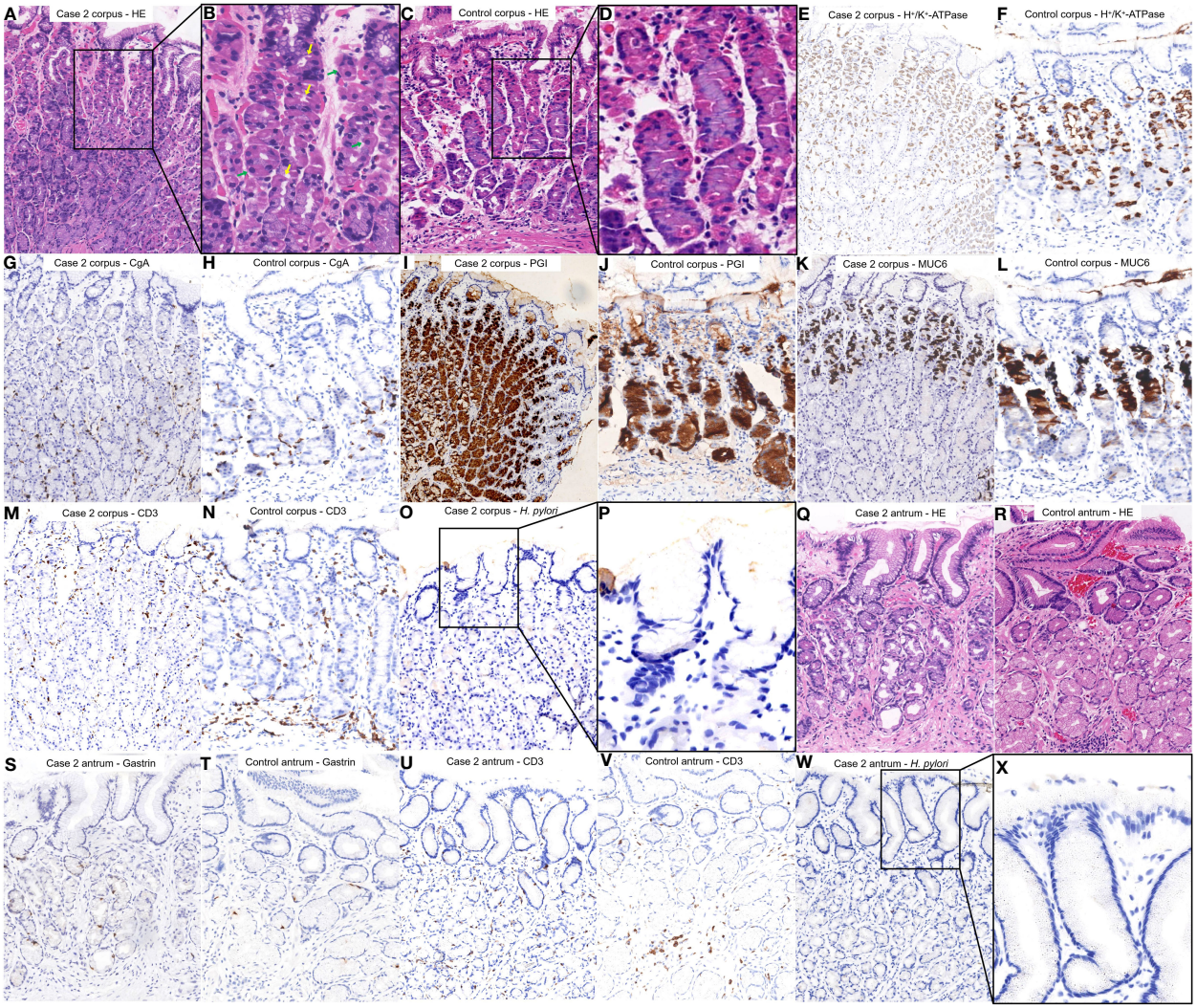



FIGURE 4
Histopathological findings from different regions of the patient's stomach in Case 1 and a healthy control case. **(A, B)** Tissue was obtained from the corpus of the patient in Case 1. The parietal cells began to pseudohypertrophy (green arrows) and protrusion into the lumen (yellow arrows). **(C, D)** Normal corpus. **(E, G, I, K, M, O, P)** were comparisons of differential staining in the same region of **(A, F, H, J, L, N)** were comparisons of differential staining in the same region of **(C)**. **(E)** H+/K+ATPase staining revealed that the number of parietal cells was not significantly reduced. **(F)** Normal $H^+$/$K^+$ATPase staining. **(G)** Chromogranin A staining exhibited no significant proliferation of enterochromaffin-like cells. **(H)** Normal Chromogranin A staining. **(I)** Pepsinogen I staining revealed that chief cells were preserved. **(J)** Normal Pepsinogen I staining. **(K)** MUC6 staining revealed that mucous neck cells were preserved. **(L)** Normal MUC6 staining. **(M)** CD3 staining revealed no significant lymphocytic infiltration. **(N)** Normal CD3 staining. **(O, P)** *H. pylori* staining revealed absence of *H. pylori*. **(Q)** Tissue was obtained from the antrum of the patient in Case 1. No inflammation or atrophy was present. **(R)** Normal antrum. **(S, U, W, X)** were a comparison of differential staining in the same region of **(Q, T, V)** were a comparison of differential staining in the same region of **(R)**. **(S)** Gastrin staining did not demonstrate notable proliferation of G cells. **(T)** Normal Gastrin staining. **(U)** CD3 staining revealed no significant lymphocytic infiltration. **(V)** Normal CD3 staining. **(W, X)** *H. pylori* staining revealed absence of *H. pylori*.

corpus revealed pseudohypertrophy of the parietal cells protruding into the lumen (Figures 4A, B). Staining for $H^+$/$K^+$ ATPase (Figure 4E), Pepsinogen I (Figure 4I), and MUC6 (Figure 4K) revealed that the parietal cells were not significantly diminished, while chief cells and mucous neck cells were well preserved. Chromogranin A staining revealed no significant proliferation of enterochromaffin-like cells (Figure 4G). CD3 staining did not indicate notable lymphocytic infiltration (Figure 4M). *H. pylori* staining did not reveal the presence of *H. pylori* (Figures 4O, P).

Histopathological examination of the tissue collected from the antrum showed no significant signs of inflammation or atrophy (Figure 4Q). Gastrin staining did not show significant proliferation of G cells (Figure 4S). CD3 staining did not indicate notable lymphocytic infiltration (Figure 4U). *H. pylori* staining did not reveal the presence of *H. pylori* (Figures 4W, X).

Serology results indicated a positive anti-parietal cell antibody and negative findings for anti-intrinsic factors and *H. pylori* antibodies. Additionally, the patient's hemoglobin level was measured at 128.00 g/L, which was slightly below the normal range of 130–175 g/L. The antithyroglobulin antibody level was recorded at 4.70 IU/ml, which was slightly elevated compared to the standard reference range of 0–4.11 IU/ml. Other laboratory test results were within normal ranges. The right column of Supplementary Table S1 shows the patients' laboratory data.

In summary, the patient was diagnosed with early-stage AIG through the following features: (i) Medical history: history of thyroid disease and no history of PPI administration and *H. pylori* infection. (ii) Serology: PCA positive. (iii) Histopathology: A major histopathologic change of pseudohypertrophy and protrusion of parietal cells into the lumen is present.

# 4 Discussion

Two patients suspected of having early-stage AIG on upper gastrointestinal endoscopy displayed the following characteristics: First, there was no atrophy of the gastric mucosa, either in the pyloric or fundic gland region. Second, the CVs in the fundic gland region exhibited irregular arrangements in localized regions that were either elongated, widened, or sparsely distributed. Third, yellowish-white cobblestone-like elevations were present in the fundic gland region, similar to the cobblestone-like changes induced by proton pump inhibitor usage. However, these elevations differed in color from the surrounding mucosa, and irregular CVs were visible on the surfaces. It is crucial to emphasize that in Case 1, the patient's gastric mucosa did not display significant swelling, whereas in Case 2, mild swelling was observed along the lesser curvature of the gastric corpus.

Both of our patients fulfilled the diagnosis of early-stage AIG. The guideline defines the diagnosis of AIG as a positive gastric autoantibody (PCA and/or IFA), adding to endoscopic manifestations and/or histopathologic manifestations fulfilling the features of AIG (12). In addition, it characterizes the histopathology of early-stage AIG as: (i) The normal two-layered structure of fundic glands, i.e., the parietal cell/mucous neck cell layer and the chief cell layer are obscured, although the parietal and mucous neck cell layer is preserved. (ii) Many parietal cells remain, although swelling (swelling = pseudohypertrophy), intraluminal protrusion, and shedding are observed. (iii) Chief cells often transform to pyloric gland cells/mucous neck cells (pseudopyloric gland cells). (iv) Hyperplasia of ECL is either absent or mild, and mild-to-moderate lymphocytic/plasma cell infiltration is observed between the gastric glands. (v) Gastrin (G) cells in the pyloric gland mucosa also show mild hyperplasia in the early stage. However, it should be noted that these changes in parietal cells are key findings for early stage. Moreover, lymphocytic infiltration/plasma cell infiltration in the stroma between the oxyntic glands and hyperplasia of G cells in the pyloric glands is also used as a diagnostic aid. In our study, two cases were characterized by the following features: (i) Medical history: history of autoimmune disease or family history and no history of PPI administration and *H. pylori* infection. (ii) Serology: positivity for PCA. (iii) Histopathology: key histopathologic changes such as pseudohypertrophy and protrusion of parietal cells into the lumen, possibly along with hyperplasia of G cells, lymphocytic infiltration and potentially pseudopyloric gland metaplasia. In summary, we believe that these two cases are consistent with the serologic features and major histopathologic features of early-stage AIG, supported by a history of autoimmune disease or family history, and excluding the interference of PPI and *H. pylori*. Therefore, we believe that these two cases can be diagnosed as early-stage AIG.

Swelling of the gastric mucosa is an important indication of inflammation and a key point that draws the attention of the endoscopist (15). According to a prior study by Ayaki M et al. (16), a mosaic pattern with mild mucosal swelling confined to the corpus could indicate early-stage AIG. Nevertheless, our study indicated that certain cases of early-stage AIG might present with minimal gastric mucosal swelling or even in the absence of any observable swelling. Recently, Kotera et al. (17) documented a case of early-stage AIG that presented with a normal endoscopic appearance. Their findings indicated that during the early phases of AIG, a limited number of lymphocytes may not lead to observable endoscopic alterations in the gastric mucosa because of the infiltration of these lymphocytes into the deeper layers. In this study, the gastric mucosa of the patient in Case 1 exhibited no significant swelling, and the pathology revealed a small amount of lymphocytic infiltration, which was consistent with the results reported by Kotera et al. (17). Conversely, the patient in Case 2 displayed mild mucosal swelling in the lesser curvature of the gastric body, but the pathology did not reveal lymphocytic infiltration. Considering that the swollen mucosa was primarily situated in a region displaying a yellowish-white, cobblestone-like elevation, we postulated that the swelling was associated with an elevation caused by parietal cell degeneration. Consequently, while gastric mucosal swelling serves as a supplementary diagnostic indicator for early-stage AIG, it is not essential for diagnosing AIG at this stage.

Irregular CVs observed on the surface of the gastric mucosa may represent a characteristic feature of early-stage AIG. CVs represent blood vessels that begin at the level of the gastric foveolar layer and descend to merge with the submucosal plexus to form a complex and tree-like three-dimensional structure. Their morphology and arrangement are intricately linked to the presence and organization of gastric foveoli and body glands (18). Kishino et al. (19) documented a case of early-stage AIG. Well-preserved microvascular and microsurface patterns were observed in the gastric mucosa within the erythematous regions of the fundic glands. Their findings indicated that this preservation could be attributed to a more profound inflammation in the lamina propria mucosa than in the subepithelial region. When *H. pylori* infection is absent, normal gastric mucosa features a distinctive regular arrangement of CVs (20–22). When *H. pylori* infects the gastric mucosa, superficial inflammation causes elongation of the gastric pits, thus rendering these venules invisible on the mucosal surface (23). In early-stage AIG, lymphocytic infiltration originates from deeper layers, allowing for the possible observation of CVs if the gastric pits remain unaffected. However, unlike the regular arrangement of CVs, their morphology and arrangement may be altered during this phase, presenting irregularities, such as elongation, broadening, or sparse distribution. This phenomenon may be attributed to pseudohypertrophy and luminal protrusion of the parietal cells, resulting in a subtle distortion of the glands. In this report, a deviation from the typical arrangement of CVs observed in

normal gastric mucosa was noted on the surface of the gastric mucosa in two patients with early-stage AIG. Moreover, biopsies demonstrated pseudohypertrophy of parietal cells and their protrusion into the lumen, providing substantial evidence to support the aforementioned concept. Based on these observations, we hypothesized that irregular patterns of CVs on the gastric mucosal surface were associated with early-stage AIG.

Yellowish-white cobblestone-like elevations may be new clues for recognizing early-stage AIG. Yellowish-white cobblestone-like elevations were observed in the lesser curvature of the gastric body in both patients with early-stage AIG. These are similar to the cobblestone-like changes reported previously. It is crucial to differentiate these features from the classic cobblestone-like alterations typically associated with prolonged proton pump inhibitor use in *H. pylori*-negative individuals and patients with middle-stage AIG (24). For example, cobblestone-like changes formed by the long-term administration of proton pump inhibitors are caused by parietal cell protrusion and demonstrate similar coloring to the surrounding mucosa (12). However, both cases of early-stage AIG showed coloration inconsistent with that of the surrounding mucosa, displaying yellowish-white cobblestone-like elevations. In addition, the cobblestone-like changes observed in middle-stage AIG result from the remnant oxyntic mucosa within the atrophic regions (25). Unlike these two cases of early-stage AIG, the yellow-white cobblestone-like elevations were surrounded by non-atrophic mucosa. Furthermore, a normal white zone was observed on the yellowish-white cobblestone surfaces. Although irregular CVs were observed on the surface, tumor-related lesions were not considered (26). In line with the pathology, we propose that the yellow-white cobblestone-like elevations in the region of the gastric fundus glands were caused by pseudohypertrophy and protrusion of parietal cells into the lumen. Therefore, yellow-white cobblestone-like elevations are different from the previously recognized cobblestone-like changes, which are expected to be a new clue for diagnosing early-stage AIG.

The histological changes observed in the two patients supported the diagnosis of early-stage AIG. There was a lack of significant lymphocytic infiltration in Case 2, which diverged from previous reports on early-stage AIG. Terao et al. (27) suggested that the identification of early-stage AIG should focus on the slight degeneration of the parietal cells and pseudopyloric gland metaplasia of the chief cells. Our histopathology revealed pseudohypertrophy of the parietal cells and pseudo-pyloric gland metaplasia, supporting the findings of Terao et al. Therefore, whether both lymphocytic infiltration and parietal cell degeneration are necessary, and the sequence of their appearance needs to be further clarified. Moreover, the overlapping staining of Pepsinogen I and MUC6 at the low base in Case 1 can be used as a clue for the diagnosis of early-stage AIG. Pepsinogen I and MUC6 staining usually have some overlap in the high base/low neck region of corpus glands, which is related to the distribution of mucous neck cells near the neck of the glands. However, for the overlapping staining at the low base of the gland, we thought it might appear in two cases: (i) The overlapping area had both chief cells and mucus neck cells, suggesting that the mucus neck cells had appeared at the base of the gastric gland. (ii) Only mucus neck cells were present in the overlapping area, suggesting that the chief cells had been replaced by pseudopyloric gland metaplasia. According to the latest diagnostic criteria for AIG (12), a significant increase in mucous neck cells at the base of the gastric glands, distribution of mucus neck cells throughout the gastric gland, and pseudopyloric gland metaplasia are all pathological manifestations of early-stage AIG. Therefore, the overlapping staining of Pepsinogen I and MUC6 at low base can serve as a diagnostic clue for early-stage AIG.

Serological tests play a crucial role in the diagnosis of early-stage AIG (28). The specificity of anti-parietal cell antibodies is somewhat limited (29, 30); however, more attention should be paid to the diagnosis of early-stage AIG. Indeed, since there are few diagnostic clues for early-stage AIG, positivity for PCA is an extremely important clue when an early autoimmune response is initiated and atrophy has not yet occurred. Serological tests in both patients suggested anti-parietal cell antibody positivity, supporting the diagnosis of early-stage AIG. Furthermore, the evaluation of gastrin, pepsinogen, vitamin B12, iron, and autoimmune antibodies, and family medical history provided additional supportive evidence for the diagnosis of early-stage AIG to some extent. However, some patients with early-stage AIG may not develop hypergastrinemia and pernicious anemia due to mild parietal cell destruction. Gastrin and vitamin B12 levels in the two reported patients were normal, suggesting that their parietal cells might not yet be significantly disrupted. This speculation was corroborated by our histopathology, which observed only major changes in the pseudohypertrophy and protrusion into the lumen of parietal cells without reporting significant destruction of parietal cells. In addition, although we detected positive PCA, it takes time from PCA production to noticeable parietal cell destruction and intrinsic factor deficiency. Close follow-up of these patients in the coming years is essential to track the changes in their condition. Through this process, we can understand the progression of early-stage AIG and validate the current diagnosis.

## 5 Conclusion

Based on the two cases reported in this study and related literature, we summarized some endoscopic features of early-stage AIG: (1) Yellowish-white cobblestone-like elevations in the region of the fundic glands may be a new clue for the diagnosis of early-stage AIG. (2) Irregular CVs observed on the surface of the gastric mucosa in the fundic gland region may be a characteristic change in early-stage AIG. (3) Swelling of the gastric mucosa within the fundic gland region may also indicate early-stage AIG. Moreover, when considering an endoscopic diagnosis of early-stage AIG, it is imperative to perform further histological and serological examinations. Through these case reports, we emphasize the importance of endoscopic features of early-stage AIG and advocate for further attention and research focused on this disease.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Ethics Committee of The First Hospital of Hunan University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YY: Conceptualization, Supervision, Writing – original draft. XS: Data curation, Methodology, Writing – original draft. RY: Formal analysis, Writing – review & editing. YW: Data curation, Writing – original draft. EX: Data curation, Writing – original draft. CT: Conceptualization, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1416292/full#supplementary-material

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# Case report: A patient with brachio-cervical inflammatory myopathy was misdiagnosed as flail arm syndrome

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Brachio-cervical inflammatory myopathy (BCIM) is a rare inflammatory myopathy characterized by dysphagia, bilateral upper limb atrophy, limb-girdle muscle weakness, and myositis-specific antibody (MSA) negativity. BCIM has a low incidence and is commonly associated with autoimmune diseases. We present a case report of a 55-year-old man with progressive upper limb weakness and atrophy, diagnosed with flail arm syndrome (FAS). The initial electromyography revealed extensive spontaneous muscle activity and increased duration of motor unit potentials (MUPs). During follow-up, evidence of myogenic damage was observed, as indicated by a decreased duration of MUPs in the right biceps muscle. Laboratory and genetic testing ruled out hereditary or acquired diseases. Negative serological antibodies for myasthenia gravis. Hereditary or acquired diseases were ruled out through laboratory and genetic testing. Whole-body muscle magnetic resonance imaging (MRI) showed extensive edema and fat replacement in the bilateral upper limbs, scapular, and central axis muscles, while the lower extremities were relatively mildly affected. Muscle biopsy revealed numerous foci of inflammatory cells distributed throughout the muscle bundle, with predominant CD20, CD138, and CD68 expression, accompanied by a light infiltration of CD3 and CD4 expression. The muscle weakness improved with the combination of oral prednisone (initially 60 mg/day, tapered) and methotrexate (5 mg/week) treatment.

KEYWORDS

**brachio-cervical inflammatory myopathy, flail arm syndrome, myositis, misdiagnosis, case report**

## Introduction

Idiopathic inflammatory myopathy (IIM) is an autoimmune disease that affects the skeletal muscle system. It is often accompanied by elevated creatine kinase (CK), myositis-specific antibody positivity, and multisystemic involvement (1). The 239th ENMC Symposium, IIM was classified into four types: dermatomyositis, inclusion body myositis, immune-mediated necrotizing myopathy, and anti-synthetase antibody syndrome (2). In 2006, Pestronk et al. reported that a small proportion of patients with IIM present severe progressive atrophy of the arms and neck with mild involvement of the lower limbs and are represented by focal B-cell foci observed on histology (3). They suggested that Brachio-cervical inflammatory myopathy (BCIM) may be one of the independent subtypes of IIM, represented by focal B-cell foci observed on histology (3). Current studies on BCIM are limited and dominated by case reports. The University of Washington reported that the prevalence of BCIM syndrome was 0.3% in 4,130 muscle biopsy samples (3). It is important to note that BCIM is not representative of mild myositis symptoms. In 2015, Kooi et al. observed dilated cardiomyopathy as a potentially lethal complication of BCIM while following up on two female patients with BCIM (4). In 2018, academics from the University of Toronto described a patient with BCIM who also tested positive for scleroderma and lupus antibodies (5). This suggests that patients with BCIM may have a combination of fatal complications and immune system comorbidities. Early recognition and treatment are crucial for patient prognosis.

Flail arm syndrome (FAS) is a variant of amyotrophic lateral sclerosis (ALS) that can progress to classic ALS later in the course of the disease (6). The onset of FAS exhibits wide clinical variability. Previous studies have concluded that atrophy of the upper limb may be initiated at different sites: distal muscle groups (40%), both proximal and distal (36%), and purely proximal initial symptoms (24%) (7). However, no studies have reported misdiagnosis of FAS in patients with BCIM. We describe in details the diagnostic process of one case with BCIM. A summary of the differential diagnosis is also provided. Furthermore, the patient had rheumatoid arthritis, hypothyroidism, diabetes mellitus, and gout, which expanded the clinical spectrum and diagnostic experience of BCIM.

## Case description

The 55-year-old man had a 22-month history of bilateral upper limb and interosseous muscle atrophy, which had progressed to weakness in the neck muscles and fatigue when climbing stairs in the last three months. The patient also presented with atrophy of the bilateral upper limb and girdle muscles, particularly the trapezius, deltoids, supraspinatus, and pectorals. He also had a metacarpophalangeal joint deformity. We assessed the patient's muscle strength using the Medical Research Council (MRC) grading system. The results showed that the biceps and triceps MRC grades were 3, the deltoid, trapezius, wrist extensors or flexors and iliopsoas MRC grade 4, and the facial muscles, gluteus maximus, hamstrings, tibialis anterior and tibialis posterior MRC grade 5. He had severely reduced muscle volume in his thoracic back and both upper extremities. No pain or numbness in the limbs was reported. In addition, there were no signs of upper motor neuron hyperactivity, including hyperreflexia, lingual tremor, palmar-mandibular reflex, Hoffman's sign, and Babinski's sign.

The patient has a medical history of rheumatoid arthritis for 10 years, gout for five years, and diabetes for one year. The laboratory examination revealed an elevated CK level ranging from 219 to 441U/L (normal range 200-400 U/L), an elevated rheumatoid factor (RF) at 195.98 IU/ml (normal range: 0-20 IU/ml), elevated anti-citrullinated antibodies at 134 IU/ml (normal range: 0-5 IU/ml), and serum anti-nuclear antibodies at a homogeneous 1:3200 titer. Serological tests for antibodies to myasthenia gravis are negative. Electromyography (EMG) revealed spontaneous fibrillation potentials and positive sharp waves in the muscles of the quadriceps, bicipital muscles, sternocleidomastoid, tibialis anterior, and rectus abdominis muscles, with no clues of RNS (repetitive nerve stimulation) abnormalities. An increased amplitude of motor unit potentials (MUPs) was observed in the right adductor hallucis longus muscle (Table 1). Magnetic resonance imaging (MRI) of the cervical and lumbar spine was performed to rule out any abnormalities in the spinal cord or intervertebral discs. Whole-genome sequencing and multiplex ligation-dependent probe amplification were performed to detect facioscapulohumeral dystrophy (FSHD), congenital myopathies, or other suspected genetic disorders. Computerized tomography (CT) scans of the head, chest, abdomen, and pelvis were conducted to detect any signs of metastatic diseases. Infection-related serological tests were conducted and the results were within normal limits.

Based on the patient's history of presenting with bilateral upper extremity weakness for over 12 months and absence of upper motor neuron damage, we suspected that the patient had early-onset amyotrophic lateral sclerosis with FAS. Consequently, we recommended that the patient take riluzole (50 mg, twice daily).

During the treatment period, the patient reported mild fluctuations in limb weakness. Six months later, the patient was readmitted to the hospital due for dysphagia. We reassessed the patient and found mild atrophy of the lingual muscles (Figure 1A), asymmetric involvement of the scapular winging (Supplementary Figure 1), worsening of amyotrophy (Figures 1B–F) and decreased strength of the quadriceps (MRC grade 4). The patient experienced difficulty swallowing 30 ml of room temperature water in a single sip, as evidenced by a water swallow test grade 3. A follow-up EMG conducted three months later showed a shortened MUP duration in the right biceps (9.9 ms, Table 1). Thus, a whole-body muscle MRI was performed, revealing diffuse edema in the patient's upper arms and forearms bilaterally in short tau inversion recovery MRI. Mild edema was also observed in the patient's right lateral femoral and gastrocnemius muscles (see Figure 2). The patient's lingual muscles presented with mild fat replacement on T1-weighted imaging, while heavy adipose tissue infiltration was present in the upper limbs, back muscles, and psoas major. In contrast, the muscles of the lower limb exhibited less fat replacement, particularly in the lateral group of both thigh muscles and the posterior group of calf muscles. An MSA test was performed in peripheral blood for this condition, but the results were negative.

TABLE 1 Changes in two Electroencephalogram results.

| Muscles | EMG 1 | | MUPs | | EMG 2 | | MUPs | |
|---|---|---|---|---|---|---|---|---|
| (Needle electromyography) | Fp | Psw | Dur | Amp | Fp | Psw | Dur | Amp |
| Left. little finger spreader muscle | - | - | 10.9 | 1009 | + | - | 11.0 | 652 |
| Right. abductor hallucis longus | - | - | 10.4 | 2189 ↑ | - | + | 9.9 | 802 |
| Left. quadriceps muscle group | - | - | 12.8 | 1434 | ++ | ++ | 12.5 | 1319 |
| Right. quadriceps muscle group | ++ | ++ | 12.5 | 928 | ++ | ++ | 12.9 | 1076 |
| Left. bicipital muscle | ++ | ++ | 11.6 | 402 | ++ | ++ | 12.0 | 420 |
| Right. bicipital muscle | ++ | + | 11.9 | 505 | ++ | ++ | 9.9 ↓ | 598 |
| Right. tibialis anterior muscle | ++ | ++ | 14.0 | 600 | ++ | +++ | 13.4 | 912 |
| Left. tibialis anterior muscle | ++ | ++ | 14.1 | 684 | ++ | +++ | 13.6 | 1245 |
| Left. sternocleidomastoid muscle | - | + | 8.8 | 913 | - | + | 8.5 | 391 |
| Left. gastrocnemius muscle | ++ | ++ | 12.2 | 392 | + | ++ | 11.3 | 2317 ↑ |
| Right. rectus abdominis muscle | - | ++ | / | / | + | + | / | / |

The two EMG tests were conducted by the same experienced neurophysiologist at the same center. Two EMG tests were performed at six-month intervals. Fp, Fibrillation potential; Psw, positive sharp waves; Dur, Duration; Amp, Amplitude; EMG, Electromyography; MUPs, Motor Unit Potentials. -, absent; +, scattered; ++, moderate; +++, numerous; /, null; ↑, increased; ↓, decreased.




FIGURE 1
During the second admission, the patient had mild atrophy of the lingual muscles **(A)**, severe atrophy of both forearms **(B)**, upper arms **(C)**, and trapezius muscles **(D)** with concomitant shoulder collapse **(E)**, with preserved muscle volume in both lower extremities **(F)** (white arrows).

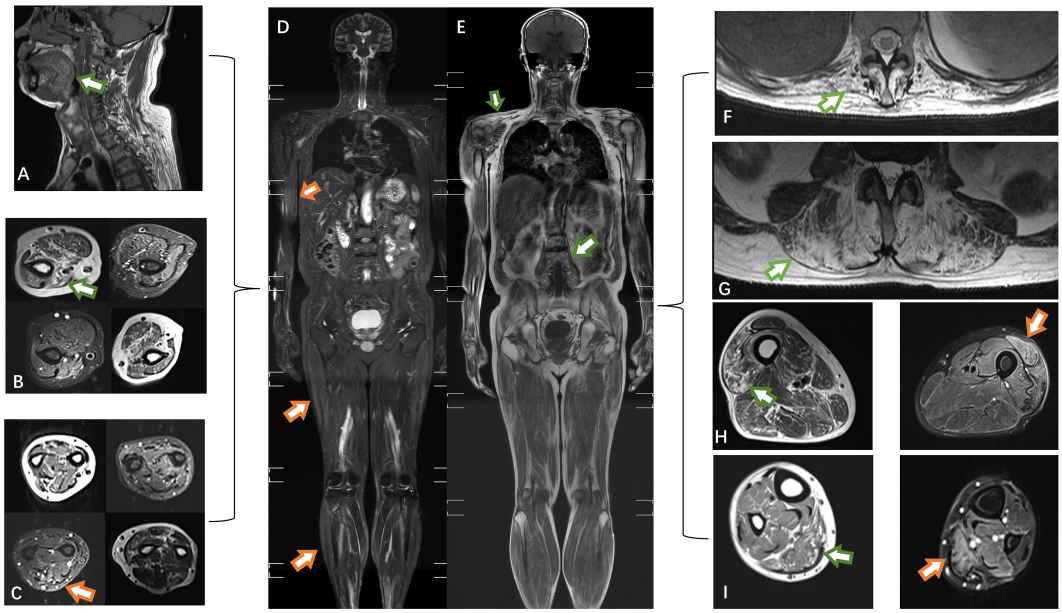



FIGURE 2
The muscles of the tongue showed mild lipoatrophy [**(A)**, green arrows]. Both the upper arm and forearm muscles exhibited bilateral asymmetric edema and lipoatrophy **(B, C)**. Edema was observed in the right biceps, lateral femoral, and gastrocnemius muscles (orange arrows) **(D)**. Atrophy was present in the trapezius and psoas muscles **(E)**. Severe fat replacement was noted in the dorsal muscles **(F, G)**. The volume of muscle in the lower extremities was preserved, with only slight involvement of the lateral group of thigh muscles compared to the posterior group of calf muscles **(H, I)**. T1-weighted imaging: green arrow; short-tau inversion recovery (STIR) MRI: orange arrow.

A muscle biopsy was conducted on the patient's biceps muscle to investigate the potential presence of myogenic damage. Figure 3 illustrates the presence of numerous foci of inflammatory cells distributed within the muscle bundles, accompanied by a large number of necrotic and regenerating muscle fibers, moderate connective tissue hyperplasia, and mild fat cell replacement, as evidenced by hematoxylin and eosin (HE) staining. Immunohistochemical staining demonstrated an abundance of CD20+ B cells and CD68+ macrophages within the inflammatory aggregates, accompanied by moderate numbers of CD138+ plasma cells and scattered CD4+ and CD8+ T cells. Some myofibers exhibited uneven enzyme activity in NADH staining, and membrane attack complexes were deposited beneath the myofibers. In addition, MHC-I staining can be observed widely positive expression on myofibre membranes (Supplementary Figure 2). Metabolism myopathy was ruled out through oil red and glycogen staining.

The patient was ultimately diagnosed with BCIM and treated with oral prednisone (initially 60 mg/day, decrement) and methotrexate (5 mg/week). After four months, the patient reported mild improvement in swallowing function and low back strength. During this period, the patient also received treatment for rheumatoid arthritis, including 99m-Tc-methylene diphosphate (99Tc-MDP).

## Discussion

This article describes the misdiagnosis and diagnosis in a patient with BCIM. The patient initially presented with a FAS phenotype, in which the EMG indicated extensive denervation potentials with chronic nerve regeneration manifestations. During follow-up, only the right biceps brachii showed shortened duration of MUPs, while CK levels were consistently normal or lightly elevated, making the diagnosis of BCIM challenging.

Progressive bilateral upper extremity atrophy is the classic presentation of BCIM. It is important to differentiate the diagnosis from other conditions such as facioscapulohumeral dystrophy (FSHD), congenital myopathies, motor neuron disease, cervical spondylosis, and peripheral neuropathies. BCIM varies among individuals, but it can be summarized by the following five features: (1) The patient experiences weakness in both upper limbs, neck, and shoulders, with normal or mild involvement of the lower limbs, frequently accompanied by dysphagia. (2) Myositis-specific antibodies are absent (3); (3) The condition is often associated with other autoimmune diseases such as arthritis, systemic sclerosis, etc (8); (4) The muscle biopsy exhibits inflammatory cell foci dominated by CD20+ and CD68+ cells (5); (5) Other infections, heredity, or other pathogenic mechanisms have been excluded.

The patient's first examination was characterized by lower motor syndrome damage that met the diagnostic criteria for FAS: progressive weakness of both upper extremities for more than 12 months, marked atrophy and subsidence of the shoulder due to the deltoid, supraspinatus, sternocleidomastoid, and teres minor, and absence of bulbar involvement and upper motor neuron symptoms (9, 10). Although the patient's first electromyogram showed significant denervation potentials in the tibialis anterior and gastrocnemius muscles, denervation potentials in the lower extremities were not an exclusion criterion for FAS syndrome

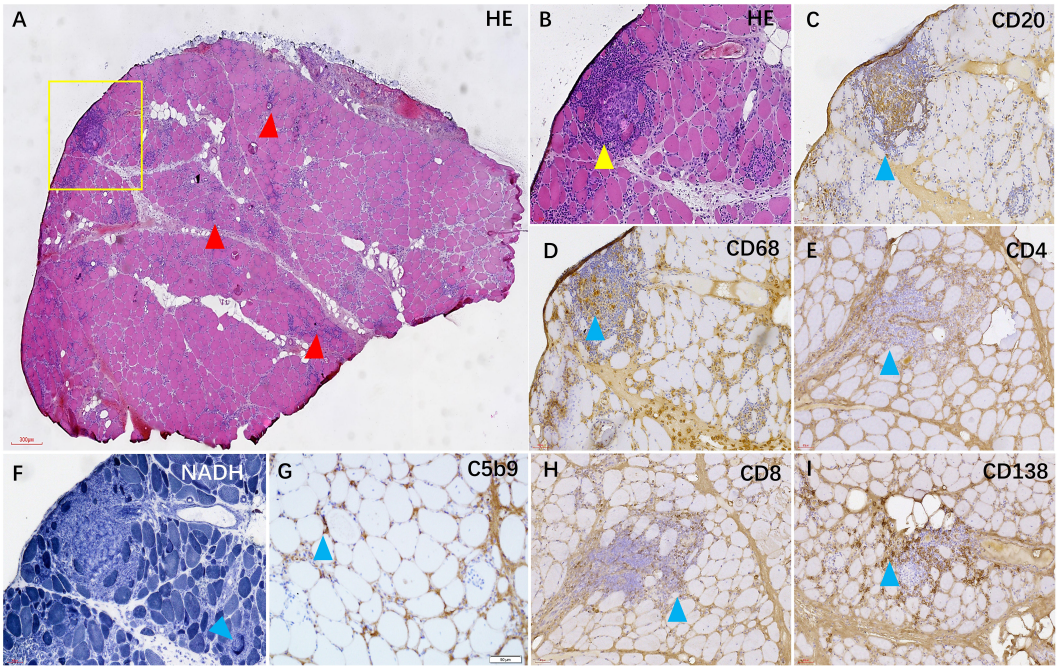



FIGURE 3
In the HE staining, numerous foci of inflammatory cells were observed in the muscle tissue [**(A, B)**, red and yellow arrows]. Immunohistochemical staining revealed that the foci were mainly composed of CD20+ B cells **(C)** and CD68+ macrophages **(D)**, accompanied by some CD138+ plasma cells **(I)** and a small number of CD4+ and CD8+ T cells **(E, H)**. Additionally, some myofibers exhibited heterogeneous NADH enzyme activity **(F)**, and C5b-9 was observed beneath the membrane of certain muscle fibers **(G)**.

(10). Recently, it was observed that the IIM-associated "Dropped head or bent spine syndrome (DH/BS)" reported by Pijnenburg et al. is highly similar to the BCIM phenotype (11). Both syndromes involve delayed diagnosis, muscular atrophy of the upper limbs, dysphagia, and autoimmune abnormalities. Meanwhile, it was found that the prognosis and mortality rates were notably poorer in DH/BS patients compared to other IIM patients (11). However, we noticed that MSA antibodies reported by neurologists for BCIM should be negative, while MSA antibodies were present in a small subset of patients in the DH/BS cohort of rheumatologists represented by A et al. Unfortunately, due to the lack of biopsy data from a larger cohort, it is not possible to determine whether BCIM is part of DH/BS. Combined with our case, we observed neck muscle weakness in our patient, but not to the extent of head droop or spinal curvature. The characteristics of 14 patients with cervicobrachial polymyositis were summarized by Khadilkar et al. (12) In 50% of their cohort, muscle strength in the lower extremities was slightly affected, commonly in the psoas major, gluteus maximus, and quadriceps (12). Similarly, in last follow up, three out of six BCIM patients had lower limb involvement as reported by Lucchini et al. (13) This is consistent with our findings, suggesting that BCIM may not be confined to muscle involvement in the upper body. However, its unique differences in involvement and pathological manifestations make it difficult to be classified among the classical subtypes of IIM (2, 14, 15). More research is needed to investigate whether BCIM progresses to a generalized inflammatory myopathy at a later stage as the disease progresses.

It is worth noting that this individual had comorbid rheumatoid arthritis, which was a significant indication of BCIM. Previous reports have shown that patients with BCIM frequently exhibit a combination of Raynaud's syndrome, Hashimoto's thyroiditis, scleroderma (13), interstitial lung disease (16), and lupus serologically positive (5). Autoimmune-related markers are crucial in screening during the early stages. Additionally, the patient's lumbar muscle involvement progressed from upper to lower extremities, indicating that BCIM may be a specific type of inflammatory myopathy with sequential involvement of sites. MRI characterization of the whole body allows for comparison of muscle involvement in the upper and lower extremities. Muscle biopsy is a valuable diagnostic tool for patients with bilateral upper extremity atrophy. In the patient's second EMG findings, only the biceps brachii muscle showed duration of MUPs decreased. Widespread fibrillation potentials typically indicate neurogenic damage (17). However, muscle necrosis caused by myositis or myotonic dystrophy can also result in secondary loss of nerve manifestations (17). Therefore, we selected the biceps muscle for muscle biopsy and observed extensive foci of inflammatory cells. Given these considerations, repeating EMG testing in patients with lower motor neuron syndrome is worthwhile for both biopsy selection and differential diagnosis.

Currently, the classification and pathogenesis of BCIM remain unclear. Calvet et al. demonstrated that thrombospondin-1 (TSP-1) can potentially serve as a biomarker for BCIM, and its elevation promotes vascular disruption and myotube atrophy (16). Most

patients with BCIM experience clinical and radiologic improvement with steroid and immunosuppressive therapy (13). CD20 and CD138 are enriched populations within inflammatory foci in the histology of BCIM. Targeting B-cell drugs, such as rituximab, could be an option for refractory BCIM, which binds to CD20 on the cell surface, utilizing antibody-dependent cytotoxicity, antibody-dependent cell phagocytosis, and direct apoptosis-inducing host effects to induce B-cell depletion (18). Furthermore, Telitacicept is a novel biological agent that binds and neutralizes two B lymphocyte stimulators and proliferation-inducing ligands. This inhibits the development and survival of both plasma cells and mature B cells (19). However, current second-line treatments, including anti-B-cell therapy, currently remain in the exploratory phase.

To summarize, it is essential to be aware that BCIM is one of the potential causes when patients present with the FAS phenotype. Due to the low prevalence of BCIM, we recommend that clinicians set a relatively low threshold for muscle biopsy in patients with atypical lower motor neuron syndrome and review electromyography at regular intervals. Despite the beneficial effect of immunotherapy on the patient in this case, continued follow-up is required to determine prognosis and potential relapse.

## Conclusion

Early FAS should be differentiated from BCIM. Serum immunologic markers, electromyography, whole-body muscle MRI, and muscle biopsy are ideal tools for diagnosing and evaluating treatment in patients with BCIM.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Ethics Committee of First Affiliated Hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

HS: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. X-JW: Data curation, Supervision, Writing – review & editing. YH: Data curation, Supervision, Writing – review & editing. Y-CW: Methodology, Writing – review & editing. Z-YW: Writing – review & editing. X-FY: Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1378130/full#supplementary-material

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# Pemphigoid diseases in patients with end-stage kidney diseases: pathogenesis and treatment

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**Background:** Pemphigoid diseases constitute a group of autoimmune blistering disorders characterized by subepithelial blistering. The association between pemphigoid diseases and both end-stage kidney disease (ESKD) and its treatment is notable. However, there is limited evidence about the management of pemphigoid diseases in patients with ESKD. This systematic review compiled case reports and relevant studies, summarized the underlying mechanisms of pemphigoid diseases in patients with ESKD, and summarized the efficacy of various therapies.

**Methods:** A systematic search of PubMed and Embase was performed for articles published between 1982 to June 2, 2024.

**Results:** Fifty-three case reports and eight relevant studies were included. Triggers for pemphigoids in patients with ESKD included materials used to treat ESKD, immune dysregulation of patients with ESKD, and rejection of renal allograft. Treatment for these patients included removing triggers, as well as administering of corticosteroids, mycophenolate mofetil (MMF), tetracyclines, rituximab, methotrexate, dapsone, azathioprine, cyclosporine, intravenous immunoglobin (IVIG), plasmapheresis, and Janus kinase inhibitors.

**Conclusion:** Removing triggers is the most effective strategy. Despite their suboptimal efficacy, corticosteroids remain the most commonly used agents in this patient population. MMF, tetracyclines, and rituximab are less used but with benefits. There are significant adverse effects associated with methotrexate treatment. Other treatment may also be beneficial and require further investigation. These findings may enable clinicians to optimize the therapeutic approach for these patients.

KEYWORDS

**pemphigoid diseases, bullous pemphigoid, end-stage kidney disease, mechanism, treatment**

# 1 Introduction

Pemphigoid diseases are a spectrum of autoimmune blistering dermatoses comprising bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), p200 pemphigoid, epidermolysis bullosa acquisita (EBA), and linear IgA dermatosis (LAD). Among them, BP is the most common subtype, with an incidence rate of 34.2 (95% confidence interval 19.2-60.7 per million person-years) (1). BP patients develop autoantibodies against BP180 and/or BP230, which are crucial proteins within the dermal-epidermal junction (DEJ) (2). MMP predominantly affects mucous membranes, especially the mouth and conjunctivae (3). Autoantibodies typically target different autoantigens such as BP180, laminin 332, and BP230 (3). Similar to BP clinically, p200 pemphigoid is characterized by autoantibodies against the 200-kDa protein of the DEJ (4). EBA is characterized by autoantibodies against collagen VII, and can present in classic or inflammatory subtype (4). The classic subtype typically exhibits skin fragility and bullous lesions at trauma-prone areas, while the inflammatory subtype resembles BP or MMP (4). LAD, the most prevalent pemphigoid disease in children, is distinguished by linear deposits of IgA at the DEJ (4).

Comorbid conditions, such as end-stage kidney disease (ESKD), have been reported in patients with pemphigoid diseases. ESKD occurs when dialysis or renal transplantation is essential to maintain patients' survival (5). The relationship between BP and ESKD, as well as its treatment, has been demonstrated in dozens of studies. Patients on dialysis are more susceptible to cutaneous conditions, including pemphigoid diseases. BP has been increasingly observed in these patients. Morimoto et al. presented several BP cases in patients receiving peritoneal dialysis (PD), suggesting a potential correlation between the dialysis process and the onset of BP (6). This relationship was further supported by J Miao et al., who reported a patient on hemodialysis had levofloxacin-induced BP, indicating the potential role of certain medications in triggering BP among patients with ESKD (7). A nationwide population-based cohort study revealed that the hazard ratio (HR) for BP in patients with ESKD was 2.12 compared to individuals without chronic kidney disease (CKD) (8). Similarly, another study identified CKD as a significant risk factor for BP, with dialysis-dependent patients showing the highest risk (9). A case-control study of 91 BP cases found that BP significantly increased the odds of comorbid ESKD (adjusted odds ratio: 3.82) (10). Studies also demonstrated that the incidence of BP among patients on dialysis was much higher than that observed in the general population (6, 11).

Managing pemphigoid diseases in patients with ESKD can be challenging due to their compromised renal function, the administration of immunosuppressants (IS), and altered immune response. These patients require treatments that can effectively manage symptoms without exacerbating the underlying renal condition. However, there is a scarcity of research focusing on the management of pemphigoid diseases among patients with ESKD. This systematic review aims to summarize all reported cases with a definitive diagnosis and provide guidance to clinicians regarding appropriate treatment methods under different circumstances.

# 2 Methods

## 2.1 Search strategy

A literature search was performed using PubMed and Embase from 1982 to June 2, 2024. The search terms included pemphigoid, epidermolysis bullosa acquisita, linear IgA bullous dermatosis, end-stage kidney disease, kidney transplantation, and dialysis. This study was conducted under the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and a PRISMA flow diagram is shown in Figure 1.

## 2.2 Eligibility criteria

Case reports were included if pemphigoid diseases were diagnosed based on at least two of the following conditions (1): subepidermal blister (2), positive direct immunofluorescence results (linear IgG or complement component C3c staining for BP) (3), positive indirect immunofluorescence results (linear deposits of IgG at the DEJ, or IgG staining on the epidermal side of salt-split skin for BP), or (4) positive serum autoantibodies (anti-BP180 antibodies (+) and/or anti-BP230 antibodies (+) for BP). Considering the impaired clearance of drugs in targeted patients, drug-induced pemphigoid diseases in patients with ESKD were included. Exclusion criteria included non-original publications and case reports not meeting the inclusion criteria.

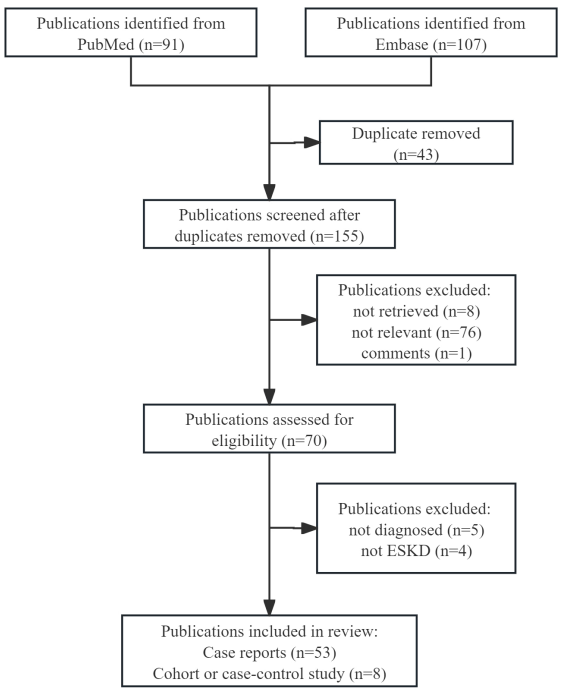



FIGURE 1
PRISMA flow diagram. ESKD, end-stage kidney disease.

## 2.3 Statistical analysis

Data were presented as an absolute number with percentage for categorical variables and mean with range for continuous ones. Descriptive statistics were used to summarize the characteristics of patient populations. The effectiveness of different treatment options was evaluated based on the reported clinical response rates.

# 3 Results and discussion

## 3.1 Study identification and patient characteristics

Fifty-one cases of the onset of BP in patients with ESKD and nine cases of other pemphigoid subtypes have been published (Supplementary Tables 1, 2). Apart from one patient whose sex was not described, the female-to-male ratio in patients with ESKD and concurrent BP was 0.52:1, lower than that of patients with BP (1.87:1) and patients with ESKD (0.71:1) (12, 13). Therefore, the reason behind male predominance in patients with concurrent ESKD and BP cannot be fully explained by male predominance in ESKD. Sex and sex hormones may have some roles on this comorbidity. The mean age was 50.5 years, also lower than the mean age of general patients with BP (74.2 years) and patients on dialysis (65 years) (14, 15).

## 3.2 Pathogenesis of pemphigoid diseases in patients with ESKD

Pathogenesis of pemphigoid diseases in patients undergoing dialysis is a multifaceted process influenced by various factors, though the precise mechanisms are not yet fully understood. Materials-induced hypersensitivity, immune dysregulation, and medication-induced immunosuppression are believed to be key contributors to their development.

### 3.2.1 Materials-induced pemphigoid diseases

Materials commonly associated with the induction of BP during dialysis include prosthetic vascular grafts, PD catheters and dialysis membranes. Vascular grafts and PD catheters serve as access points for dialysis. The initial lesions of fistula-triggered BP are typically located around the fistula site, as evidenced by eleven cases (6, 16–23). In one patient with BP, bullous lesions were limited to his hand distal to the fistula (24). Two patients experienced BP after changing the dialysis membrane from a polymethylmethacrylate membrane to a cellulose triacetate membrane or rinsing of dialysis circuit (25). These materials may induce BP via an allergic reaction and subsequent eosinophilia in the bloodstream (21, 25). BP is associated with blood eosinophilia, since 50%-60% of patients with BP exhibit blood eosinophilia (26). At the same time, blood eosinophilia is not uncommon in patients with ESKD, accounting for 5% of patients with dialysis and 20%-36% transplant patients with acute allograft rejection (27). Mutsuyoshi et al. reported three hemodialysis patients with idiopathic hypereosinophilia syndrome, which is characterized by blood eosinophilia and damage to multiple organs including skin (28). Therefore, eosinophils of patients with blood eosinophilia may infiltrate into skin. Eosinophils may contribute to pemphigoid diseases by forming eosinophil extracellular traps and releasing toxic proteins, which cause the separation of DEJ (29, 30) (Figure 2). These observations indicate a potential link between dialysis-related factors and the onset of pemphigoid diseases, possibly through exposure to foreign antigens and immune dysregulation. Moreover, 40%-84% of patients on hemodialysis exhibit pruritus (31, 32). The pathogenesis of uremic pruritus may be related to dry skin, higher dermal number of mast cells and lower clearance of pruritogenic molecules (33). Skin damage caused by frequent plaster removal for medication and scratching due to pruritus further contributes to the development of BP (18). Therefore, it is crucial to assess and manage pruritus appropriately in these patients. Patient-reported outcome tools and other effective measures may help clinicians to monitor pruritus and avoid scratching-associated skin conditions (34).

### 3.2.2 Medication-induced pemphigoid diseases

Studies have also suggested a potential association between medication use in patients with ESKD and pemphigoid diseases. IS may mask pemphigoid diseases because of its anti-autoimmune nature. After tapering IS, a significant number of autoantibodies may be generated and contribute to pemphigoid diseases. This is evidenced by nine patients who developed pemphigoid diseases after decreasing or withdrawing of IS (35–43). Resolution of BP after restarting IS therapy has been observed. The average interval between medication changes and pemphigoid diseases was 4.48 months (range: 4 days-12 months) in these patients (excluding one case with unclear data). Furthermore, drugs such as tacrolimus have been shown to reduce the population of regulatory T cells, subsequently leading to increased autoantibodies production (44). Substituting tacrolimus with corticosteroids and mycophenolate mofetil (MMF), which inhibits both cellular and humoral immunity, helped alleviate BP (45). Two BP cases were induced by mammalian target of rapamycin (mTOR) inhibitors, as evidenced by immediate resolution upon drug discontinuation followed by relapse after rechallenge (46). Other agents, such as cefixime and levofloxacin, were also considered to induce pemphigoid diseases in patients with ESKD (7, 47). Mechanisms of drug-induced pemphigoid diseases included the possibility that certain drugs could change the structure of autoantigens, expose previously sequestered autoantigens, promote autoantibodies production by acting as antigenic haptens, disrupt the DEJ directly, and cause cross-reaction of the immune response (7, 47).

### 3.2.3 Rejection-associated pemphigoid diseases

Thirteen cases associating BP with kidney transplant rejection have been reported (23, 36, 37, 40, 41, 43, 48–54). Among them, most were chronic rejection, with only four cases having acute

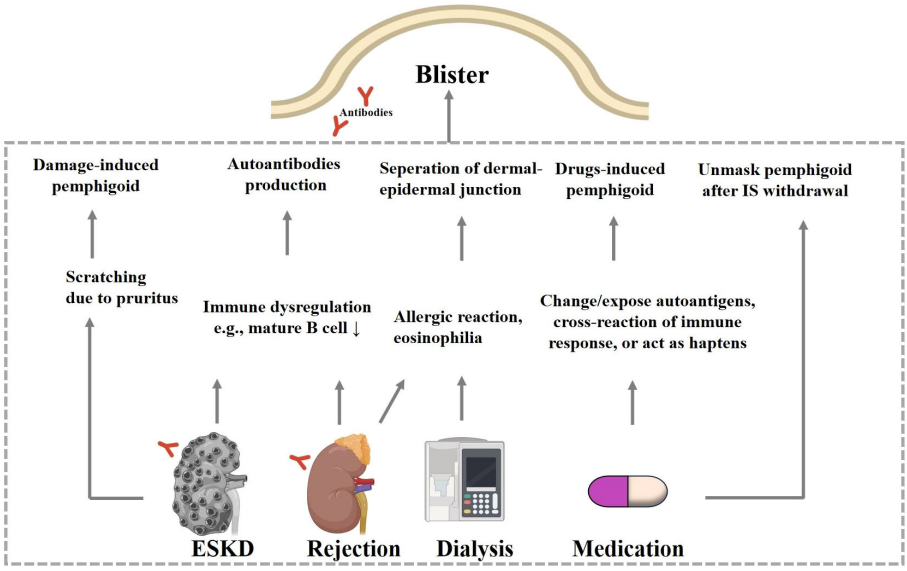



FIGURE 2
Hypothesized mechanisms of ESKD-associated pemphigoid diseases. Patients with ESKD develop pemphigoid diseases via skin damage due to scratching and via autoantibodies production due to shared autoantigens in kidney and skin. Renal allograft rejection is also accompanied by immune dysregulation. Materials used during the dialysis process may cause eosinophilia via hypersensitive reaction, and these eosinophils may then infiltrate to the BMZ and result in dermo-epidermal separation. When the dose of immunosuppressant or other drugs is adjusted. ESKD, endstage kidney diseases; IS, immunosuppressant.

rejection (36, 37, 51, 54). Mucosal involvement has been observed in two patients (48, 52). One patient developed pemphigoid disease with autoantibodies to both laminin γ1 and γ2 subunits during renal transplant rejection (42). Immune dysregulation during rejection response may contribute to pemphigoid diseases. Interestingly, in post-transplantation patients who have normal graft function, a broad array of autoantibodies can also be generated, which may explain why pemphigoid occurs in these patients (55). Furthermore, genetic predisposition and environmental triggers such as infections or trauma may play a role in pemphigoid pathogenesis in patients with ESKD.

### 3.2.4 Immune dysregulation of patients with ESKD

Pemphigoid diseases and ESKD may have a shared pathogenesis. First, components shared by the basement membrane zone (BMZ) and the glomerular basement membrane (GBM), acting as autoantigens, may induce autoantibodies. For instance, two cases of pemphigoid diseases comorbid with Alport syndrome, a genetic kidney disease characterized by abnormal type IV collagen, were reported (56, 57). Type IV collagen is typically localized to the base of BP blisters. The specific autoantibodies towards the α-5 chain of type IV collagen have been described to cause both subepidermal blisters and renal insufficiency (58). These autoantibodies were also found in rats experiencing renal allograft rejection, explaining the association between rejection and BP (59). One case with BP comorbid with anti-GBM disease also provided evidence (60). Second, the dysregulation of the immune system in patients on dialysis may lead to aberrant autoimmune responses, contributing to the pathogenesis of pemphigoid diseases. Loss of NK and mature B cell subset, as well as an increase of a proinflammatory monocyte subset has been observed in severe CKD (61).

Overall, these findings underscore the complexity of pemphigoid pathogenesis in patients with ESKD and highlight the need for further research to elucidate the underlying mechanisms. Understanding these mechanisms may provide insights into potential therapeutic targets and strategies for managing pemphigoid diseases in this vulnerable population.

## 3.3 Treatment

### 3.3.1 Triggers removal

As described previously, triggers of pemphigoid in patients with ESKD include materials and drugs used in treatment. Removing prosthetic vascular graft, prerinsing the dialysis circuit with dexamethasone solution (5 mg/L), changing dialysis membrane or disinfectant, and discontinuing inducing drugs may benefit patients (6, 21, 24, 25, 46, 62, 63). In our studied population, BP-associated drugs include furosemide, levofloxacin, cefixime, everolimus, and sirolimus. Additionally, other BP-inducing drugs, including gliptins and PD-1/PD-L1 inhibitors, should be considered (64). While most patients manifested symptoms relatively quickly after the presence of triggers, three patients had symptoms even after triggers had

presented for years (18, 22, 63). Signs of allergic response or rejection response also suggest the presence of triggers.

The transplanted kidney is another trigger for pemphigoid diseases. In cases where patients are refractory to other treatments, renal graft removal may be necessary. Thirteen cases were resolved without recurrence after nephrectomy, with relevant antibodies disappearing in two cases (21, 23, 36–40, 48, 50, 52, 65). One case was resolved after graft atrophy (66). Although most cases benefited from nephrectomy, the condition of BP may worsen because of a sustained post-nephrectomy immune response (36). To avoid this situation, it may be necessary to continue IS therapy for a certain period after nephrectomy.

### 3.3.2 Corticosteroids

In the realm of dermatology, the effectiveness of corticosteroids in treating pemphigoid diseases is well-established and corticosteroids remain a mainstay treatment. Studies have shown the effectiveness of corticosteroids in managing BP, even in complex cases like post-transplant recipients or in patients experiencing kidney transplant rejection (35, 41). Among 59 reported cases using corticosteroids, 14 (23.73%) patients were recalcitrant (23, 25, 37, 44, 46, 48, 50, 52, 62, 67–70). The dosage of corticosteroids was reported in twenty-two cases who responded well. Among them, oral prednisone was initiated at 5-75 mg/day with an average of 44.71 mg/day. In cases reported by dose per kilogram, oral prednisone was initiated at 0.5-1.5 mg/kg/day with an average of 0.94 mg/kg/day. This starting dose is higher than the recommended dosage of 0.5 mg/kg/day according to the European Academy of Dermatology and Venereology (71). Resolution typically can be observed within weeks, as reported in five cases. Among recalcitrant patients, two cases only used topical steroids, and others used prednisolone with the average daily dose of 50 mg. Triggers removal benefited patients who responded minimally to corticosteroid, suggesting the importance of triggers identification. After tapering or stopping the dose of corticosteroids, five patients relapsed (38, 39, 50, 72, 73). Severe infection was reported in one case (6).

Corticosteroids treatment of pemphigoid diseases in patients with ESKD requires additional caution. The importance of individualized dosing and vigilant monitoring for adverse effects should be highlighted, due to the renal impairment and altered drug metabolism of patients. To help reduce the dosage of systemic corticosteroids and minimize the risk, adjunctive therapies such as azathioprine, MMF, and biological agents, may be considered.

### 3.3.3 Dapsone

Dapsone, an antibiotic with anti-inflammatory properties, has also been a mainstay in treating pemphigoid diseases and a second-line chemoprophylactic drug for *pneumocystis* pneumonia in solid organ transplant recipients. However, specific studies on the use of dapsone in patients with concurrent ESKD and pemphigoid diseases are limited. This kind of treatment was reported in eight cases and benefited four patients with an average reported dose of 62.5 mg/day (20, 72, 74, 75). Adverse effects including epigastric pain and mild hypertension were reported (73). It is worth noting that dapsone-induced methemoglobinemia (MHb) occasionally developed in renal transplant recipients. A cohort study found that 12/26 (46.15%) post-transplantation patients developed MHb after receiving dapsone (76). Therefore, dapsone treatment should be used with caution in patients with ESKD.

### 3.3.4 Immunosuppressive agents

#### 3.3.4.1 Mycophenolate mofetil

MMF effectively suppresses both cellular and humoral immune responses, making it a potentially safe and efficient agent for managing pemphigoid diseases in patients with ESKD. Notably, MMF is a potent IS commonly used in organ transplant recipients (77). It has been used as an IS drug in nine patients with ESKD (16, 23, 35, 37–39, 41, 43, 51). However, the onset of BP has been observed in six cases after discontinuing MMF and other IS drugs. Three patients with ESKD used a combined therapy of MMF (at daily dose of 500 mg, 500 mg twice and 2,000 mg) and corticosteroids, and achieved resolution (42, 45, 70). A randomized clinical trial has demonstrated that MMF can halt the progression of immunoglobulin A nephropathy, a leading cause of ESKD in many countries (78). Therefore, MMF is a potential choice for the management of pemphigoid diseases in patients with ESKD, especially those who have undergone renal transplantation.

#### 3.3.4.2 Methotrexate

Methotrexate (MTX) is an inexpensive agent that can be used in pemphigoid diseases and renal allograft rejection. Only two patients with ESKD were treated with low-dose MTX for their BP, with a weekly dose of 10 mg and 5 mg, respectively (67, 68). Both cases developed life-threatening pancytopenia, indicating the toxicity of MTX in these patients. One patient died despite receiving calcium folinate and hemodialysis, while the other recovered after undergoing continuous veno-venous hemofiltration, receiving component blood transfusion, and receiving cytokine supportive treatment. Although a retrospective cohort study found that using low-dose MTX (5-10 mg/week) among patients with BP who have low renal clearance is safe, MTX should not be advised in patients with creatinine clearance less than 10 mL/min (79). Preexisting renal insufficiency and impaired renal MTX elimination can increase the risk of MTX toxicity (80). Therefore, MTX should not be prescribed to these patients.

#### 3.3.4.3 Cyclosporine

Cyclosporine was used as an anti-rejection drug in three patients with ESKD, and the onset of BP in two patients were observed during cyclosporine administration (49). Additionally, one patient developed BP after tapering cyclosporine (46). In one case, cyclosporine, in combination with corticosteroids, azathioprine and IVIG, failed to treat BP or suppress rejection (52). Although there is evidence to support the efficacy of

cyclosporine in focal segmental glomerulosclerosis, which is a leading cause of ESKD (81), its benefits in patients with concurrent ESKD and pemphigoid diseases have yet to be assessed.

#### 3.3.4.4 Azathioprine

Azathioprine (AZA) has been utilized to prevent graft rejection in two patients with ESKD (49, 50). However, the onset of BP was observed in one patient after the discontinuation of AZA (50). Additionally, four patients with ESKD used AZA (50-100 mg/day for 2-4 weeks) in combination with other drugs to treat BP, with two achieving resolutions (41, 52, 82). The utilization of AZA was successful to reduce the reliance on corticosteroids in one patient (35). Therefore, AZA may be a safe and effective strategy to treat pemphigoid diseases in conjunction with renal allograft rejection, but further research is needed to validate its efficacy.

### 3.3.5 Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG), derived from healthy donors, is a blood preparation containing immunoglobulin and other components. It is recognized as a beneficial treatment in various autoimmune conditions and renal allograft rejection (83). The use of IVIG has also been shown to increase successful transplant rates in patients with ESKD (84). However, the use of IVIG presents therapeutic challenges and opportunities when treating pemphigoid diseases in patients with ESKD. IVIG has been reported to treat BP in three patients with ESKD, but all attempts were unsuccessful (52, 62). These patients ultimately recovered after the removal of triggers, underscoring the priority of identifying and removing triggers over drugs administration. One patient with concurrent LAD and ESKD achieved remission for more than one year by administrating IVIG (35 g/day for 3 days, repeated after 2-week intervals for the first 4 months, and repeated after 3-week intervals for the next 4 months) (73). Given its effectiveness on patients with ESKD, IVIG may offer benefits in managing pemphigoid diseases that occur during renal allograft rejection, as well as patients with pemphigoid diseases awaiting renal transplantation. However, the administration of IVIG requires careful monitoring for potential side effects such as fluid overload and acute renal failure. Further clinical trials are needed to evaluate its safety and effectiveness.

### 3.3.6 Tetracyclines

Tetracyclines, either alone or in combination with nicotinamide, have been shown to benefit patients with pemphigoid disease (85). One patient with concurrent LAD and ESKD responded to tetracycline (2 g/day) and nicotinamide (1.5 g/day), but experienced severe diarrhea (73). Doxycycline, a second-generation tetracyclines, does not require dose adjustment when used in patients with renal impairments (86). Two of the three patients recovered by using doxycycline in conjunction with topical corticosteroids (18, 19), while the other was recalcitrant to doxycycline and other drugs, including systemic corticosteroids, dapsone, and niacinamide (44). A recent multicenter randomized controlled trial showed that doxycycline displayed a comparable efficacy in BP treatment to oral corticosteroids with minimized adverse events (87). These advantages make doxycycline a promising drug for managing of pemphigoids diseases in patients with ESKD. Although there was no report of minocycline treatment, similar benefits can be expected.

### 3.3.7 Plasmapheresis

Plasmapheresis can be used to remove autoantibodies, immune complexes and cytokines that participate in pathogenesis of various autoimmune diseases, including pemphigoid diseases. Hence, it has emerged as a significant treatment option for these diseases. However, plasmapheresis failed to treat BP in two patients with ESKD and caused several side effects, including thrombocytopenia, coagulopathy, and sepsis. One of the patients recovered after the removal of a renal graft (44, 48). Both cases had prominent mucosal lesions concomitant exacerbating renal conditions, indicating the possibility of cross-reactive autoantibodies and underscoring the importance of removing responsible pathogenic factors. Albeit these abortive cases, the clinical efficacy of plasmapheresis cannot be denied. A large randomized controlled trial has exhibited the safety and effectiveness of plasmapheresis in patients with anti-neutrophil cytoplasm antibody-associated vasculitis, an autoimmune disease that can lead to renal failure (88). Additionally, a multicenter cohort study showed that plasmapheresis, together with IS, significantly improved renal survival rates in patients with anti-complement factor H-associated hemolytic uremic syndrome (89). Therefore, further exploration of how plasmapheresis performs in patients with pemphigoid diseases combined with ESKD is warranted.

### 3.3.8 Biological agents

The importance of biological agents (such as rituximab, dupilumab, omalizumab, and mepolizumab) in the treatment of pemphigoid diseases has gained increasing recognition. A meta-analysis involving 296 patients with pemphigoid diseases showed that these drugs have benefits comparable to oral corticosteroids and are significantly safer (90). In our studied population, two patients receiving rituximab transfusions (for 2 or 4 infusions), and experienced symptom alleviation (37, 70). Rituximab, a B-cell depleting drug, has demonstrated efficacy in improving acute antibody-mediated renal transplant rejection (AMR), although its therapeutic effect in chronic AMR remains insignificant (91). Dupilumab has been utilized in nine patients with renal insufficiency as a safe and effective drug for various skin conditions, including atopic dermatitis, reactive perforating collagenosis, and uremic pruritus (92–95). Its potential use in patients with concurrent pemphigoid diseases and ESKD is promising. Additionally, it is worth mentioning that off-label use of tralokinumab, an anti-interleukin-13 antibody for treating atopic

dermatitis, has successfully treated BP in a patient with ESKD (69). Further investigation is needed to assess the safety and benefits of these biological agents in the treatment of pemphigoid diseases in patients with ESKD.

### 3.3.9 Janus kinase inhibitors

JAK inhibitors work by inhibiting the activity of one or more enzymes from the Janus kinase family, thereby disrupting the JAK-STAT signaling pathway, which plays a crucial role in immune response and inflammatory processes. A study by Brosius et al. illustrated the potential of JAK inhibitors as an alternative therapy for diabetic kidney disease (DKD), a condition often coexists with pemphigoid diseases and is the most common cause of ESKD (96). This result suggests that JAK inhibitors may also be effective in managing pemphigoid diseases in patients with ESKD. Moreover, the pharmacokinetics of tofacitinib, a JAK inhibitor, has been studied in patients with varying degrees of renal impairment (97). This is crucial for ESKD patients, as it enables individualized treatment strategies in managing pemphigoid diseases.

While the benefits are promising, the use of JAK inhibitors in patients with ESKD poses specific challenges. A phase two clinical trial on the efficacy of baricitinib, a JAK1/JAK2 inhibitor, in DKD, highlighted the necessity for tailored dosing and vigilant monitoring in such patients (98). Additionally, the risk of adverse effects, such as infections or anemia, could be heightened in these patients, necessitating a cautious approach and thorough risk-benefit analysis before initiating JAK inhibitor therapy. The results of a study by Sugawara et al. on the prediction of non-responders to JAK inhibitors in patients with rheumatoid arthritis further emphasized the importance of personalized medicine (99). This approach is also relevant for patients with ESKD, whose individual factors such as residual renal function, comorbidities, and concurrent medications must be considered.

Therefore, JAK inhibitors may be effective drugs for managing pemphigoid diseases combined with ESKD, yet it is imperative to approach their use with caution. The results from ongoing research and clinical trials will be key in further elucidating the efficacy and safety of these drugs in this patient population.

## 4 Conclusion

This review provides a comprehensive overview of pemphigoid in patients with ESKD, emphasizing the mechanisms and therapeutic strategies (Table 1). Gaining a better understanding of the pathophysiology of the pemphigoid diseases in patients with ESKD is essential for improving treatment strategies, allowing clinician to minimize invasive options. Overall, the identification and removal of triggers are the most important and effective approach for treating pemphigoid diseases in patients with ESKD. The relatively ideal drugs are MMF, corticosteroids, and biological agents (rituximab, especially). MTX is not recommended due to its severe adverse effects. Other treatment strategies, such as dapsone, azathioprine, cyclosporine, intravenous immunoglobulin, tetracyclines, plasmapheresis, and Janus kinase inhibitors, may be considered depending on individual circumstances. The use of these treatments in patients with ESKD must be approached with caution,

TABLE 1 Evidence-based suggestion of pemphigoid therapy in patients with end-stage kidney disease.

| Therapy | Number of cases | Response rate (%) | Effective Dosage | Suggestion |
|---|---|---|---|---|
| Nephrectomy | 13 | 100 | – | Recommendation |
| Other triggers removal | 13 | 100 | – | |
| Mycophenolate mofetil | 3 | 100 | 500-2000 mg/day for 2 months | |
| Corticosteroids | 59 | 76 | >40 mg/day for 2 weeks, then taper gradually | |
| Rituximab | 2 | 100 | 375 mg/m$^2$/week for 2-4 weeks | |
| Tetracyclines (doxycycline) | 3 | 67 | 100 mg twice a day, taper after 6 weeks and discontinue after 8 weeks | |
| Dapsone | 8 | 50 | 50 mg/day | Cautious use |
| Azathioprine | 5 | 60 | 50-100 mg/day for 2-4 weeks | |
| Cyclosporine | 1 | 0 | – | |
| Intravenous immunoglobulin | 4 | 25 | 35 g/day for 3 days, repeated after 2-week intervals for the first 4 months | |
| Plasmapheresis | 2 | 0 | – | |
| Janus kinase inhibitors | 0 | – | – | |
| Methotrexate | 2 | 0 | – | Not recommended |

considering the potential for altered drug handling and increased risk of adverse effects. Personalized treatment plans, careful monitoring, and a multidisciplinary approach are essential for the safe and effective management of pemphigoid diseases in this patient population.

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L-Y-YY: Visualization, Writing – original draft. Y-LW: Writing – original draft. Y-GZ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1427943/full#supplementary-material

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# Case report: PCA-2-associated encephalitis with different clinical phenotypes: a two-case series and literature review

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Purkinje cell cytoplasmic antibody type 2 (PCA-2), identified in 2000, targets the widely distributed microtubule-associated protein 1B in the central and peripheral nervous systems, leading to diverse clinical phenotypes of neurological disorders. We report two cases of PCA-2-associated encephalitis, each presenting with distinct onset forms and clinical manifestations, thereby illustrating the phenotypic variability of PCA-2-related diseases. The first patient was diagnosed with PCA-2-associated autoimmune cerebellitis and undifferentiated small cell carcinoma with metastasis in mediastinal lymph nodes of unknown primary origin. The second patient was diagnosed with PCA-2-associated limbic encephalitis. Our findings underscore the superior sensitivity of positron emission tomography-computed tomography over brain magnetic resonance imaging in the early detection of PCA-2-associated encephalitis. Given the high risk of relapse and suboptimal response to traditional immunotherapy in PCA-2-related neurological disorders, this study highlights the need for a deeper understanding of their pathogenesis to develop more effective treatments to control symptoms and improve patient prognosis.

KEYWORDS

PCA-2, MAP1B, limbic encephalitis, autoimmune cerebellitis, paraneoplastic neurologic syndrome, PET-CT

**Abbreviations:** AE, autoimmune encephalitis; CSF, cerebrospinal fluid; ICIs, immune checkpoint inhibitors; MAP1B, microtubule-associated protein 1B; MRI, magnetic resonance imaging; PCA-2, Purkinje cell cytoplasmic antibody type 2; PET-CT, positron emission tomography-computed tomography; PNS, paraneoplastic neurologic syndrome.

# 1 Introduction

Purkinje cell cytoplasmic antibody type 2 (PCA-2), a newly discovered paraneoplastic antibody, was first reported by Vernino et al. in 2000 (1). Its target antigen, the microtubule-associated protein 1B (MAP1B) (2), is widely distributed in the central and peripheral nervous systems, leading to various clinical disease phenotypes. The most common of these include peripheral neuropathy, cerebellar ataxia, and encephalopathy/cognitive decline (1–3). Paraneoplastic neurologic syndrome (PNS) is an indirect effect of cancer on the nervous system that is not caused by the direct invasion or secondary effects of the tumor and its metastases. It is usually associated with the presence of specific serum antibodies and can involve any part of the nervous system. The current diagnostic criteria for PNS classify PCA-2 as a high-risk antibody (>70% associated with cancer). The most common malignancies associated with PCA-2 are small-cell lung cancer, non-small-cell lung cancer, and breast cancer (4). Despite PCA-2 being the seventh most common intracellular antigen antibody, reports on the phenotypes of nervous system diseases caused by PCA-2 are relatively scarce, likely owing to its low detection rate of only 0.024% (2). Our center recently admitted two patients diagnosed with PCA-2-associated encephalitis who presented with completely different onset forms and clinical manifestations. Here, we report these two cases and retrospectively analyze PCA-2-related neurological diseases.

# 2 Case description

## 2.1 Case 1

A 57-year-old male patient, a smoker for over 20 years, presented with an unsteady gait lasting 1 month and dizziness worsening over the past 5 days. Gait instability was manifested by his inability to walk in a straight line, whereas dizziness occurred independently of body position, occasionally accompanied by blurred vision. There were no reports of nausea, vomiting, tinnitus, hearing loss, recent unconscious episodes, limb convulsions, or significant changes in urinary or fecal continence or weight. Neurological examination revealed responsiveness, dysarthria (poetic-like language), pronounced horizontal nystagmus in both eyes, and unsteady bilateral finger-to-nose and heel-knee-tibia tests. The Romberg sign was positive with both eyes open and closed; other findings were normal. Laboratory tests indicated an elevated carcinoembryonic antigen level at 10.44 ng/mL (normal value: <5.0 ng/mL).

Brain magnetic resonance imaging (MRI) showed no abnormal signals or atrophy in the cerebellum (Figures 1A–C). Cerebrospinal fluid (CSF) examination by lumbar puncture showed elevated protein levels (0.63 g/L [reference range: 0.15–0.45 g/L]), white blood cell count (40×10^6/L [reference range: 0–8×10^6/L]), and immunoglobulin G (36.63 mg/L [reference range: 0–34 mg/L]). Macrogene next-generation sequencing of the CSF was negative, but the cell-based assay revealed positivity for anti-PCA-2 (MAP1B) in serum and CSF (both titers 1:30, Figures 2A–D). Additionally, anti-mGluR1, mGluR2, mGluR8, KLHL11, Homer3, ARHGAP26, ATP1A3, CARP VII, GluR δ2, CASPR2, Yo, Hu, Ri, CV2, Ma1, Ma2, amphiphysin, SOX1, Tr, Zic4, recoverin, titin, PKCγ, and GAD65 were tested negative. The positive anti-PCA-2 strongly indicated a lung tumor, confirmed by both plain and contrast-enhanced lung computed tomography (CT). Nodules (~1.0 cm) of undetermined nature were seen in the left upper lobe of the lung, and the mediastinal lymph nodes were also enlarged. Whole-body positron emission tomography-computed tomography (PET-CT) showed hypermetabolic lymph nodes in the mediastinum (4R group) and metastatic lymph nodes with an unknown primary focus, although the metabolism of the left lung was not high (Figure 1D). Subsequent endobronchial ultrasound-guided fine-needle aspiration biopsy for the mediastinal (group 4R) metabolic lymph nodes showed undifferentiated small cell cancer (Figure 1E). Pathological immunohistochemistry revealed the following: CK-pan (±), TTF-1 (+), Syn (±), LCA (+), and CD56 (±).

## 2.2 Case 2

A 45-year-old male patient, a smoker for 25 years, presented with intermittent memory confusion lasting 6–7 days. This manifested as forgetting his mobile phone password and not recognizing colleagues. He also experienced two episodes of urinary and fecal incontinence but maintained clear consciousness and normal responsiveness. The patient had recently lost approximately 5 kg in weight. Four days after admission, he developed visual hallucinations and nocturnal confusion. He did not experience dizziness, walking instability, or limb convulsions throughout the course of his illness. Neurological examination showed slightly poor orientation, significantly decreased recent memory, and slightly decreased long-term memory; no other abnormalities were noted. The brain MRI of the bilateral temporal lobe and hippocampus was normal (Figures 3A–C). However, a 24-hour electroencephalogram displayed slight epileptiform discharges in the bilateral temporal lobes.

CSF examination by lumbar puncture elevated levels of protein (0.9 g/L [reference range: 0.15–0.45 g/L]) and immunoglobulin G (80.33 mg/L [reference range: 0–34 mg/L]). Macrogene next-generation sequencing of the CSF sample yielded negative findings, but cytokeratin 19 levels were elevated at 6.33 ng/mL (reference range: <5.0 ng/mL). A lung CT scan revealed inflammatory nodules (~0.4–0.7 cm) in the right lobes of the lung. The tissue-based assay was positive for serum paraneoplastic antibody, and the cell-based assay was positive for anti-PCA-2 (MAP1B) (titer 1:30, Figures 2A, B, E). Meanwhile, anti-NMDAR, AMPA1, AMPA2, LGI1, CASPR2, GlyR1, $GABA_AR$, $GABA_BR$, IgLON5, DPPX, DRD2, GAD65, mGluR1, mGluR5, neurexin-3α, ganalionic AchR, KLHL11, GluK2, AK5, AGO, CaVα2δ, AQP4, MOG, and GFAP were tested negative. Granular-type (1:3200) antinuclear antibodies were also found, but not other types of antinuclear antibodies. The Rheumatology and Immunology Department indicated that the presence of a single antinuclear antibody particle type was a secondary change. To further screen for the primary cause, the patient underwent whole-body PET-CT imaging, which revealed hypometabolism in the left parietal, frontal, and temporal lobes; left caudate nucleus; left hippocampus; and right cerebellum (Figure 3D). There was low metabolism in the nodules in the upper lobe of the right lung and

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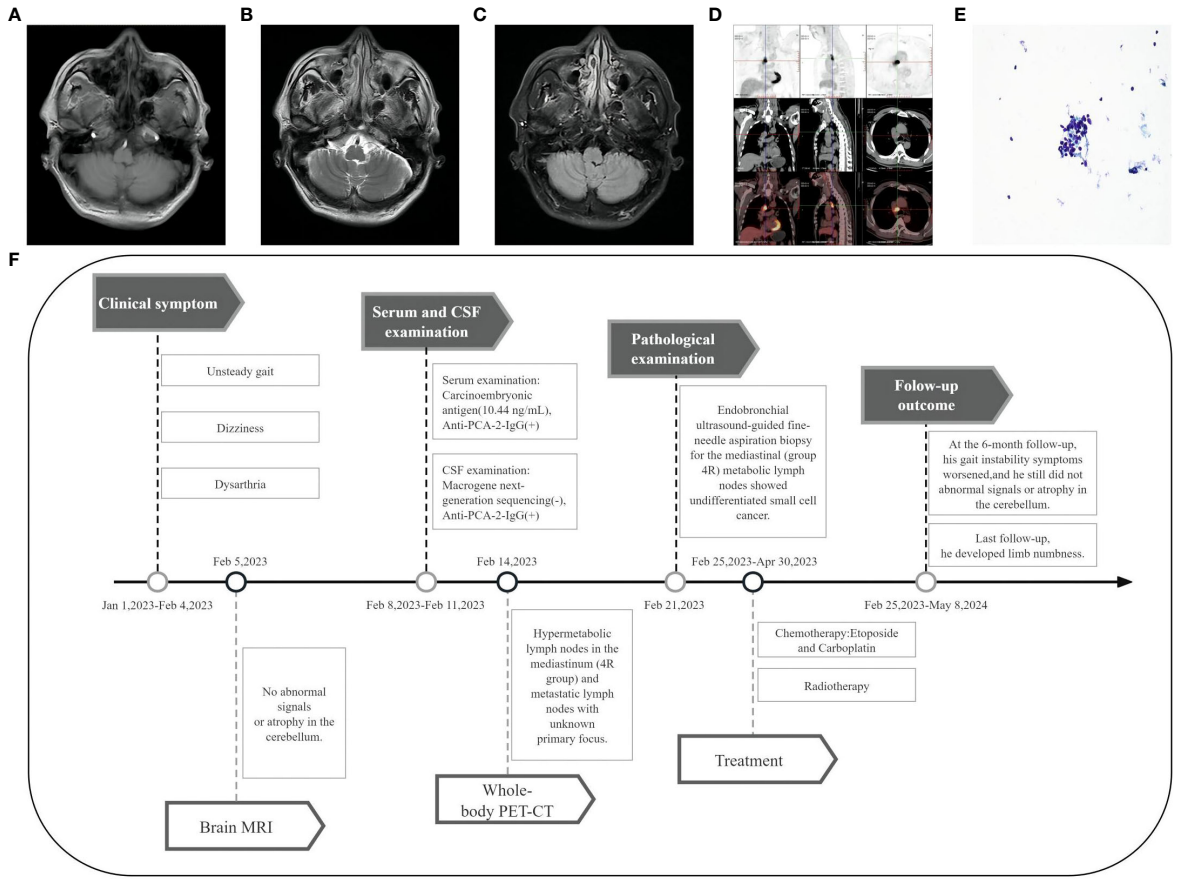



FIGURE 1
Imaging and clinical course of Case 1. **(A-C)** Brain MRI showed no abnormal signals or atrophy in the cerebellum. **(D)** PET-CT showed hypermetabolic lymph nodes in the mediastinum (4R group), with the largest measuring 3.2 cm × 2.1 cm. **(E)** Fine-needle aspiration cytology of the mediastinal lymph node (Papanicolaou stain [× 400 magnification]) showed undifferentiated small cell carcinoma cells. **(F)** Timeline of the clinical course in Case 1.

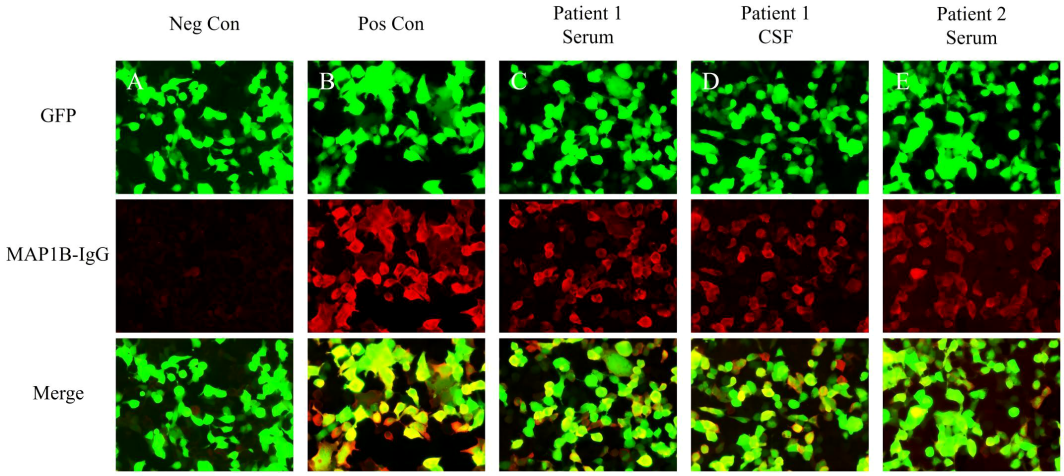



FIGURE 2
Test results of serum and CSF using indirect immunofluorescence assays. **(A)** Negative controls without MAP1B antibodies in the serum. **(B)** Positive controls from a patient with classical anti-MAP1B. **(C)** Serum MAP1B-IgG test results (1:30) of Patient 1. **(D)** CSF MAP1B-IgG test results (1:30) of Patient 1. **(E)** Serum MAP1B-IgG test results (1:30) of Patient 2. GFP, green fluorescent protein; Neg Con, negative control; Pos Con, positive control.

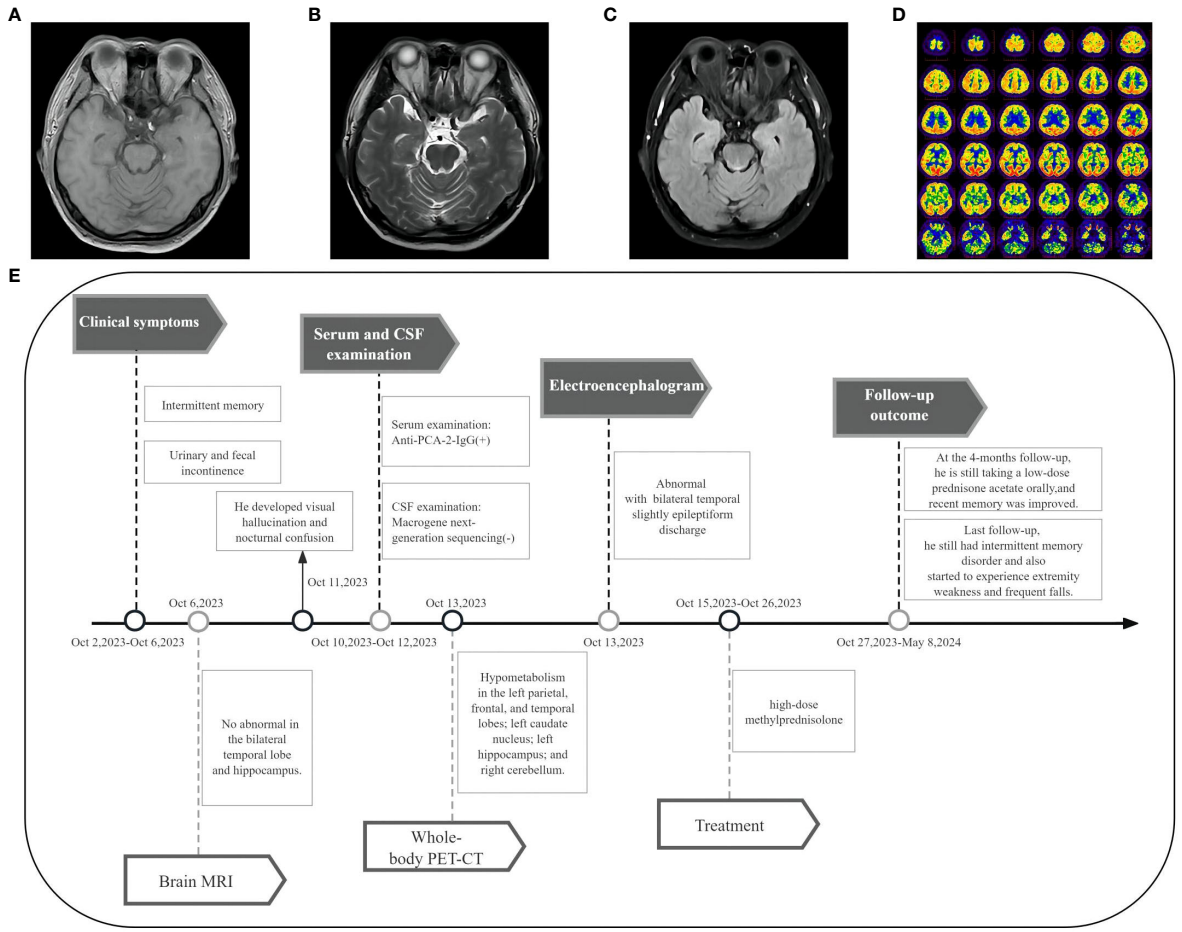



FIGURE 3
Imaging and clinical course of Case 2. **(A-C)** Brain MRI showed no abnormal signals in the bilateral temporal lobe and hippocampus. **(D)** PET-CT showed hypometabolism in the left parietal lobe, frontal lobe, temporal lobe, left caudate nucleus, left hippocampus, and right cerebellum. **(E)** Timeline of the clinical course in Case 2.

high density in the gallbladder cavity, either from the contrast agent or bile stasis. Other considerations included gallbladder neck duct stones and double renal pelvis and right ureteral calculi with secondary right renal pelvis and right middle and upper ureteral dilated effusions. No tumor was found during PET-CT imaging.

# 3 Timeline

The timeline of case 1 (Figure 1F).
The timeline of case 2 (Figure 3E).

# 4 Diagnostic assessment, treatment, and follow-up outcomes

## 4.1 Case 1

Patient 1 presented with subacute onset and clinical manifestations of cerebellar damage such as dizziness and an unsteady gait. Laboratory tests revealed leukocytosis (> 5×10^6/L) in CSF, and the cell-based assay revealed positivity for anti-PCA-2 (MAP1B) in serum and CSF. Undifferentiated small cell cancer found in mediastinal (group 4R) metabolic lymph nodes is also the most common tumor type associated with anti-PCA-2. The patient was finally diagnosed with PCA-2-associated autoimmune cerebellitis and undifferentiated small cell carcinoma with mediastinal lymph node metastasis of unclear primary focus. He was subsequently transferred to the Department of Oncology, diagnosed with lung cancer (small-cell TXN2M0 IIIA stage), and was administered chemotherapy with 3 cycles of etoposide (200 mg on day 1 and 150 mg on days 2–3) and carboplatin (500 mg on day 1). Mediastinal (group 4R) metabolic lymph node radiation was started, and 60 Gy was delivered in 30 fractions of 2 Gy each over 42 elapsed days after cycle 3 of chemotherapy. At the 6-month follow-up, his dizziness had improved, but gait instability symptoms worsened, and he could not walk unassisted. At the last follow-up, the patient had stable disease, but he developed limb numbness. Thus, he was recommended for repeat tests for paraneoplastic syndrome-related antibodies to clarify the current titer change of PCA-2 and whether it was combined with other types of antibodies. Additional immunotherapy was also recommended to improve gait

instability. However, immunotherapy was refused owing to concerns about the possibility of increasing the primary tumor focus with steroids and other immunotherapies.

## 4.2 Case 2

Patient 2 had limbic system symptoms such as decreased recent memory and abnormal mental behavior. The CSF examination showed elevated levels of protein and immunoglobulin G. Whole-body PET-CT imaging revealed hypometabolism in the left parietal, frontal, and temporal lobes, left caudate nucleus, left hippocampus, and right cerebellum. The electroencephalogram displayed slight epileptiform discharges in the bilateral temporal lobes. Moreover, the cell-based assay was positive for anti-PCA-2 (MAP1B). Finally, the patient was diagnosed with PCA-2-associated limbic encephalitis and treated with 12 days of intravenous methylprednisolone pulse-therapy (1 g on days 1–3, 0.5 g on days 4–6, 0.24 g on days 7–9, and 0.12 g on days 10–12), followed by oral prednisone acetate (60 mg/day, reduced by 5 mg every two weeks). To date, 8 months after initial presentation, the patient is still on oral prednisone acetate therapy (5 mg/day). At the 4-month follow-up, his recent memory had improved, but he still had intermittent memory disorder. At the last follow-up, the patient also started to experience extremity weakness and frequent falls. He also experienced a significant weight loss of approximately 15 kg. Repeated paraneoplastic antibody tests in the serum and CSF and PET-CT were recommended to screen for tumors. However, the patient refused owing to economic reasons and preferred to continue the oral low-dose prednisone acetate treatment.

# 5 Discussion

PCAs, including PCA-1 (Yo), PCA-2 (MAP1B), and PCA-Tr (DNER), are high-risk antibodies for PNS and can cause autoimmune cerebellar ataxia. Although the symptoms of autoimmune cerebellar ataxia caused by anti-PCAs antibodies may be similar, there are differences in several aspects such as sex, tumor occurrence, merging of other antibodies, and treatment effects (4, 5). Moreover, because MAP1B is widely distributed in the central and peripheral nervous systems, there are more clinical manifestations in PCA-2-related nervous system diseases than in other PCA-related diseases. In a recent analysis of PCA-2-related diseases using data from the Mayo Clinic, 61% of the 95 patients with clinically verifiable information had subacute signs and symptoms. The neurological manifestations varied, ranging from a single symptom to a combination of several symptoms. Approximately 47% of the patients had multiple clinical manifestations, and the main clinical manifestations were peripheral neuropathy (53%), somatesthesia disorder (45%), cerebellar ataxia (32%), encephalopathy/cognitive decline (27%), gastrointestinal motility disorder (8%), borderline encephalitis (7%), and Parkinson's/dystonia/chorea (5%) (2). Although both patients in this study had PCA-2-related neurological diseases, the onset forms were completely different; Patient 1 developed the disease in the form of unstable gait, dizziness, and poetic-like language, whereas Patient 2 presented with intermittent memory disorder and also developed visual hallucinations and nocturnal confusion during the disease course, reflecting the varied clinical phenotypes of PCA-2-related diseases.

PCA-2-associated limbic encephalitis accounts for only 7% of all PCA-2-related neurological diseases. Currently, only 10 cases of PCA-2-associated limbic encephalitis have been verified (Supplementary Table 1) (2, 6), but almost all of these cases were combined with other antibodies. In our study, only a single PCA-2 was found in Patient 2, suggesting that PCA-2 could be the responsible antibody for limbic encephalitis. Therefore, when diagnosing and treating limbic encephalitis, the possibility of PCA-2 should be considered in addition to anti-NMDAR, anti-LGI1 and anti-GABAR, which are common causes of marginal lobe encephalitis. The main differences between PCA-2 related limbic encephalitis and common limbic encephalitis are in clinical manifestations, tumor occurrence, and treatment effects. The clinical manifestations of anti-NMDAR encephalitis usually include prodromal symptoms such as fever and headache, followed by obvious neurological and psychiatric symptoms such as blurred consciousness, epileptic seizures, and autonomic instability, which usually require hospitalization in the intensive care unit (7). Approximately 38% of cases are associated with tumors, which are predominant among middle-aged and young women, are mainly ovarian teratomas (4), and are sensitive to immunotherapy. Anti-$GABA_BR$ limbic encephalitis is more common in elderly males with smoking habits, and its clinical manifestations often include behavioral changes and refractory epileptic seizures. More than 50% of cases are related to tumors, with the most common being small cell lung cancer (4). The characteristic clinical manifestations of anti-LGI1 limbic encephalitis include the subacute onset of memory decline, epileptic seizures, and/or facial arm muscle tone disorders, with a less than 10% probability of concomitant tumors (4). Its recurrence rate of anti-LGI1 limbic encephalitis is high and immunotherapy is effective at the beginning of the disease (8).

PCA-2 is a high-risk antibody for tumor development, with the tumor probability being as high as 79%. Tumors can appear simultaneously with antibody positivity or before or after antibody positivity. In a study by Gadoth et al., tumors were found after and before antibody positivity in 43% and 17% of patients, respectively; 20% of the patients had no tumor after screening. Tumor and neurological symptoms occurred simultaneously in 9% of the patients (2). However, there are currently no data on the median time to tumor detection after the onset of neurological symptoms because the updated PNS criteria indicate that patients with high-risk antibodies need to undergo repeat tumor screening every 4–6 months for 2 years. Knowing the median time to detect tumors after the onset of neurological symptoms will be helpful in developing appropriate guidelines for the regular screening for tumors in PCA-2-positive patients. Moreover, PCA-2 is more likely to be combined with other antibodies; approximately 67% of patients with PCA-2 have other antibodies (2). The most common co-existing antibodies are CRMP5 (26%), P/Q-VGCC (21%), GAD65 (15%), ANNA-1 (13%),

VGKC (Kv1)-complex (7%), nicotinic ganglionic (α3) AChR (6%), nicotinic muscle AChR (3%), GABA-B receptor (3%), amphiphysin (2%), N-VGCC (2%), AMPA receptor (2%), and AGNA-1 (SOX-1) (2%) (2). Various clinical manifestations associated with PCA-2 may also be related to these co-existing antibodies, but the antibodies responsible for each clinical manifestation are yet to be defined.

In the study by Jitprapaikulsan et al., all patients with PCA-2 co-existing with CRMP5 or ANNA1 antibodies had cancer, indicating the importance of antibody clusters in predicting underlying cancers (9). Although PCA-2 often co-exists with other onconeural autoantibodies, the lung cancer detection rate is similar between PCA-2 patients with and without co-existing onconeural autoantibodies (66% and 63%, respectively) (2). In addition, PCA-2 is not only associated with tumors but also with neurological diseases after the use of immune checkpoint inhibitors (ICIs) in tumor therapy. To date, five patients with PCA-2-related neurological diseases have been reported (Supplementary Table 2) (6, 10–13). One patient developed PCA-2-related neurological disease after treatment with a PD-1 inhibitor. In this patient, it is unclear whether the presence of PCA-2 was a pathological change induced by the tumor itself or by ICIs. PCA-2-related adverse events after the use of ICIs require further research.

The current two patients showed different MRI and PET findings. Patient 1 initially did not show abnormal signals or atrophy in the cerebellum even 6 months after disease onset. However, cerebellar atrophy might be found on brain MRI in the later stage of disease progression, suggesting the need for long-term imaging follow-up. Patient 2 did not show abnormal signals in the bilateral temporal lobe and cerebellum by brain MRI examination 4 days after disease onset, but his whole-body PET-CT showed hypometabolism in the left parietal lobe, frontal lobe, temporal lobe, left caudate nucleus, left hippocampus, and right cerebellar brain after 10 days. Moreover, Patient 2 did not show symptoms of cerebellar ataxia, but PET-CT showed cerebellar hypometabolism. We believe that this may be a subclinical molecular metabolic lesion itself or a cerebrum lesion that led to cerebellar cross disconnection.

Vernino et al. reported a case of limbic encephalitis in which the brain MRI was normal at the beginning, but the subsequent brain MRI showed abnormalities in the left medial temporal lobe (1). This supports the idea that normal brain MRI findings should not be used as the basis for ruling out limbic encephalitis. Lesions can be detected on PET-CT during the early stages or on the follow-up brain MRI. Although abnormal signals in the bilateral temporal lobe on brain MRI are one of the diagnostic criteria for autoimmune encephalitis (AE), some patients with AE show normal findings at disease onset. In one study, MRI changes were observed in only 40% of cases, but PET-CT findings were abnormal in 82%. In addition, PET-CT showed more abnormalities than initial electroencephalogram, MRI, and CSF tests in patients with AE, and the most common abnormality was hypometabolism in brain regions. PET-CT imaging may be more sensitive than MRI in showing increased fluorodeoxyglucose metabolism in normal-appearing medial temporal lobes (14).

Antibody-related AE shows specific metabolic patterns. In those related to neuronal surface antibodies (e.g., anti-NMDAR encephalitis), the metabolism of the frontal parietal and medial temporal lobes is increased, whereas that of the occipital lobe is decreased. In anti-LGI1 encephalitis, abnormal metabolism occurs in different brain regions, including the medial temporal, hippocampus, and cerebellum. Patients with facial arm dystonia show basal ganglia abnormalities. In AEs related to neuronal intracellular antibodies, hypometabolism is observed in the parietal, frontal, occipital, temporal, and hippocampus lobes in patients with anti-GAD65 and anti-Ma2 encephalitis. Patients with anti-Hu encephalitis show both hypometabolism and hypermetabolism in the medial temporal lobe and hypometabolism in cortical regions (e.g., frontal, occipital, and parietal lobes) (15). Therefore, the position of the antigen bound by antibodies inside and outside the cell influences the metabolism of the lesion site on PET-CT. Furthermore, as this position relates to different metabolic changes on PET-CT, PET-CT can be used for the early differentiation of limbic encephalitis caused by different autoimmune antibodies, particularly those caused by neuronal intracellular and extracellular antigens. However, there are limited reports on the PET-CT imaging findings of PCA-2-associated limbic encephalitis, emphasizing the need for further studies.

Traditional immunotherapy such as steroids, immunoglobulin, and plasmapheresis may only moderately improve symptoms, and approximately 50% of patients have a poor response. The general effect may be attributed to antibody targeting of neuronal antigens. The reason why traditional immunotherapy has a general effect may be that the target antigen of this kind of antibody is in the neuron, which is not easily accessed by the antibody; thus, this type of antibody does not directly produce pathological effects but attacks the neuronal antigen through the immune response mediated by T cells. In patients with PNS, CD3+ and CD8+ T-lymphocytes predominantly infiltrate the brain or dorsal root ganglia, supporting cytotoxic T-cell-mediated neuronal loss rather than antibody-mediated dysfunction (16, 17). However, antibodies against cell surface antigens can bind to cell surface proteins on living neurons, and postmortem tissue examination shows that anti-IgG deposition around neurons does not lead to substantial cell death (17). Thus, diseases associated with antibodies to cell surface antigens have a better response to immunotherapy, whereas those associated with intracellular neuronal antibodies have a poor response. PCA-2-associated neurological diseases have various phenotypes, but those with a poor response to traditional immunotherapy have not been identified. One prospective study showed that twice as many patients treated with a combination of plasmapheresis and cyclophosphamide had improvements in disability as those treated with plasmapheresis alone. Therefore, for patients with a poor response to first-line immunotherapy, more aggressive immunosuppression with early initiation of second-line agents such as cyclophosphamide should be considered (18).

The treatment strategies differ for patients with positive PCA-2 with and without concurrent tumors. In Patient 1, treatment was focused on the primary lesion, and thus, there was no attempt at immunotherapy. However, despite chemotherapy and radiotherapy, the patient's gait instability worsened. This indicates that T-cell-mediated Purkinje cell destruction is irreversible. Moreover, Patient 2 had no tumor and was treated with

intravenous methylprednisolone immunotherapy, and the symptoms of memory confusion and senseless talking were significantly improved. This indicates that some patients still respond to first-line immunotherapy. On follow-up, Patient 1 developed limb numbness, and Patient 2 developed limb weakness and consequently experienced frequent falls. This newly developed neurological symptom may be related to PCA-2 itself or in combination with other antibodies. PCA-2 is often combined with CRMP5 and/or ANNA1 antibodies, and they can cause sensory or motor neuropathy. However, peripheral nerve examination was not performed in both patients; thus, it was impossible to determine the existence of peripheral neuropathy. Moreover, there were no tests for CRMP5, ANNA1, and other antibodies; as such, it was unclear whether other antibodies, which may have caused new symptoms, were present. Prognostic differences among PCA-2 phenotypes have not been reported, but patients with peripheral neuropathy with co-existing PCA-2 and ANNA1 antibodies and/or CRMP5 antibodies have a lower survival rate (9).

In conclusion, we report two cases of PCA-2-associated encephalitis with completely different onset forms, clinical manifestations, imaging findings, tumorigenesis, and therapeutic responses. The limitation of this work is that neither patient was retested for antibodies; therefore, it was unclear whether the new symptoms were related to changes in anti-PCA-2 antibody titer or the combination of other antibodies. In future research, we should focus on the potential correlation between antibody titer and symptom severity. Finally, given the high risk of relapse and the poor effect of traditional immunotherapy on PCA-2-related neurological diseases, future studies should pay more attention to their pathogenesis to establish more effective treatment methods for controlling symptoms and improving prognosis.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

XL: Conceptualization, Data curation, Software, Writing – original draft, Writing – review & editing. YL: Conceptualization, Data curation, Software, Writing – original draft, Writing – review & editing. DM: Formal analysis, Resources, Writing – review & editing. JB: Formal analysis, Resources, Writing – review & editing. PS: Formal analysis, Writing – review & editing, Resources. XW: Writing – review & editing, Formal analysis, Resources. LC: Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1431585/full#supplementary-material

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# Overlap of membranous nephropathy and IgA nephropathy in a patient with Kimura's disease: a case report and literature review

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**Introduction:** Kimura's disease (KD) is a rare chronic inflammatory disorder characterized by subcutaneous lymphoid hyperplasia with peripheral eosinophilia. Kidney involvement is reported in 15%–18% of adult patients with KD, in many cases as nephrotic syndrome. We present a case of overlapping membranous nephropathy and IgA nephropathy associated with KD.

**Case report:** A 27-year-old man was admitted with a history of bilateral leg edema for the last 2 months and concomitant progressive increase of cervical mass and fever. Laboratory findings were as follows: peripheral leukocyte count, 10,080/mm$^3$; eosinophils, 3,200/mm$^3$ (31.7%); serum creatinine, 0.83 mg/dL; and eGFR: 140 mL/min per 1.73 m$^2$. Urinalysis revealed the presence of hematuria and proteinuria and the following results: 24-h proteinuria, 12.9 g; serum albumin, 1.3 g/dL; and elevated IgE level, 750 kU/L. Serologies for hepatitis B, hepatitis C, HIV, and VDRL were all negative. Complement C3 and C4 levels were normal. No monoclonal protein was detected in blood and urine. Parasite infestation was discarded. A biopsy of the cervical lymph node revealed eosinophilic lymphoid hyperplasia, suggesting KD. A kidney biopsy revealed findings consistent with the overlapping of membranous nephropathy with IgA nephropathy. The patient was treated for KD with prednisone 1 mg/kg/d with progressive dose tapering and posterior association of methotrexate 15 mg/week. A renin–angiotensin system inhibitor was prescribed for nephrotic syndrome. The cervical mass regressed, and proteinuria achieved partial remission, with an increase in serum albumin level and normalization of eosinophils and IgE levels.

**Conclusion:** Although uncommon, kidney involvement must be considered in patients with KD. Glomerular diseases are the most frequent form of kidney injury.

KEYWORDS

Kimura's disease, nephrotic syndrome, membranous nephropathy, IgA nephropathy, kidney biopsy

## Introduction

Kimura's disease (KD) is a rare chronic inflammatory disorder characterized by lymphoid hyperplasia with peripheral eosinophilia. It was first described by Kim and Szeto in 1937 and coined in 1948 by Kimura, a Japanese pathologist who detailed the pathological features of the disease (1). KD usually affects young men (male-to-female ratio, 4:1) in their second to third decade of life, and it is more common in East and Southeast Asia (2–4). KD etiology is unknown, but some associated risk factors are autoimmune diseases, allergy, cancer, and parasite infestation (5). The classic presentation of KD involves painless soft tissue swelling, mainly in the head and neck, as well as a single or multiple papules, nodules, and/or masses. Regional lymph nodes and salivary glands are usually affected, and the most common involved site is the periauricular area. Peripheral blood analysis reveals eosinophilia and an increase in serum IgE levels. The histologic aspect of lymph node in KD depicts angiolymphoid hyperplasia and intense eosinophilic infiltration (2, 5).

Kidney disease is the most common finding regarding systemic manifestations, affecting 15%–18% of adult patients with KD (3). Renal manifestation ranges from asymptomatic urinalysis abnormalities to chronic kidney disease. Proteinuria is reported in 12%–16% of patients with KD (6) and nephrotic syndrome is reported in approximately 60% of kidney involvement in KD (7). Kidney biopsy may present different histologic presentations such as membranous nephropathy (MN), IgA nephropathy (IgAN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranoproliferative glomerulonephritis (MPGN) (3).

Herein, we report a case of overlapping MN and IgAN in a patient with KD.

## Case report

A 27-year-old Brazilian man was admitted complaining of increasing cervical mass and fever for the last 2 months, which had been recently associated with concomitant progressive bilateral leg edema. The patient denied fever, sweating, weight loss, contact with animals, use of medication, pruritus, or skin lesions. Physical examination upon admission revealed a patient with anasarca, as well as a bilateral cervical mass, more prominent on the left, with enlarged submental lymph nodes. The cervical mass was painless and there was no evidence of phlogistic signs. The spleen and liver were not palpable in the abdominal examination.

A cervical computerized tomography (CT) evidenced multiple confluents and enlarged lymph nodes in the left cervical (Figure 1A) and supraclavicular areas. Those lymph nodes exhibited high tracer uptake in the PET-CT scan (Figure 1B).

Laboratory workup showed the following: hemoglobin, 14.4 g/dL; leukocyte, 10,080/mm$^3$; neutrophils, 3,630/mm$^3$; lymphocytes, 2,340/mm$^3$; monocytes, 1,070/mm$^3$; and eosinophils, 3,200/mm$^3$. His serum creatinine was 0.83 mg/dL [estimated glomerular filtration rate (eGFR) by CKD-EPI: 140 mL/min per 1.73 m$^2$], without electrolytic or acid–base disorders. Urinalysis revealed hematuria and proteinuria, with a 24-h proteinuria of 12.9 g. Metabolic investigation revealed the following: serum albumin, 1.3 g/dL; total cholesterol, 434 mg/dL; low-density lipoprotein, 320 mg/dL; high-density lipoprotein, 79 mg/dL; serum triglycerides, 177 mg/dL; IgE, 750 kU/L; IgA, 358 mg/dL; IgG, 324 mg/dL; and IgM, 73 mg/dL. The normal ranges of laboratory tests are presented in Supplementary Table 1. Serologies for hepatitis B, hepatitis C, HIV, and VDRL were all negative. Complement C3 and C4 levels were normal. No monoclonal protein was detected in blood or urine. Autoimmune panel (antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibodies) was negative. Parasite infestation was ruled out. The patient presented IgG+ for cytomegalovirus and Epstein–Barr virus, and had negative serologies for Toxoplasma and rubeola. Serum anti-PLA2R was negative. Ultrasound evaluation showed kidneys with normal size and echographic aspects.

A cervical lymph node biopsy revealed proliferation of polymorphic cell consisting of plasma cells, mature lymphocytes (Figure 1C), and a dense infiltrate of eosinophils (Figure 1D). There was a proliferation of vascular structures at the periphery of the lymph node with dilated lumens, irregular contours, and thin walls, sometimes containing some red blood cells within it, with some smooth muscle fibers and lined by endothelium of flattened cells, without atypia. Immunohistochemistry was positive for CD15 in the dense eosinophil infiltrate, positive for CD3 and CD20 in rare lymphocytes, and negative for CD30, cytokeratins AE1/AE3, CD1a, and CD21. Bone marrow biopsy detected no proliferative process. The association of clinical and histological findings was consistent with KD.

A kidney biopsy was performed in the scenario of nephrotic syndrome. Light microscopy revealed the expansion of the mesangial

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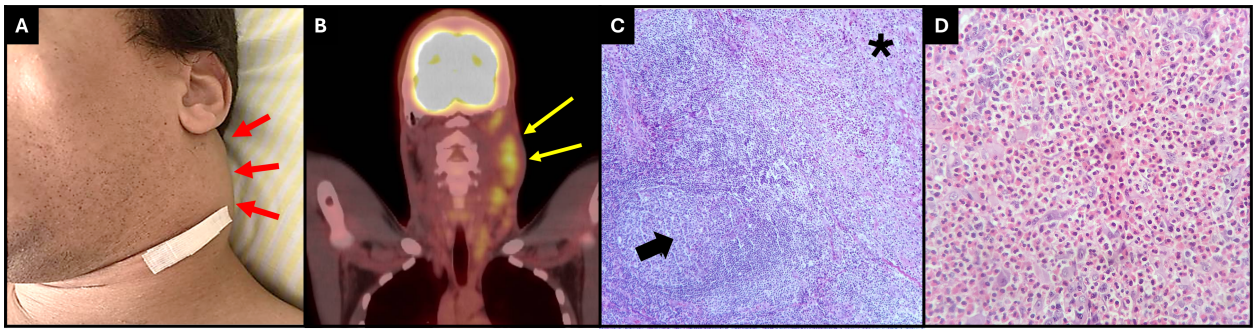



FIGURE 1
**(A)** Picture revealing the patient's left neck mass (red arrows) **(B)** PET-CT scan reveals a high uptake of tracer in left cervical lymphonodes. (yellow arrows). **(C)** Lymph node showing zone of eosinophil-rich polimormorphic infiltrate, proliferation of reactive endothelium, and interstitial collagen deposition in a nodular fashion (black asterisk). The rest of the nodal parenchyma reveals numerous reactive lymphoid follicles (black arrow) (HE, 100×). **(D)** High magnification of the eosinophil-rich polymorphic infiltrate (HE, 400×).

matrix and glomerular basement membrane (Figure 2A) thickness with spike-like projections (Figure 2B). Immunofluorescence staining was global and diffuse positive for IgA (+2/+3) in the mesangium (Figure 2C), for IgG (+2/+3) (Figure 2D) and C3 (+2/+3) in capillary walls, and for kappa and lambda (+2/+3) in capillary walls and the mesangium. Immunohistochemistry highlighted a positive global and diffuse staining for PLA2R (Figure 2E) and IgG4 (Figure 2F) on capillary walls. Electron microscopy revealed electron-dense deposits in the subepithelial and mesangial region (Figures 2G, H). These findings were consistent with the overlapping of MN grade I/II associated with IgAN (MEST-C: M:0, E:0, S:0, T:0, C:0).

The patient was treated for KD with prednisone 1 mg/kg/d with progressive dose tapering and posterior association of methotrexate 15 mg/week. A renin–angiotensin system inhibitor was prescribed for nephrotic syndrome. The cervical mass reduced drastically, and the patient reached partial nephrotic syndrome remission. After a 3-year follow-up, his laboratory findings were as follows: Cr, 0.79 mg/dL; eGFR, 118 mL/min/1.73 $m^2$; 24-h proteinuria, 1.8 g; serum albumin, 3.7 g/dL; and normal eosinophil and IgE levels.

## Discussion

KD is usually characterized by painless subcutaneous nodules in the head and neck. The diagnosis is confirmed by biopsy, and lymph node histology reveals angiolymphatic hyperplasia and intense eosinophilic infiltration. The pathogenesis of KD remains undetermined, but there is evidence of T-cell immunity dysregulation associated with allergy, parasite infections, vaccination, IgG4-related disease, and eosinophil and IgE disorders. Previous studies have shown that type 2 helper T (Th2) cytokines are elevated in patients with KD (1, 4, 8).

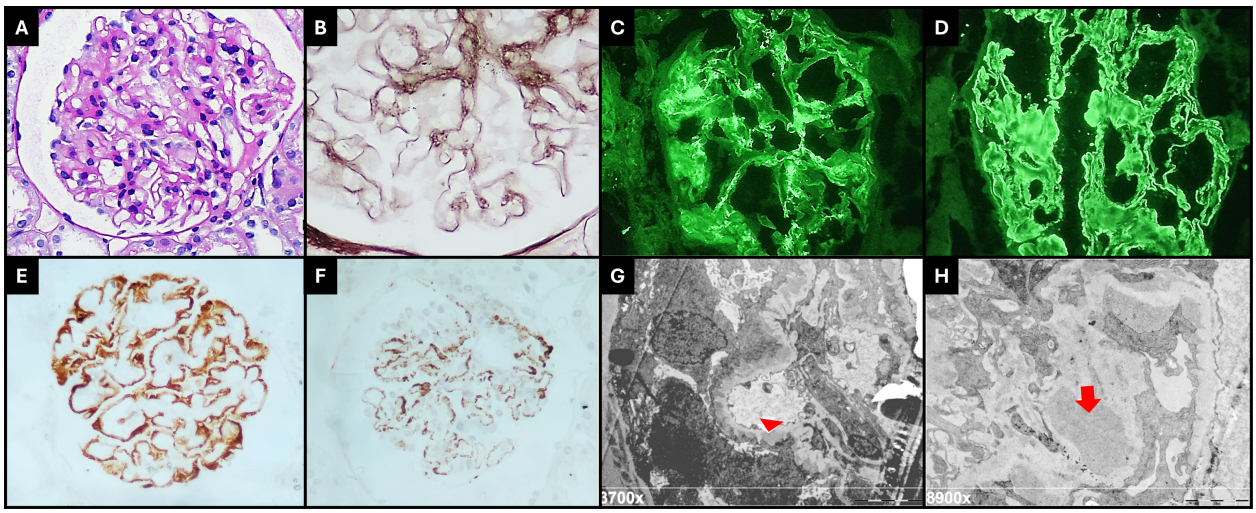



FIGURE 2
**(A)** Glomeruli show mild mesangial cell hipercellularity and matrix expansion (PAS, 400×). **(B)** The capillary walls are slightly thickened, and spikes are visible on Jones silver stain (400× + zoom). Immunofluorescence microscopy revealed diffuse granular deposits of IgA on mesangium and paramesangium [**(C)**, 400×], and IgG was diffusely positive on capillary walls, with a membranous pattern [**(D)**, 400×]. Immunohistochemistry staining for PLA2R [**(E)**, 400×] and IgG4 [**(F)**, 400×] were positive on capillary walls with a global and diffuse distribution. Electron microscopy shows subepithelial deposits (red arrow head) with surrounding basement membrane reaction, global podocyte foot process effacement [**(G)**, 3,700×], large electron-dense mesangial deposits (red arrow), and increased matrix [**(H)**, 8,900×].

Kidney involvement is well documented in association with KD, especially nephrotic syndrome. Proteinuria usually appeared simultaneously with skin lesions, but in some cases, it can appear months or even years before (9). The pathogenesis of nephropathy seems to be related to alteration in the immune system, since nephrotic syndrome usually responds to immunosuppressive therapy (10). Another hypothesis is the existence of common etiological factors for both KD and glomerular lesion. Infectious agents or toxins may alter T-cell immunoregulation or induce an IgE-mediated type I hypersensitivity. This process results in the release of cytokines, which increases the permeability of glomerular basement membrane in glomeruli, causing proteinuria (3). Renal histology is variable and includes MN, IgAN, MCD, FSGS, and MPGN, with MN being the most common presentation (3, 11, 12). Other kidney disorders include interstitial lesions, such as eosinophil infiltration, and renal insufficiency (3, 11). We performed a narrative review from literature searching for the association of glomerular diseases and KD. Table 1 summarizes clinical cases and treatment of KD associated with MN or IgAN.

The present case illustrates an overlapping of MN and IgAN in a patient with KD. The occurrence of overlapping MN and IgA is rare in the literature and, to the best of our knowledge, has not been previously reported. IgAN is the most common primary glomerular disease worldwide, with a major prevalence in young patients. On the other hand, MN is more frequent in patients at age ≥40 years and may frequently be associated with systemic diseases. The main kidney manifestation of IgAN is hematuria, while MN is characterized by proteinuria and nephrotic syndrome. The histology of IgAN is characterized by IgA immunocomplex deposits in the mesangium, and proliferative forms occur in many cases. The histology of MN presents thickening of the glomerular basement membrane due to subepithelial granular IgG deposits associated with M-type phospholipase A2 receptor antibody (anti-PLA2R) in most primary subtype cases. The patients with overlap syndrome show features of

TABLE 1 Glomerular diseases related to Kimura's disease, treatment, and therapeutic response.

| | Number of patients | Histologic diagnosis | Treatment | Response |
|---|---|---|---|---|
| Yang, 2019 (11) | 12 | MCD: 9 cases<br>IgAN: 2 cases<br>MN: 1 case | Steroids | 8/10 Complete remission |
| Okura, 2014 (13) | 1 | MN: 1 case | Steroids | Complete remission |
| Natov, 1998 (9) | 1 | IgAN: 1 case | Steroids | Complete remission |
| Chen, 2016 (12) | 29 | Mesangium proliferation: 14 cases<br>MCD: 8 cases<br>FSGS: 3 cases<br>MN: 2 cases<br>MPGN: 1 case<br>ATN: 1 case | *Tripterygium wilfordii*, Prednisone, Leflunomide, Tacrolimus, MMF, or Renin–angiotensin system blockers | 22 complete remission, 4 partial remission |
| Yi, 2022 (14) | 1 | MN: 1 case | Steroids and tacrolimus | Complete remission |
| Obata, 2010 (15) | 1 | MN: 1 case | Steroids | Complete remission |
| Vissing-Uhre, 2021 (16) | 1 | MN: 1 case | Steroids<br>Cyclosporine<br>Cyclophosphamide<br>Rituximab | Complete remission |
| Lee, 2014 (17) | 1 | MN: 1 case | Steroids<br>Cyclosporine<br>Surgical resection | Complete remission |
| Gaillard, 2017 (18) | 1 | MN: 1 case | Steroids<br>Mycophenolate | Complete remission |
| Zhang, 2019 (19) | 1 | IgAN: 1 case | Steroids<br>Cyclophosphamide | Complete remission |
| Liu, 2008 (20) | 8 | Mesangial proliferation with or without IgA deposition: 6 cases<br>MN: 2 cases | Steroids | Complete remission |
| Hu, 2014 (21) | 1 | IgAN: 1 case | Steroids | Complete remission |
| Matsuda, 1992 (22) | 2 | MN: 1 case<br>MCD: 1 case | Steroids | Complete remission |

MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; ATN, acute tubular necrosis; MMF, mycophenolate mofetil.

both diseases (23). The incidence of MN–IgAN overlap is rare, with onset during middle age and predominantly affecting male patients. It is reported that MN–IgAN presents a higher proteinuria level, including nephrotic syndrome, compared to isolated IgA, and a similar (or less) frequency of nephrotic syndrome to MN. The galactose-deficient IgA1 levels are low in the MN–IgAN overlap or similar compared to IgAN and plasma anti-PLA2R positivity, which is less frequent than in MN (23–25).

A study on histological features showed that MN–IgAN exhibits significantly increased mesangial cell proliferation, matrix expansion, and inflammatory cell infiltration, with higher proportions of arteriole hyalinosis and lesions when compared to MN alone (26). MN–IgAN treatment in the literature is variable, which is similar to MN management, including renin–angiotensin system inhibitors for mild cases and corticosteroids plus cyclophosphamide or mycophenolate and/or calcineurin inhibitors for severe cases. The prognosis of MN–IgAN seems to be significantly better than IgAN, but outcomes have similar results when compared to MN (23–25).

MN is the most common histological pattern in patients with KD and proteinuria (3). Although it could be considered as secondary MN, there are reports with anti-PLA2R subepithelial deposition in these cases, typically of idiopathic MN (13). As MN is well documented in KD, it is difficult to consider two independent diseases occurring at the same time. KD seems to be associated with immunological disorder and MN is mediated by immunocomplexes. The production of antibodies against PLA2R antigens can be part of immune system dysregulation due to KD. On the other hand, the association between IgAN and KD is extremely rare, with few cases reported in the literature (9, 11). Considering that both KD and IgAN are more common in the Asian population, it would be possible to explain the independent occurrence of these diseases. However, the response of nephrotic syndrome and IgAN related to corticosteroids raises the hypothesis of immune dysregulation secondary to KD (9).

There is no consensus about the treatment for KD with kidney involvement. Corticosteroids have been the main and initial treatment for skin lesions and nephrotic syndrome. However, other immunosuppressive therapies are being used, including cyclosporin, mycophenolate, tacrolimus, rituximab, and cyclophosphamide. Other drugs have been used for KD treatment such as methotrexate and mepolizumab (27, 28). Irradiation and surgical removal have already been used for masses and subcutaneous nodules (3). Recurrence is common and proteinuria/nephrotic syndrome can relapse before or after skin lesions (9). Our case was managed with corticosteroids, renin–angiotensin system inhibition, and methotrexate with posterior prednisone dose reduction, progressing to partial response of proteinuria and complete cervical mass regression, without recurrence.

In conclusion, although uncommon, renal involvement as a glomerular disease must be considered in patients with KD.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Ethics Committee - Hospital Alemão Oswaldo Cruz. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

## Author contributions

GB: Data curation, Writing – original draft. PN: Conceptualization, Investigation, Supervision, Writing – original draft. SM: Conceptualization, Formal analysis, Investigation, Supervision, Writing – review & editing. AA: Formal analysis, Investigation, Supervision, Writing – review & editing. LC: Investigation, Methodology, Writing – original draft. YM: Formal analysis, Methodology, Writing – original draft. VS: Investigation, Writing – review & editing. ÉO: Investigation, Writing – review & editing. LP: Investigation, Writing – review & editing. AB: Investigation, Writing – review & editing. MF: Investigation, Writing – review & editing. PC: Investigation, Supervision, Writing – review & editing. AC: Investigation, Supervision, Writing – review & editing.

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## Supplementary material

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# Effectiveness of baricitinib in acquired reactive perforating collagenosis: a case report

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**Background:** Acquired reactive perforating collagenosis (ARPC) poses a clinical challenge with an unclear pathogenesis. This disease has been frequently proven resistant to immunosuppressive treatments, significantly affecting the quality of life of patients. In this report, we highlight the efficacy of baricitinib as a viable option for maintenance therapy in ARPC.

**Case summary:** An 81-year-old woman presented to our hospital with recurrent pruritus and cup-like ulcerated lesions on her trunk and limbs persisting for 1 year. She exhibited limited response to oral antihistamines and topical steroids. Past medical history revealed a prolonged history of coronary heart disease and type 2 diabetes spanning several years to decades. Histopathological examination revealed cup-shaped depressions filled with necrotic inflammatory debris. In the dermis, a mixed inflammatory infiltrate composed of lymphocytes and histiocytes was observed. Van Gieson staining indicated the elimination of fibrous tissue extending from the dermis into the epidermis. Consequently, a diagnosis of ARPC was established. Due to the inadequate response to conventional treatments and the severe itching, we initiated baricitinib therapy for ARPC, resulting in gradual symptom improvement. Follow-up assessments showed no adverse reactions and normal laboratory findings.

**Conclusion:** The case report suggests that baricitinib might offer significant therapeutic benefits for ARPC.

KEYWORDS

**acquired reactive perforating collagenosis, baricitinib, case report, diabetes, Th2-type inflammation**

## Introduction

Acquired reactive perforating collagenosis (ARPC) is a rare dermatosis often characterized by severe pruritus. First described in 1967 by Mehregan et al. (1), it typically presents as umbilicated hyperkeratotic papules or a dome-shaped lesion with a central crater, frequently affecting the extremities. The Koebner phenomenon has been observed in some patients. In addition, it is commonly associated with diabetes and chronic kidney disease (2). Despite having been recognized for many years, the pathogenesis and etiology of ARPC remain unknown. Moreover, there is a lack of clarity in the treatment consensus for ARPC. In this case report, we present a rare instance of ARPC associated with diabetes, which was effectively managed with baricitinib therapy.

## Case report

In September 2023, an 81-year-old woman was referred to the Department of Dermatology with a 1-year history of pruritic skin lesions. These lesions initially presented as umbilicated papules, but progressed to ulcerated plaques, predominantly on the trunk and limbs (Figure 1). The Koebner phenomenon was positive as new ulcerated plaques appeared on the normal skin after scratching. She had previously been diagnosed with eczema and had received antihistamines and topical corticosteroids without experiencing improvement in the pruritus and lesions. Her medical history included coronary heart disease for several years and type 2 diabetes mellitus (T2DM) for decades. At present, her T2DM is stable due to insulin treatment.

Upon admission, a series of serological tests, including acquired immunodeficiency syndrome (AIDS) screening; rapid plasma reagin test; hepatitis B virus serological markers; hepatitis C virus antibodies; T-SPOT; liver and kidney function tests; whole blood cell test; and C-reactive protein, anti-streptolysin "O," antinuclear antibody, extractable nuclear antigen, and antineutrophil cytoplasmic antibody tests, yielded negative results, except for fasting blood glucose (7.89 mmol/L), glycosylated hemoglobin (8.5%), erythrocyte sedimentation (27 mm/h), and total IgE (682.6 kU/L).

A skin biopsy was subsequently performed, with the results of hematoxylin and eosin staining revealing a cup-shaped depression filled with necrotic inflammatory debris and a mixed inflammatory infiltrate composed of lymphocytes and histiocytes in the dermis. Elastica van Gieson staining showed fibrous tissue being ejected through the epidermis (Figure 2). In line with the clinical findings, a diagnosis of ARPC was considered. On the one hand, the patient's itching was severe [Numeric Rating Scale (NRS) score of 9]; on the other hand, dupilumab did not achieve the expected effect in our other cases. Therefore, we initiated a therapeutic challenge with oral baricitinib at 2 mg QD. At 10 days after treatment, there was no significant improvement in her eruptions and itching. However, we recommended that the patient continue with the baricitinib regimen.

Surprisingly, her eruptions and itching showed complete improvement by the eighth week. At this point, the patient decided to discontinue the baricitinib treatment. Unfortunately, her lesions and itching gradually reappeared after discontinuation, prompting her to revisit the Department of Dermatology on December 28, 2023. During the physical examination, cup-like




FIGURE 1
**(A–D)** Multiple umbilicated papules and nodules with a central keratotic crust on the patient's trunk and limbs.

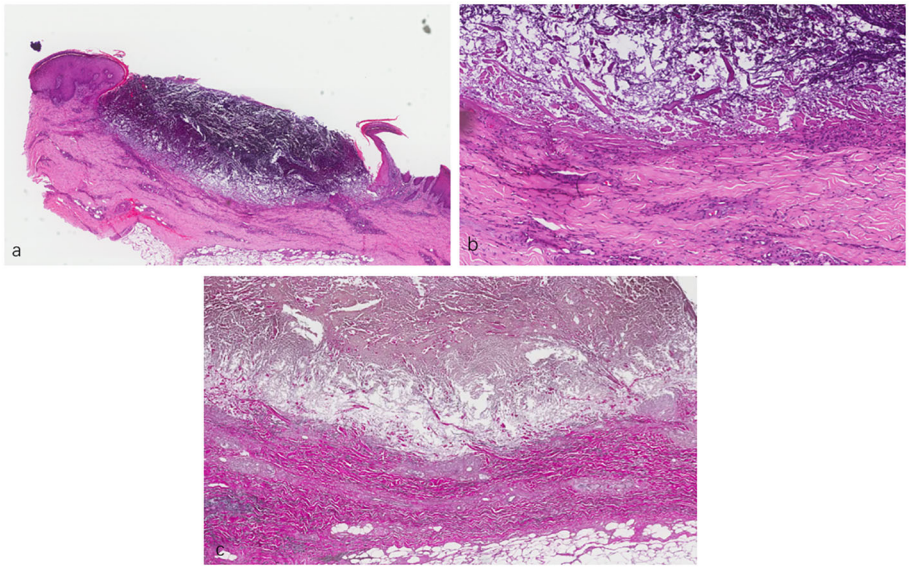



FIGURE 2
**(A, B)** Lesional skin biopsy showing a cup-shaped depression plugged with necrotic inflammatory debris. **(C)** Van Gieson staining showing elimination of fibrous tissue through the dermis into the epidermis. **(A)** ×40. **(B)** ×200. **(C)** ×400.

ulcerated lesions on her trunk and limbs were noted, along with multiple scar formations (Figure 3). The NRS score increased to 4 (Figure 4). Laboratory examinations during the second admission revealed negative results for the liver and kidney function tests, whole blood cell tests, and C-reactive protein, except for fasting blood glucose (15.54 mmol/L), glycosylated hemoglobin (10.2%), and total IgE (706.61 kU/L). With the patient's consent, we resumed maintenance therapy with baricitinib at 2 mg QD. In April 2024, we conducted our last telephone follow-up of the patient, during which her eruptions and itching showed complete improvement.

## Discussion

ARPC is most frequently documented with concomitant T2DM and chronic kidney disease, as well as other systemic pathologies including malignancies, hypothyroidism, liver disorders, neurodermatitis, AIDS, and malignant hypertension (3). The giant variant typically presents as large (>1 cm) crateriform lesions. Central adherent keratotic plugs, severe pruritus, and erythematous halos are characteristics of this condition. Our patient exhibited a typical presentation of the "giant" variant of this disease, forming lesions with the presence of crusted plaques and central keratin plugs. Lesions often develop on the trunk or the limbs, areas easily accessible by hand (4). However, the treatment of perforating dermatoses is challenging. There is currently no consensus on treatment. Several therapeutic options have been reported as first-line therapy in ARPC, including topical corticoids, local and systemic retinoids, and UVB phototherapy, with variable results. Dynamic phototherapy, amitriptyline, and doxycycline have also been the subject of some studies (5, 6).

The etiology of ARPC is unknown; however, many theories have been posited for ARPC, tying superficial trauma of the skin to the elimination of biochemically altered type IV collagen fibers from the basement membrane. An early proposed mechanism for ARPC hypothesized that microcrystal-like deposits in the dermis

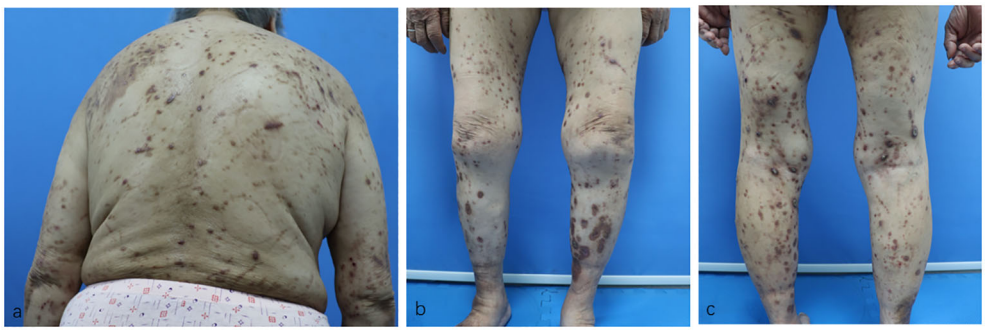



FIGURE 3
**(A–C)** Residual hyperpigmented lesions, atrophic scars, and a few superficial erosions on the patient's trunk and limbs after baricitinib treatment.

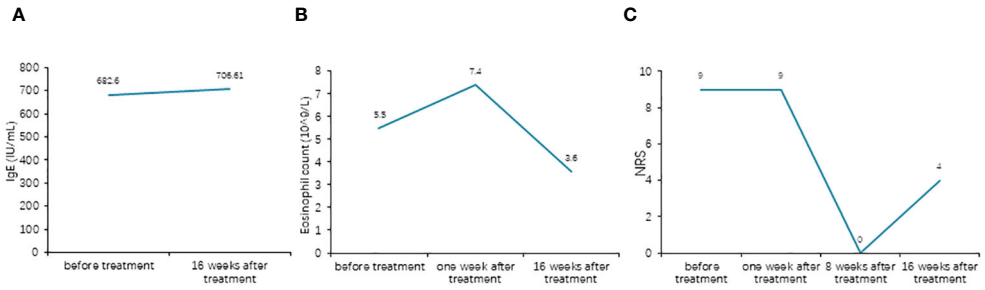



FIGURE 4
**(A)** Comparison of the total IgE levels before and after treatment. **(B)** Comparison of the eosinophil counts before and after treatment. **(C)** Comparison of the Numeric Rating Scale (NRS) scores before and after treatment.

biochemically altered the collagen fibers. Scratching then causes microtrauma, leading to the degradation of the basement membrane and the transepidermal elimination of collagen fibers (7). Furthermore, altered collagen may be induced by hypoxic states due to the vessel wall thickening associated with diabetic microvasculopathy. Allopurinol, a xanthine oxidase inhibitor, might decrease the elevated uric acid levels correlated with T2DM, reducing the crystal deposits within the dermis. However, recent studies have observed enhanced dermal infiltration of $CD3^+$ T cells with a predominance of T helper 2 (Th2) cells in ARPC, similar to atopic dermatitis (AD). In addition, the cytokines interleukin 4 (IL-4) and IL-13, which act on neurons to promote itching, were also significantly upregulated in ARPC (8). Moreover, there is now an increasing amount of clinical data that support the use of dupilumab in ARPC (8, 9). These findings suggest that Th2-type inflammation is involved in the pathogenesis of ARPC. Our patient was successfully treated with a Janus kinase (JAK) inhibitor.

JAK inhibitors are a novel class of oral immunosuppressant medications licensed for the management of AD, psoriasis, rheumatoid arthritis, and alopecia areata. By inhibiting the action of four key tyrosine kinases, i.e., JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), they affect various cell lineages, including CD8-positive T cells, and suppress the interferon gamma and interleukin pathways (10). Baricitinib is a JAK1/JAK2 inhibitor used to treat severe rheumatoid arthritis, alopecia areata, and AD (11–13). More widespread cytokine perturbation via JAK inhibition is beneficial when the disease pathogenesis is complex and not well understood (14). In our case, baricitinib was significantly more effective than the conventional treatment for ARPC. Baricitinib reduced the lesion size and improved pruritus within 4 weeks of treatment. After 8 weeks of treatment, the patient achieved clearance of skin lesions and relief from pruritus, with no adverse events (AEs).

## Conclusion

To the best of our knowledge, this case marks the inaugural utilization of baricitinib in the treatment of ARPC. This case underscores the efficacy of baricitinib for ARPC and advocates its consideration in instances of conventional treatment-resistant ARPC. While certain studies have indicated the involvement of type 2 inflammation in the pathogenesis of ARPC, further clinical and foundational research is imperative to corroborate this conclusion.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

JZ: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. YD: Resources, Writing – review & editing. YC: Data curation, Resources, Writing – review & editing. YS: Project administration, Resources, Writing – review & editing. YG: Project administration, Resources, Supervision, Validation, Writing – review & editing.

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# Dual challenge inside the womb: a case report of concomitant fetal atrio-ventricular block associated with maternal anti-SSA antibodies and fetal tachyarrhythmia diagnosed as Wolff-Parkinson-White syndrome after birth

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Fetal autoimmune atrioventricular block (AVB) is a rare but potentially life-threatening condition. It results from the passage of maternal anti-SSA/Ro or Anti SSB/La auto-antibodies into the fetal circulation, leading to inflammation and fibrosis of the AV node and often to irreversible damage. Besides AVB, these antibodies can also cause cardiomyopathies, but there is no evidence linking them to tachyarrhythmias. We present the case of a patient with significant risk factors for fetal AVB: a prior history of *hydrops fetalis*, high anti-SSA/Ro antibody levels and hypothyroidism. In this case, the use of dexamethasone and intravenous immunoglobulin may have contributed to reversing the first-degree atrioventricular block detected at 19 weeks of gestation. Additionally, at 21 weeks, the fetus developed a tachyarrhythmia that needed treatment with flecainide. Soon after the birth, the newborn underwent ECG Holter and Wolff-Parkinson-White Syndrome (WPWS) was diagnosed. To our knowledge, the coexistence of fetal AVB and WPWS has never been described.

KEYWORDS

**case report, fetal atrio-ventricular block, congenital heart block, Wolff-Parkinson-White syndrome, pregnancy, anti-SSA/Ro antibodies**

## Introduction

Fetal autoimmune AVB is amongst the manifestations collectively referred to as neonatal lupus. Fetal AVB results from the passage of maternal anti-SSA/Ro and/or anti-SSB/La autoantibodies into the fetal circulation, leading to inflammation and fibrosis of the atrioventricular node, often causing irreversible damage. Fetal AVB occurs in 2–5% of pregnancies in women with anti-SSA/Ro and/or anti-La/SSB antibodies, but the rate in subsequent gestations may be as high as 17% (1). Thyroid pathology also increases the risk of fetal AVB in mothers with anti-SSA/Ro antibodies. On the other hand, WPWS is a congenital heart condition that occurs in 0.1% of neonates (2). It is characterized by an abnormal electrical pathway between the atria and ventricles that leads to tachycardia. To the best of our knowledge, there is only one other case in the literature describing WPWS in a newborn with neonatal lupus (3). Herein, we present a unique case of coexistence of immune AVB and WPWS in the offspring of a woman with anti-SSA/Ro antibodies, underlining the diagnostic and therapeutic challenges faced throughout pregnancy.

## Case description

We present the case of a 29-year-old Caucasian female with hypothyroidism, medicated and controlled with levothyroxine 37.5 µg/day. She had a normal body mass index (20.4 kg/m$^2$) and denied toxic habits. Her family history was irrelevant. She denied previous surgeries and other physical or mental issues. She got pregnant for the first time in the beginning of 2022. This pregnancy, desired and planned, was uneventful until 21 weeks of gestation (WG), when the routine obstetric ultrasound identified a severe *hydrops fetalis*. The fetal echocardiogram revealed a third-degree AVB (atrial heart rate 140 bpm, ventricular heart rate 47 bpm). Initial laboratory results showed positive antinuclear antibodies (titer 1:1280) with strongly positive anti-SSA/SSB antibodies. At this point, the couple was informed of the poor prognosis of the situation and medical termination of pregnancy was performed at 23 WG.

At this time, the patient's concerns were tied to her desire to become a mother and the fear of the recurrence of this situation. She was subsequently referred to preconceptional counseling at our rheumatology/obstetrics multidisciplinary clinic in a tertiary hospital, that took place in July of 2022.

A comprehensive medical history revealed that the patient had been experiencing chilblains, fatigue and sporadic mechanical arthralgia over the past two years. She denied symptoms such as *sicca* syndrome, oral ulcers, alopecia, skin lesions, *Raynaud* phenomenon, fever, weight loss or any other symptoms of connective tissue disease. Physical examination yielded unremarkable findings. A more detailed laboratory work-up revealed high anti-SSA/Ro titers. Anti-dsDNA and antiphospholipid antibodies were negative. Inflammatory parameters (erythrocyte sedimentation rate and C-reactive protein), complement levels (C3 and C4 levels) and thyroid function were normal. No significant changes were detected through capillaroscopy, salivary gland ultrasound or biopsy. Echocardiogram and thoracic CT also showed no remarkable findings.

Given her intention to conceive again, preconception counseling was provided, which involved a discussion about the increased risk of AVB in the subsequent gestation (up to 17% according to international series) (1). She was advised to seek care at a high-risk pregnancy clinic, with multidisciplinary appointments and a recommendation to undergo weekly fetal echocardiograms starting at 16 WG. Additionally, she was prescribed hydroxychloroquine at a dose of 400mg/day.

Six months later, the patient became pregnant again and received care at our obstetric-rheumatology unit. She reported no symptoms. The routine first trimester ultrasound showed no abnormalities. The risk of preeclampsia, assessed by a score that includes clinical data, blood pressure, Doppler of the uterine arteries and laboratory results [pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF)], revealed a low risk. Anti-SSA/Ro titers remained high [anti-Ro52 4236 UQ CU (chemiluminescent units); anti-Ro60 >27496 UQ CU], while anti-SSB/La was slightly above the normal range (7.4 UQ; cut-off 5 UQ). As programmed, weekly fetal echocardiograms were initiated at 16 WG.

At 19 WG, the patient reported extreme fatigue, without dyspnea, thoracic pain or other symptoms. Two consecutive fetal echocardiograms revealed a prolonged mechanical PR interval (150-157 msec), suggestive of a first-degree AVB (Figure 1), with no structural or functional heart disease. Given her high-risk profile (previous *hydrops fetalis*, hypothyroidism and high levels of anti-SSA/Ro antibodies), it was decided to initiate dexamethasone 8 mg/day (together with calcium and vitamin D3 supplementation) and intravenous immunoglobulin (IVIG) at a dose of 1 g/Kg (4). The Nephrology team was consulted at this point to consider plasmapheresis if the heart block progressed to second degree. Fortunately, four days later, the first-degree fetal AVB had reversed (PR interval 116-130 msec) and anti-SSA antibody titers had decreased [anti-Ro52 1232 FLU (fluorescence units); anti-Ro60 15647 FLU]. For the first time, complement consumption was noted (C4 4 mg/dl), probably related to the IVIG therapy, as the patient dramatically improved her fatigue (5). The IVIG perfusions were maintained twice a week and dexamethasone was gradually tapered down to 4 mg/day.

At 21 WG, a fetal echocardiogram revealed short periods of paroxysmal supraventricular tachycardia (fetal heart rate 260 bpm; normal PR interval 124-129 msec) (Figure 2). The patient was initially advised with general measures, such as ensuring adequate hydration, and avoiding stimulants and anxiety-inducing situations. However, at 22 WG, a subsequent fetal echocardiogram showed that the fetus was in supraventricular tachycardia, with only small periods in sinus rhythm, and a small pericardial effusion was noted. Flecainide at a dose of 100 mg every 8 hours was introduced at this point. Despite being the safest antiarrhythmic choice regarding the risk of bradycardia, the patient and the fetus remained under close monitoring. After 3 weeks (6 perfusions) of IVIG, this therapy was discontinued, as tachyarrhythmias in children potentially triggered by this drug were reported in the literature (6, 7). Complement levels of C4 remained low throughout the IVIG therapy (from 19-21 WG) and returned to normal range in the beginning of third trimester. Dexamethasone was stopped at 28 WG, considering serial normal fetal echocardiograms. Flecainide was continued

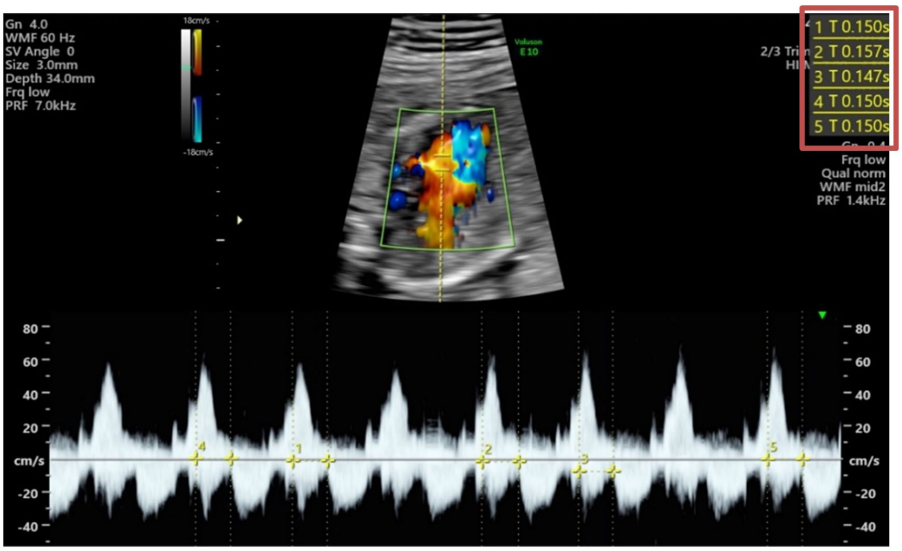



FIGURE 1
Fetal echocardiogram (2D image with color Doppler and flow Doppler) at 19 weeks of gestation, showing a prolongation of mechanical PR interval. On the top right corner of the image are presented the different measurements: 150, 157, 147, 150, 150 milliseconds.

throughout pregnancy with dose adjustments based on serum drug levels.

At 37 WG, the patient reported extreme fatigue and antibody titers increased once again (anti-Ro52 695 FLU; anti-Ro60 8498 FLU). Due to the similarity of the clinical presentation to what occurred at 19 WG, it was decided to repeat IVIG infusion before delivery. This also aimed to enhance immunomodulation in the newborn. Once again, the extreme fatigue resolved with this medication.

At 38 WG, she went into labor after spontaneous rupture of membranes and a vacuum extraction was performed. A healthy female baby weighing 2490g (percentile 5.2) was bornshowing no rash, cytopenia, hepatic dysfunction or any other manifestation of neonatal lupus. The neonate was started on propranolol due to the previous *in utero* tachyarrhythmia. At 1 month-old, a Holter monitoring revealed a short PR interval and a slurred QRS complex, consistent with WPWS (Figure 3).

In June of 2024, the baby is now 10 months old and exhibits normal psychomotor development. The child is still under antiarrhythmic treatment, which will be maintained until she reaches one year of age. Regular follow-up appointments with pediatric cardiology are ongoing, and no new episodes of rhythm alteration were identified so far. Figure 4 illustrates the timeline of events, from the beginning of pregnancy until the postpartum period.

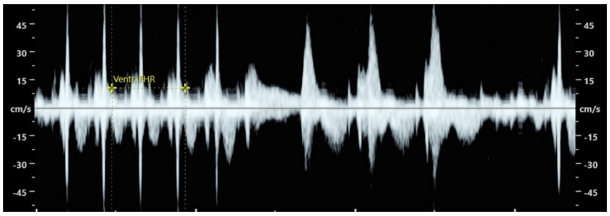



FIGURE 2
Fetal echocardiogram (Flow Doppler) at 21 weeks of gestation, revealing fetal supraventricular tachycardia alternating with sinus rhythm (a more explicit video is presented in Supplementary Material).

## Discussion

Neonatal lupus erythematosus (NLE) encompasses several fetal and child manifestations associated with maternal anti-Ro/SSA and, less frequently, anti-La/SSB auto-antibodies. This condition may affect children born to mothers with a pre-existing connective tissue disorder, primarily Sjogren's syndrome or systemic lupus erythematosus. However, most cases are documented in asymptomatic antibody carriers (8). Manifestations linked to these antibodies include rash (in approximately 10%), transient cytopenia (around 20%) and mild transaminases elevation (approximately 30%). These complications resolve spontaneously as maternal antibodies disappear from the baby´s circulation (9). The most concerning manifestation associated with these antibodies is autoimmune congenital heart block, which may result in irreversible fetal complications and death. Anti-SSA/SSB antibodies can cross the placental barrier as early as week 11 of gestation, causing damage to fetal conduction tissues through inflammation, calcification and fibrosis, ultimately blocking signal conduction at the AV node (10).

To prevent AVB, the 2020 American College of Rheumatology Guidelines for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases recommends hydroxychloroquine during pregnancy for all women with anti-SSA/Ro and/or anti-SSB/La antibodies (10). Studies have indicated that exposure to hydroxychloroquine during fetal development may reduce the recurrence of congenital heart block by more than 50% (11, 12). This protective effect is

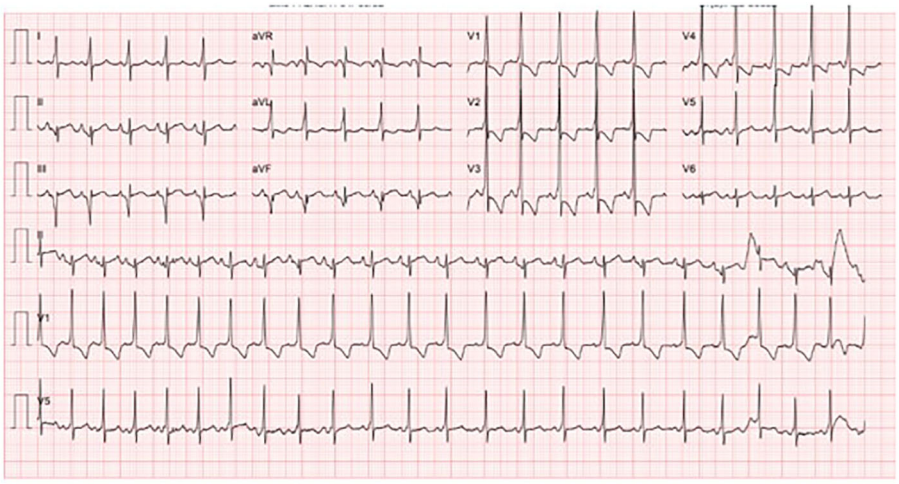



FIGURE 3
Holter of the newborn at 1 month-old. It. It is noticeable a short PR interval and a slurred QRS complex (delta wave) compatible with a Wolf-Parkinson-White Syndrome.

attributed to hydroxychloroquine's ability to inhibit Toll-like receptor 7 stimulation, preventing a cascade of events that lead to the secretion of pro-inflammatory substances and subsequent cardiac fibrosis (13, 14). Despite limited data, the safety profile of hydroxychloroquine makes it a favorable option.

Pregnant women with positive anti-SSA/Ro antibodies and a history of a previous infant with congenital heart block or other NLE manifestations should be referred for fetal heart evaluation by a pediatric cardiologist (10). Fetal cardiac conduction intervals, particularly the AV interval, should be closely monitored. American guidelines for the management of reproductive health in rheumatic diseases recommend weekly fetal echocardiography starting at weeks 16–18 and continuing up to week 26 in these high-risk patients with a previous fetal AVB (15).

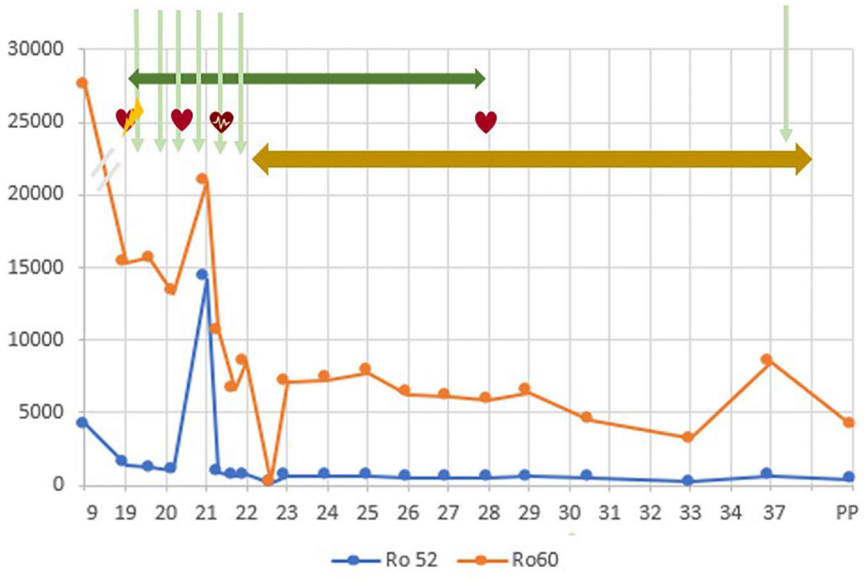



FIGURE 4
Timeline of events, from the beginning of pregnancy until the postpartum period. In X axis, the weeks of gestation. In Y axis, units of anti-SSA/Ro antibodies (at 9 WG, in UQ; from 19 WG on in FLU units). The blue line represents the Ro52 levels and the orange line represents the Ro60 levels.
PP, postpartum
First degree AV block
Sinus rhythm
Supraventricular tachycardia
Intravenous immunoglobulin
-Dexamethasone
Flecainide

Fetal AVB is considered a dynamic condition where lower-degree AVB can spontaneously revert or, on the other hand, progress to a higher-degree AVB within 24 hours (15). Treatment of fetal first-degree AVB is controversial but, recognizing that once third-degree AVB is installed the damage is irreversible, it is still recommended by international guidelines (10).

Regarding complete or third-degree AVB, no therapy has shown to improve mortality and morbidity rates associated with this condition. However, concerning incomplete AVB, the optimal pharmacological approach remains a matter of debate and an individual choice of the multidisciplinary clinic, based on local experience and available treatments. Various therapeutic interventions have been reported, mostly in single cases or small series, including corticosteroids, IVIG, plasmapheresis, beta-adrenergic agents, B cell depletion therapies, immunosuppressive agents and hydroxychloroquine (8).

According to American College of Rheumatology Guidelines for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases, if first or second-degree heart block are detected in a fetal echocardiogram, a brief course of dexamethasone is recommended (15). As a fluorinated steroid, dexamethasone can cross the placenta, exerting its effects on the developing fetus (8). Considering corticosteroids have anti-inflammatory effects, maternal administration of dexamethasone might prevent fetal AVB progression to a higher degree by mitigating the inflammatory response and potentially preventing the establishment of fibrosis of the conduction system. There may be a potential "window of opportunity" for treatment, before fibrosis is installed. Nevertheless, there are concerns about prolonged fetal exposure to corticosteroids, as it may lead to fetal growth restriction, oligohydramnios and potential long-term neurodevelopmental effects (16).

Regarding treatment with IVIG, the evidence is controversial and there is no standardized regimen. Some studies have concluded that IVIG in a dose of 400 mg/kg was ineffective as prophylactic therapy for preventing fetal AVB in high-risk pregnancies (17, 18). However, contrasting evidence suggests that IVIG may prevent the progression of immune-mediated fetal AVB by decreasing maternal serum antibody levels and potentially inhibiting the transfer of pathogenic anti-Ro/La antibodies across the placenta (19). This hypothesis is supported by murine model studies, case reports and small series using IVIG at a dose of 1mg/kg at different gestation timings (4, 20–22).

Our case report describes a patient with three significant risk factors for fetal AVB: a prior history of *hydrops fetalis*, high anti-SSA/Ro antibody levels and hypothyroidism. In a subsequent pregnancy, under hydroxychloroquine, a first degree AVB [PR interval of ≥150 msec (21)] was detected in a routine fetal echocardiogram at 19 WG, during an episode of extreme fatigue of the mother. At this point, the additional use of dexamethasone and IVIG might have contributed to revert the AVB, as there was a gradual reduction of maternal antibody titers and improvement in maternal symptoms. The unexpected turn of events occurred with the onset of fetal tachyarrhythmia starting at 21 WG, leading to the discontinuation of IVIG, due to concerns about its potential iatrogenic effect, and to the introduction of flecainide. In this case, starting antiarrhythmic therapy was a crucial but difficult decision, due to the potential of eliciting an AV block, a feared complication since the beginning of pregnancy. Only after birth the cause of the fetal tachyarrhythmia was identified: a concomitant WPWS diagnosis in the newborn detected by Holter.

As far as we are aware, there is only one other manuscript describing a case of NLE concomitant with WPWS. This Thai paper describes a case series of 6 newborns with NLE, all exhibiting cutaneous manifestations. Among them, one newborn had abnormal electrocardiogram changes compatible with WPWS, while no heart blocks were described (3).

Uncertainty remains regarding whether this occurrence of WPWS could potentially be another manifestation of the presence of anti-SSA/Ro antibodies, or merely a coincidental event with significant therapeutic implications.

This case highlights the importance of a multidisciplinary approach in evaluating and surveilling pregnant women with anti-SSA/SSB antibodies before, during, and after pregnancy. Prenatal management holds crucial clinical implications regarding fetal prognosis. Early detection of a fetal AVB can provide a "window of opportunity" to reverse the situation. Prompt intervention in an incomplete AVB can optimize fetal-maternal outcomes and mitigate the risks associated with autoimmune-mediated fetal AVB. However, there is a need for further research to establish clear protocols for the management of incomplete heart block in fetuses of mothers with positive anti-SSA/SSB antibodies. The additional diagnosis of WPWS in the newborn increased the complexity of this case.

## Patient perspective

"At 19 weeks of gestation, during my fourth fetal echocardiogram, a first-degree AV block was detected. This was my biggest fear, due to my SSA antibodies and past experience. Later in pregnancy, fetal tachyarrhythmia was also identified. The medical team (rheumatology, cardiology, and obstetrics) overseeing my care acted promptly to reverse the situation and stabilize the baby's cardiac health, always explaining all procedures and their possible side effects. I remained well throughout the treatments, diligently following all medical advice, hoping for a happy outcome. Each treatment was accompanied by some anxiety, fearing that the SSA antibody levels would rise again and affect the baby. However, with the support of my family and the medical team, I felt confident and secure that this situation represented a challenge we would overcome, and that we would have our baby in our arms. Every week was a victory for all of us. At 38 weeks, Mara decided to be born beautiful and healthy".

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

AC: Writing – original draft, Writing – review & editing. MR: Writing – review & editing. AL: Writing – review & editing. MS: Writing – review & editing. MP: Writing – review & editing. AA: Writing – review & editing. AC: Writing – review & editing. LP: Writing – review & editing. SC: Writing – review & editing.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1397103/full#supplementary-material

SUPPLEMENTARY MATERIAL

We attach a short video of the fetal echocardiogram at 21 weeks of gestation, showing fetal supraventricular tachycardia alternating with sinus rhythm.

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# Amnestic syndrome in the course of seronegative limbic encephalitis complicated by drug-resistant epilepsy: a case report

Kacper Łoś[1]*, Joanna Kulikowska[2], Monika Chorąży[2], Alina Kułakowska[2], Napoleon Waszkiewicz[1] and Beata Galińska-Skok[1]

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We present the case of a 35-year-old female patient admitted to the hospital with symptoms of rapidly increasing disturbances of consciousness and fever for 48 hours. A lumbar puncture, bacteriological and virological examinations, and initial imaging studies did not show abnormalities. Brain magnetic resonance imaging (MRI), repeated several times, showed hyperintense confluent lesions in both temporal lobes and atrophy of both hippocampi. General examination, cerebrospinal fluid culture, the panel of antineuronal antibodies, and tumor markers remained negative on subsequent repeats. Despite several laboratory and imaging studies, the etiology of the disease could not be established, infections were excluded, and no autoantibodies were found. A diagnosis of probable limbic encephalitis, amnestic syndrome resulting from organic brain damage, and drug-resistant epilepsy was made. The patient, with limbic encephalitis complicated by drug-resistant status epilepticus, was treated with cycles of immunoglobulin and subsequent plasmapheresis. She was then transferred to the Department of Psychiatry for diagnosis and treatment of intermittent psychotic disorders. During hospitalization, the patient was observed to have multiple epileptic seizures with temporal and frontal morphology, amnestic syndrome with confabulations, and periodic psychotic disorders with the occurrence of visual hallucinations. Antiepileptic treatment was escalated by including cenobamate in increasing doses. To control the mental disorders, duloxetine, tiapride, and cognitive function exercises were introduced. There was a slight improvement in memory, a cessation of confabulations, and an emergence of the patient's criticism of the symptoms presented. The psychotic symptoms subsided, and the number of epileptic seizures decreased. The described case portrays a unique co-occurrence of disease symptoms that are difficult to treat. It shows the therapeutic difficulties

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that can occur in patients with suspected autoimmune encephalitis. Furthermore, it shows the need for multispecialty care of a patient with psychotic symptoms in the course of epilepsy accompanied by amnestic syndrome.

KEYWORDS

seronegative limbic encephalitis, epilepsy, amnestic syndrome, psychotic symptoms, autoimmunology

## 1 Introduction

Encephalitis is a varied group of inflammatory diseases of the central nervous system (CNS). The estimated incidence of encephalitis in highly developed countries is approximately 5-10 per 100,000 population per year (1). The most commonly diagnosed cause of encephalitis is infectious factors, including encephalitis associated with the herpesviridae family or other viruses. The symptoms of autoimmune encephalitis (AE) can have a varied clinical phenotype, are initially uncharacteristic, and often take the form of behavioral disturbances. Autoimmune encephalitis is often a paraneoplastic syndrome, so there should be increased oncological vigilance in the diagnosis. Epileptic psychosis affects only approximately 6% of epileptic patients, the majority of whom are patients with a long history of epilepsy or who do not follow medical treatment. The most common form is postictal psychosis, which is associated with focal epilepsy, mainly temporal lobe epilepsy. It usually develops after cluster partial or generalized tonic-clonic seizures between 24 hours and a week after the onset of seizures.

Limbic encephalitis is dominated by impairments in short-term memory, attention, planning, and information processing, the severity of which depends on the duration of the disease (2). In addition to cognitive decline, there are also neuropsychiatric symptoms: aggression, apathy, or depression (3). Transient epileptic amnesia (TEA) is a syndrome characterized by short-term, recurrent memory impairment. It most often begins in middle age or older, and episodes of memory impairment may be the only or first clinical sign of temporal lobe epilepsy (TLE) (4). Moreover, bilateral damage to the temporal lobes, especially the hippocampus, often causes serious memory problems. It is worth mentioning that despite apparently similar structural damage, patients may differ in the pattern of impairment and preservation of memory functions (5).

## 2 Case description

A 35-year-old woman, with increasing disturbances of consciousness and fevers for 48 hours, was admitted to the hospital with suspected neuroinfection. The patient did not have somatic or psychiatric conditions in her medical history. Her family denied the patient's use of psychoactive substances, trips abroad, exposure to toxic agents, risky sexual contact, and tick bites. The patient had previously led a stable family life with her husband, with whom she co-parented a 4-year-old son. Until the admission to the hospital, she had been professionally active.

The patient was observed to have a rising fever of up to 41 degrees Celsius in the hours before hospitalization, which did not respond to treatment with antipyretic drugs. Furthermore, 24 hours after the onset of the fever, a disturbance of consciousness appeared, and the patient remained allopsychically disoriented, which alarmed the family, who called an ambulance. In the hospital emergency department, the patient presented with impaired consciousness (Glasgow Coma Scale; GCS 9pts), and no focal neurological symptoms were detected, including meningeal symptoms.

## 3 Diagnostic assessment

Computed tomography of the head was performed, which showed no abnormalities. A baseline panel of laboratory tests was conducted, which revealed no significant abnormalities. A lumbar puncture was performed and empirical treatment of meningitis was instituted, following local epidemiological guidelines. General examination of the cerebrospinal fluid also showed no abnormalities (cytosis 1 cell, total protein 44mg/dl). A cerebrospinal fluid culture was performed. On the first day of hospitalization, several generalized tonic-clonic epileptic seizures occurred. Benzodiazepines were used to interrupt the prolonged seizures, but despite the cessation of the seizures, the disturbances of consciousness increased. An electroencephalography (EEG) was performed, in which multiple, almost continuous delta waves and sharp-wave discharges were observed with predominance on the left side. A diagnosis of nonconvulsive status epilepticus (NSE) was made. A repeated lumbar puncture showed no abnormalities (cytosis 2; total protein 42mg/dl). Due to her worsening neurological condition (GCS 6pts), and lack of response to ongoing anticonvulsant treatment, the patient was intubated, mechanically ventilated, and she was put into a pharmacological coma, in which she remained for the next 46 days. Over several weeks, a brain MRI with gadolincontrast was performed several times (Figure 1). The result of the first examination was normal. A subsequent examination showed segmental thickening of the cerebral cortex in the left parietal-occipital lobe which was less marked in the right, without features

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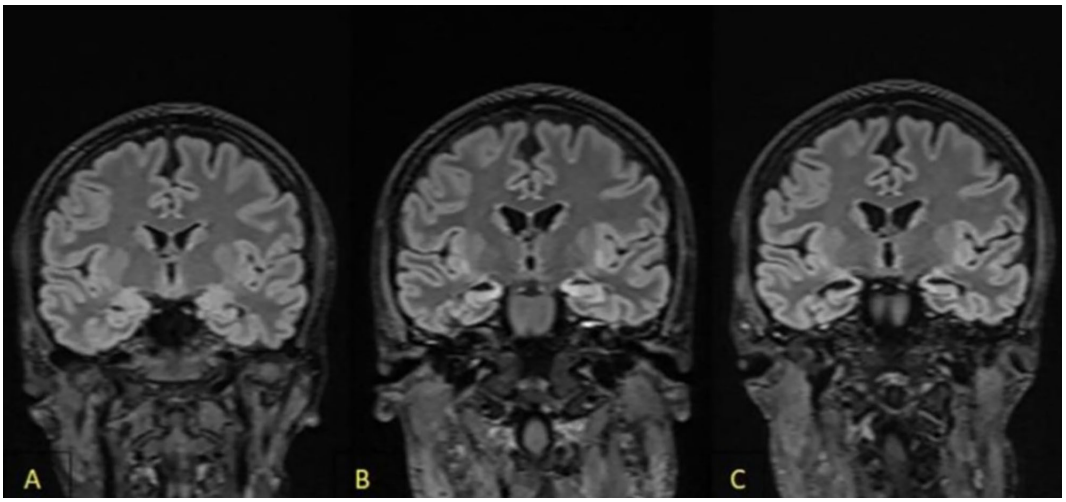



FIGURE 1
Magnetic resonance imaging (FLAIR). **(A)** On admission: hyperintensive bilateral lesions in both temporal lobes, mainly affected the hippocampi. **(B)** Hypertensive bilateral hippocampal lesions with atrophy during treatment in the intensive care unit. **(C)** Increased hippocampal atrophy during treatment in the psychiatry unit.

of diffusion restriction and contrast enhancement; the description suggested that the MR image obtained might correspond to edematous changes after an epileptic seizure. A follow-up examination performed 1 week later described regression of these lesions and, after another month, described nonspecific lesions of the temporal lobes and insulae bilaterally with marked cerebral atrophy; the image suggested inflammatory lesions. Extensive diagnostic imaging of the whole body was performed and no tumor lesions were visualized. During hospitalization, a panel of neuronal autoantibodies (including surface and onconeuronalantibodies), cerebrospinal fluid cultures, a panel of tumor markers, virology tests, a rheumatology panel, and diagnostics for porphyria were performed several times; the results remained negative (1). Positive results for 14-3-3 protein and tau protein were obtained and Creutzfeldt-Jackob disease was suspected. Diagnostics were further enhanced with RT-QuIC testing, which did not detect abnormal prion which is a specific indicator of Creutzfeldt-Jakob disease (Table 1). During ventilator therapy and pharmacological coma, paroxysmal activity persisted in the EEG in the form of rhythmic, generalized sharp wave complexes, intensified by photostimulation, against an isoelectric line background. Taking into account the overall clinical picture, autoimmune encephalitis was suspected. According to the references from Lancet Neurology from 2016, the patient met the criteria for possible autoimmune encephalitis: subacute onset of symptoms (<3 months), presence of psychiatric symptoms, epileptic seizures that cannot be explained by another cause, and MRI features suggesting encephalitis. Although the pleocytosis was not detected in repeated analyses of the cerebrospinal fluid, according to the criteria, it was not necessary to make the diagnosis. Moreover, analyzing the guidelines, it is also possible to make a diagnosis of limbic encephalitis, which includes subacute onset with memory deficit (<3 months), bilateral MRI abnormalities in the medial parts of the temporal lobe, and epileptiform activity on EEG involving the temporal regions. Considering the probable autoimmune encephalitis and after excluding other possible causes of the patient's symptoms, it was decided to treat her with plasmapheresis and immunoglobulins. The therapy included a supply of immunoglobulins at a dose of 2g/kg body weight and plasmapheresis. Several attempts were made to bring the patient out of her pharmacological coma, but numerous seizures and persistent disorders of consciousness were observed. After obtaining an image in the EEG with a burst-suppression pattern, it was decided to make another attempt to bring the patient out of her pharmacological coma. A gradual improvement in the patient's general condition was noticed so the patient was transferred to the Neurology Department. In the following days, epileptic seizures of focal morphology from the temporal and frontal lobe with impaired consciousness, sometimes undergoing secondary generalization, were observed with a frequency of 3-4 times a day. Antiepileptic therapy (valproinianacid+lamotrigine+lacosamide; VPA+LTG+LCM) was escalated. Mental disturbances in the form of periodic agitation, and anxiety with accompanying psychotic symptoms such as visual hallucinations appeared. The patient refused to take medication. Due to the inability to control the mental disorder, the patient was transferred to the Department of Psychiatry to stabilize her mental state. During the psychiatric hospitalization, the patient was observed to have amnestic syndrome with confabulations and periodic disturbances of consciousness with the occurrence of visual hallucinations. The patient in the initial period of her stay in the psychiatric ward remained auto- and allopsychically confused, she declared that she came to the hospital this morning. She did not know the reasons for her admission to the ward. She did not want to take medication due to severe anxiety and had a lack of understanding of why she should take pharmacotherapy. A similar situation occurred every day for 14 days. The patient did not know that she was married and during visits she did not recognize her life partner. Periods of anxiety occurred mainly in the morning, after waking up, while in the

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TABLE 1 Diagnostic tests performed.

| Imaging examinations | |
|---|---|
| Brain MRI | Attached |
| **Computed Tomography (CT) of the head**<br>**Angio-CT of the head and neck**<br>**CT of the chest with contrast**<br>**CT of the abdomen and pelvis with contrast,**<br>**Transvaginal ultrasound**<br>**Ultrasound of the thyroid gland**<br>**Cystoscopy**<br>**Colonoscopy**<br>**Gastroscopy**<br>**Positron emission tomography of the whole body** | **Without any clinically significant abnormalities** |
| **The most important laboratory tests** | |
| Cerebrospinal fluid (CSF)culture | Negative |
| **Bacteriological tests (RT-PCR);** H. Influenza, N. meningitidis, S. Pneumonia, Streptococcus gr. B (S. Agalactiae), L. Monosytogenes, E.coli K1, | **Negative** |
| **Serological tests**<br>IgG and IgM antibodies against Borrelia burgdorferi (CSF+ serum)<br>IgG and IgM against Toxoplasma gondii<br>Tick-borne encephalitis (IgG+IgM: CSF + serum)<br>Anti-HIV<br>Anti-HCV<br>Anti-HBs<br>VDRL (CSF+ serum) | |
| **Virological tests (RT-PCR; CSF + plasma)** CMV, EBV, HSV1,HSV2,HHV-6,HHV-7, VZV, MV, B19V, AdV, HEV, HPeV, SARS-CoV-2 | **Negative** |
| **Surface antigens (CSF + serum)** NMDA, AMPA1, AMPA2, DPPX, LGI1, CASPR2, GABAB | **Negative** |
| **Onconeuronal antibodies:**<br>**Hu, Yo, Ri, Ma2/Ta, CV2, amphiphisin, recoverin, SOX1, titin, Zic4, GAD65 i Tr (DNER)** | **Negative** |
| **Isoelectrofocusing of the cerebrospinal fluid** | **Oligoclonal stration type 4** |
| Evaluation of total complement activity, p-ANCA, c-ANCA, ANA; antibodies to phospholipids, ANA Plus profile (JO-1, PL-7, ZOB, profile anti-MPO, neuronal IgG profile; antibodies to beta2glycoprotein, cyclic citrulline, granulocytic cytoplasm, cardiolipins, myeloperoxidase, prothrombin, phospholipase receptors | **Negative** |
| **Tau protein (Erlangen Score (ES))** | **High tau protein values >362 pg/mL** |
| **14-3-3 protein** | **Positive** |
| **RT-QuIC** | **Negative** |
| Tests for porphyria<br>- Determination of excretion of porphyrin precursors (delta-aminolevulinic acid (ALA) and porphobilinogen (PBG)) and porphyrins in urine<br>- Determination of the fluorescence spectrum of porphyrins in plasma | **Negative** |

*(Continued)*

TABLE 1 Continued

| Imaging examinations | |
|---|---|
| **The most important laboratory tests** | |

evenings the psychotic disorders intensified. The patient manifested psychomotor restlessness, became verbally aggressive, and visually hallucinated. Due to the behavioral disorders, treatment with tiapridal was initiated; previous treatment with risperidone and haloperidol in the Neurology Department was ineffective. States of psychomotor agitation were managed with lorazepam 2.5 mg administered *ad hoc*. Initially, she required an injectable preparation due to severe agitation. Antidepressant and anti-anxiety treatment with a duloxetine preparation of up to 60mg/d was used. In the initial period, the patient's statements were covered with numerous confabulations, an in-depth interview suggested memory gaps going back approximately 10 years. She could not remember her child, her husband, the death of her father, or any significant life situations that had occurred over a decade. Short-term memory impairment was also observed. The memory scratch reached about 2 hours, and around lunchtime, she was unable to recall what she had eaten for breakfast. During the day, her level of tension, and anxiety decreased. Assessment of cognitive function, using the Montreal Cognitive Assessment Scale (MoCA), indicated impaired short-term (immediate) and long-term memory, a significant limitation in learning new material, serial and retrograde amnesia, impaired temporal orientation, and confabulations. Immediate recall, attentional processes, perception, procedural memory, and self-psychic orientation remained undisturbed. The patient scored 19/30 in the MoCA scale. In the further stage of hospitalization, confabulations decreased in intensity, memory concerning important life events improved, and she recognized her husband. The patient was able to recognize friends, and remembered the name of the physical therapist and the attending physician, but did not recognize the faces of people she met during hospitalization (prosopagnosia). In a follow-up MoCA test, the patient scored 1 point higher for attention. She was still confused about time. The patient understood all instructions, was able to follow them correctly, and was able to perform psychological tests. Due to the persistence of epileptic seizures several times a day, cenobamate was included in her therapy at an increasing dose as recommended, achieving a significant reduction in seizure frequency at a dose of 100 mg/d. The patient was transferred to a reference epileptology department for several days of observation, where a long-term EEG study was performed and further therapeutic recommendations were made. Long-term video-EEG showed focal lesions, with a tendency to generalize, in both hemispheres of the brain with a predominance on the left side, and the clinical picture suggested seizures with temporal and frontal morphology. As a result of a prolonged stay in the intensive care unit, the patient was a non-walker with features of polyneuropathy. Motor rehabilitation was carried out in the hospital wards. Before discharge from the hospital, the patient was able to walk independently with the help of another person (Figure 2).

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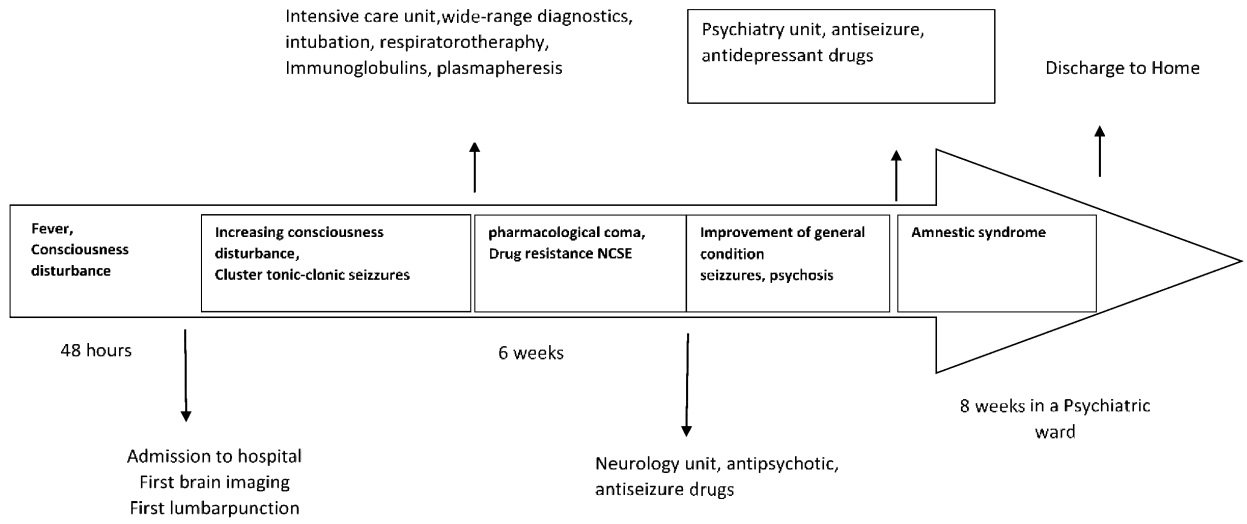



FIGURE 2
Timeline.

## 4 Discussion

The presented case describes a patient with limbic seronegative encephalitis complicated by amnestic syndrome and drug-resistant epilepsy. Despite a wide panel of studies performed, it was not possible to find an etiology of the disease. It is also very difficult to choose the appropriate pharmacological treatment for a patient with the presented symptoms, especially because of the potential side effects of drugs. In most cases of encephalitis, pleocytosis is observed in the cerebrospinal fluid; a study by J. Héberte et al. on a cohort of 95 patients with AE showed that in approximately 30% of cases, the cerebrospinal fluid remained normal (6). The most common cause of encephalitis is viral etiology; however, subsequent repeat PCR tests from both her blood and CSF for viruses have remained negative (1). The dynamics of the changes in the subsequent repeated MRI examinations indicated bilateral involvement of the temporal lobes, mainly the medial area (hippocampus) in the form of hyperintense lesions mainly visible in T2 and FLAIR sequences. Analyzing the diagnostic criteria for AE, it was found that the patient met the diagnostic criteria for probable autoimmune encephalitis: subacute onset, disturbance of consciousness, presence of short-term memory disorders, seizures that could not be explained by any other cause, and MRI signs suggestive of encephalitis. At the same time, the patient met the diagnostic criteria for limbic encephalitis: subacute onset, seizures, memory disturbances, psychiatric symptoms suggestive of temporal lobe involvement, bilateral MRI lesions involving the temporal lobe, and an epileptogenic EEG pattern involving the temporal region. It should be emphasized that although the presence of autoantibodies is not necessary for the diagnosis of limbic encephalitis, they should be actively sought because of possible clinical implications. In the described patient, autoantibodies could not be identified, but despite this, an extensive oncological screening was performed, in which no proliferative lesions were found. It is worth noting that such a group of patients should remain under the close care of physicians, who should demonstrate high oncological vigilance. The treatment included cycles of immunoglobulin and plasmapheresis, after which the patient was successfully brought out of a drug coma. Improvement of her clinical condition after immunotherapy indicated a likely ongoing autoimmune process. It should be noted that the diagnosis of autoimmune encephalitis is a difficult one to make, and even the detection of autoantibodies does not make the diagnosis certain. A study conducted by E.P. Flanagan et al. from the Mayo Clinic shows that approximately 1/3 of autoimmune encephalitis diagnoses are incorrect, and the most common reason is the incorrect interpretation of the detected autoantibodies (7). Infections are a potential factor in the immune response. Infectious agents (bacteria, viruses, parasites) can lead to the development of autoimmune disease through molecular mimicry. According to this theory, infection with a virus or bacteria with epitopes that show similarity to host antigens can lead to the activation of autoreactive lymphocytes and the development of a response to their antigens, the expression of which increases under the influence of fever, local hypoxia, and increased production of reactive oxygen species accompanying the infection. The production of autoantibodies, as a consequence, can lead to symptoms characteristic of autoimmune encephalitis. In the described patient, the agent that could have caused the infection was not found. It should be noted that there may be mutations of various pathogens that we have not yet detected, which may not show up in potential tests (8). In the course of the investigation, a positive result for the 14-3-3 protein was obtained, so the suspicion of Creutzfeldt-Jakob disease was raised; however, significant clinical improvement after treatment ruled out this disease entity. It is worth remembering that the 14-3-3 protein is a non-specific protein, has high sensitivity but low specificity, and is found in many diseases with neurodegeneration.

For many years, there have been reports about the important role of the gut microbiome and the gut-brain axis in the pathogenesis of neurological and psychiatric diseases (9). The

mechanism is not clearly understood, however, on the one hand, the initiation of neurodegeneration in the gastrointestinal tract is emphasized, and on the other hand, the activation of inflammatory processes that are reflected in autoimmune processes, for example, in animal models of multiple sclerosis (10, 11). Many authors raise the inflammatory hypothesis as a model to explain the development of psychiatric diseases such as depression. In the described patient, the gut microbiota was not studied, however, the possibility should be noted of the co-occurrence of multiple biological mechanisms and molecular pathways leading to encephalitis without an identified etiologic factor. Perhaps in the future, in similar patients, procedures in the form of intestinal microbiota transplantation or dietary interventions or not yet described procedures will be one of the elements of therapy or prevention of relapse (12).

Since the beginning of the pandemic, questions have been raised about the impact of the SARS-CoV-2 virus on the nervous system (13). On the one hand, a link to neurodegenerative processes is suggested, and on the other hand to inflammatory processes. The molecular mimicry mechanism mentioned earlier as well as hyperstimulation of the immune system may also play a role. The initiation of autoimmune processes is also discussed as a possible complication after vaccination against SARS-CoV-2, mainly with a mechanism of mRNA (14). The described patient was vaccinated with the mRNA vaccine (three doses, the last one 12 months before the onset of the disease), while current diagnostic capabilities, as well as available literature data, do not currently allow verification of such a hypothesis. This underscores the role of publishing as many clinical cases of unclear etiology as possible from different regions of the world, which perhaps in some time will enable their joint analysis and verification of certain hypotheses.

Very numerous (several times a day) epileptic seizures with temporal and frontal morphology were observed. The applied and modified pharmacotherapy (VPA+LTG+LCM) did not bring clinically significant improvement. Only the use of cenobamate (from a dose of 100mg/d), the efficacy of which has been confirmed in drug-resistant epilepsies, resulted in a reduction in seizure frequency (15). Psychiatric symptoms, including psychosis, are one of the most common and often observed symptoms in autoimmune and limbic encephalitis (60% of cases) (16). In the described patient, psychiatric symptoms in the form of psychotic symptoms with concurrent visual hallucinations appeared after several months of illness. It was noted that they were probably related to concurrent and difficult-to-control epileptic seizures of focal onset. Due to the duration of epileptic seizures in correlation with psychosis, it was not possible to diagnose post-epileptic psychosis (according to the definition of >24h) or interictal psychosis, which most often occurs in patients with a long duration of illness (>15 years) (17). The occurrence of psychosis is in a significant relationship with the frequency of epileptic seizures. The temporal morphology on peri-ictal psychosis is often difficult to distinguish from seizures with impairedconsciousness. (18). It is worth noting the damage to the patient's CNS, including the hippocampus, and her characteristics involving severe anxiety. Benzodiazepines and low-dose antipsychotics are used in the treatment of epileptic psychoses, but guidelines for the treatment of this group of patients have not been established thus far. A significant complication of most neuroleptics is the lowering of the seizure threshold, which, with the occurrence of 4-6 seizures per day in the described patient, was a particular clinical challenge. Another significant difficulty was the selection of a neuroleptic that would be effective in controlling psychotic disorders, while at the same time not causing the deterioration of cognitive functions present in a patient with amnesia. Initially, in the Neurology Department, psychotic symptoms were treated with haloperidol to 5mg/d and then with risperidone up to 4mg/d, without clinical success. After transfer to the psychiatry department, due to the ineffectiveness of previous treatment and the patient's significant risk of lowering her seizure threshold, it was decided to treat with tiapride up to 100mg/d. Tiapride is the drug that has the least effect among neuroleptics on lowering the seizure threshold (19). Cognitive impairment is also a significant side effect of neuroleptic treatment. Given the small effect of tiapride on the ability to remember new information and the small sedative effect, it was decided to prescribe this drug (20). The antidepressant and anti-anxiety drug duloxetine was included, which, in addition, by increasing the secretion of interleukin 10 (IL-10), has the potential to reduce the body's inflammatory process (21). In addition, it is an anti-anxiety drug with properties that improve cognitive function. A significant symptom resulting from organic brain damage in the described patient was amnestic syndrome. It is known that non-progressive bilateral temporal lobe damage in humans causes severe amnesia (5). In particular, they have been identified as playing a key role as amnesia has been reported in patients with bilateral lesions confined to this structure (hippocampal amnesia) (22). Typically, patients with hippocampal amnesia experience significant problems in acquiring new episodic memories, such as personally experienced autobiographical events. This atherotroic amnesia is widely credited with typifying such patients. However, much controversy remains about how to characterize the aspects of memory loss associated with bilateral hippocampal lesions (23). During the neuropsychological examination, the patient understood the questions, correctly acquired and extracted new information, and tried to perform various operations in direct memory, but there were significant difficulties in maintaining attention. She created statements appropriate to the questions asked, experienced profound disorder in remembering new information, and had retrograde amnesia with a temporal gradient. At the time of the examination, the patient was aware of the memory deficit. There were disturbances in encoding information into long-term memory. The disease picture suggested an amnesic syndrome associated with damage to the medial temporal lobes. During her hospital stay, psychoeducation was also applied, cognitive functions were exercised, and there was only a 1-point improvement in the MoCa test. The patient consolidated her memory regarding important life events, remembered the names of her husband and child, and recognized their faces. However, she was not able to remember new faces and she only learned 2 new names: those of the attending physician and the rehabilitation therapist. Prosopagnosia may be related to damage to temporal lobe structures, which was visualized in the brain MR examination of the described

patient. In the further course of treatment, the patient was cooperative and satisfied with the prospect of being discharged from the hospital and returning to her family.

The presented case describes an extremely rare co-occurrence of difficult-to-treat disease symptoms. The case draws attention to the therapeutic difficulties that can occur in patients with suspected autoimmune encephalitis and demonstrates the need for multispecialty care of patients with psychotic symptoms in the course of epilepsy accompanied by amnestic syndrome. Finally, the case demonstrates that we are still not always able to determine the etiology of the disease.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

KŁ: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – original draft. JK: Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft. MC: Data curation, Supervision, Writing – review & editing. AK: Supervision, Visualization, Writing – review & editing. NW: Resources, Supervision, Writing – review & editing. BG: Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Breaking CNS immuno-privilege: TNFα-inhibitor triggers aseptic meningitis in a patient with rheumatoid arthritis

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Blood-brain barrier dysfunction might be driven by peripheral inflammation. TNFα inhibitors (TNF-$\alpha_i$) are occasionally associated with a wide spectrum of neurological immuno-mediated disorders. However, patients with systemic autoimmune disorders, including rheumatoid arthritis (RA), might be prone to develop further organ-specific, including central nervous system (CNS), autoimmunity. Here we report the case of a patient, affected by RA and treated with etanercept, who suddenly developed focal neurological symptoms. Cerebrospinal fluid, magnetic resonance imaging (MRI), and positron emission tomography (PET)/MRI findings are reported and support the diagnosis of TNF-$\alpha_i$-associated aseptic meningitis.

KEYWORDS

**rheumatoid arteritis, etanercept, aseptic meningitis, blood-brain barrier, cerebrospinal fluid, PET-MRI**

## Introduction

Peripheral inflammation might induce blood-brain barrier (BBB) dysfunction, breaking the central nervous system (CNS) immune privilege and inducing local inflammation (1). Indeed, TNFα inhibitors (TNF-$\alpha_i$) are occasionally associated with a wide spectrum of neurological immuno-mediated disorders (2) that are commonly divided into demyelinating (3–8) and non-demyelinating (9–15). Multiple sclerosis (MS), radiologically isolated syndrome (16), transverse myelitis, and neuromyelitis optica spectrum disorder (NMOSD) are commonly included in demyelinating disorders, while neurosarcoidosis, CNS vasculitis, leptomeningitis, or meningoencephalitis define the non-demyelinating CNS events.

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Conversely, patients with systemic autoimmune disorders, including rheumatoid arthritis (RA), might be prone to develop further organ-specific, including CNS and meningeal, autoimmunity (15). Therefore, the presence of CNS involvement in a systemic autoimmune disorder treated with TNF-$\alpha_i$ constitutes a diagnostic challenge for physicians. Here we report the case of a patient, affected by RA and treated with *etanercept*, who developed aseptic meningitis.

## Case report

A 68-year-old woman was evaluated for a sudden onset transient paresis of the left lower limb lasting for 15 minutes. She reported a few similar spells before, always very brief, occasionally involving the contralateral limb. She was diagnosed with RA 2 years before, without any evidence of either peripheral nervous system (PNS) or CNS involvement. She was temporarily treated with acetylsalicylic acid for the neuroradiologic evidence of microvascular ischemic disease, which was discontinued after spontaneous ecchymosis. Ongoing disease-modifying drugs included low-dose prednisone, etanercept (28 infusions, the last 1 week before the onset of symptoms), and methotrexate. Moreover, she took alendronate for osteoporosis, venlafaxine for depression, and beta-blocker for tachycardia. Neurological examination was normal, while a brain CT scan revealed a slight disappearance of parafalcial cortical sulci bilaterally, confirmed by a high field (3T) magnetic resonance imaging (MRI) scan (Figure 1). In addition, a high field (3T) positron emission tomography (PET)/MRI confirmed the cortical hypermetabolism along the falx cerebri (Figure 1E). Altogether, brain imaging revealed an inflammation along pachy- and leptomeningeal sheets.

The etiology of this process was investigated with cerebrospinal fluid (CSF) analysis, which disclosed a moderate pleocytosis (125 cells/μL, all mononuclear cells) with a mild increase in protein concentration (54 mg/dL) and CSF/serum quotient of albumin ($Q_{ALB}$) (11.2 x$10^{-3}$, $Q_{ALB}/Q_{LIM}$: 1.31, mild BBB damage) (1). Moreover, while isoelectric focusing did not disclose any IgG oligoclonal band (IgGOB), quantitative parameters of intrathecal IgG synthesis were increased (IgG Index 1.2, nv <0.7; $IgG_{LOC}$ 21.0 mg/L). CSF microbiological

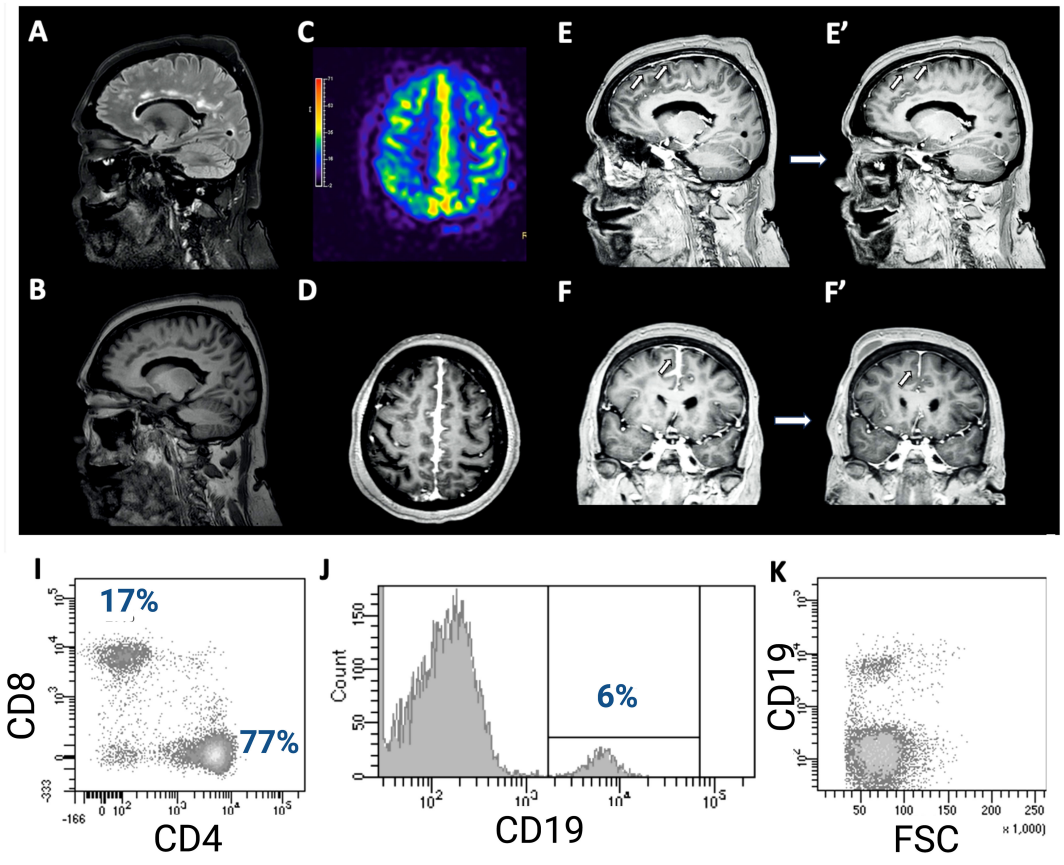



FIGURE 1
**(A)** Brain MRI showing a slight T2-FLAIR hyperintensity of the cortical gyri in the fronto-parietal area at the vertex, in the parasagittal area, with obliteration of the sulci. Comparing T1 sequences **(B)** and contrast-enhanced T1 sequences **(D–F)**, there is a noticeable pathological pachymeningeal and leptomeningeal enhancement along the profile of the cerebral falx, especially in the posterior region, further confirmed by PET/MRI **(C)**. In addition, a diffuse slight dural meningeal thickening was also reported. Follow-up brain MRI 4 weeks later shows significant improvement of the meningeal enhancement **(E', F')**. The total body PET/MRI confirmed the cortical hypermetabolism along the falx cerebri, showing also a slightly hypometabolic left parietal cortex **(E)**. Flowcytometry analysis of CSF-infiltrating cells revealed both CD4+ and CD8+ T-cells **(I)** with an increased ratio (4.5), as well as a small percentage of B cells (6%, **(J)**), with normal physical parameters **(K)**.

screening (Streptococcus agalactiae, Streptococcus pneumoniae, Cryptococcus neoformans, cytomegalovirus, enterovirus, herpes simplex virus 1, herpes simplex virus 2, herpes simplex virus 6, human parechovirus, varicella zoster virus, M. tuberculosis cDNA, E. coli K1, Haemophilus influenzae, Lysteria monocytogenes, Neisseria meningitidis) was negative, while the immunophenotype of CSF-infiltrating leucocyte revealed that CSF-infiltrating cells were all lymphocytes, namely both B (6%) and T cells (94%, 77% $CD4^+$, 17% $CD8^+$) (Supplementary Figure). No T cell had increased HLA-DR expression. Physical parameters and the lack of HLA-DR expression suggested the recruitment of inactivated B cells. Immunological screening in serum revealed an elevated rheuma-test (153 kU/L, nv <30), while C-reactive protein, angiotensin-converting enzyme (also in CSF), complement factors, and erythrocyte sedimentation rate were normal. Moreover, anti-nuclear, anti-neutrophilic cytoplasmic, anti-double-stranded DNA, anti-extractable nuclear antigen, anti-anticardiolipin, and $\beta_2$-glycoproteinI antibodies were negative, as well as neoplastic and paraneoplastic markers. Therefore, these findings were strongly consistent with an immuno-mediated CNS-restricted inflammation. Since there were neither systemic symptoms nor serological tests suggestive for RA worsening or progression, TNF-$\alpha_i$ was considered as the trigger of this picture. Therefore, said therapy was discontinued, and the patient was treated with methylprednisolone 1 g daily for 5 days, then slowly tapered with oral prednisone. The 1-month follow-up MRI showed radiological improvement with significant resolution of the abnormal meningeal enhancement. The patient did not experience any further spells in the following 6 months.

## Discussion

Our patient reported transitory neurological deficit, characterized by left limb weakness. To evaluate the ischemic etiology, brain imaging was acquired, revealing a severe and diffuse inflammatory meningeal involvement, further confirmed by standard CSF analysis (moderate pleocytosis). Although the clinical symptom could not be considered as a typical or atypical clinically isolated syndrome (17, 18), the MRI picture also disclosed white matter lesion around ventricles, which, especially in presence of an ongoing TNF-$\alpha_i$, called for a carefully exclusion of any demyelinating disorder. Since white matter lesion etiology is wide, and in presence of a putative radiologically isolated syndrome, the evaluation of their characteristic is strongly recommended to increase the specificity of criteria for MS diagnosis (19). In our case, the patient presented periventricular lesions, which were not suggestive for MS. Indeed, callosal lesions touched the top of the *corpus callosum*, not the bottom, suggesting an arteriolar pathology rather than a perivenular inflammation (20, 21). In addition, the radiological scenario was characterized by diffuse meningeal inflammation, which is not suggestive of MS. Finally, the dissemination in space criterion was not met in the absence of any cortical-juxtacortical or infratentorial or spinal cord lesion. In addition, the absence of IgGOB or any contrast-enhancing lesions did not allow us to fulfill the dissemination in time criterion. Therefore, a better explanation was more convincing (18).

CSF microbiological screening excluded an infective origin of the severe meningeal inflammation, while total body PET/MRI did not identify any malignancy, ruling out meningeal carcinomatosis.

Therefore, the inflammatory etiology seemed to be more plausible. To distinguish TNF-$\alpha_i$ aseptic meningitis from rheumatoid meningitis the evaluation of serological markers, as well as of clinical symptoms, is mandatory.

In our patient, the lack of any clinical or biochemical sign of disease worsening (i.e., the absence of systemic involvement and the normal immunological screening, except for a mild increase of rheumatoid factor), together with the absence of relevant BBB damage suggested an aseptic meningeal involvement.

Indeed, meningeal involvement as an expression of RA (rheumatoid meningitis) is a rare condition that normally presents with an increase in acute phase reactants and in anticitrullinated protein antibodies, that we did not find in this case (22–29). Notably, two case of rheumatoid meningitis were treated with etanercept (24, 26). However, a few cases of RA developed aseptic meningitis when treated with infliximab (14, 30), etanercept (31), and adalimumab (32, 33), suggesting that it is an extremely rare TNF-$\alpha_i$ -induced adverse event (15).

From a clinical point of view, the epileptic etiology of the transient symptoms was excluded, since the electroencephalography showed short sequences of slow bitemporal waves that were not consistent with either atonic seizures (high voltage slow wave) or focal negative motor seizures (involving the motor area). Ultimately, the most reliable cause of these stroke-like episodes seems to be the involvement of cortical vessel walls by the leptomeningeal inflammation. From an immunological point of view, the absence of activated B and T cells in CSF, as well as the lack of CSF-restricted IgGOB and of any parenchymal lesion, in the presence of the BBB damage (increased $Q_{ALB}$) that we observed in our patient seems to drive a bystander recruitment of lymphocytes, questioning the presence of a specific CNS-derived-antigen and suggesting a TNF-$\alpha_i$-induced innate-immunity disorder. The link between TNF-$\alpha_i$ and BBB function warrants further investigation.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

BK: Conceptualization, Data curation, Formal analysis, Writing – original draft. MF: Formal analysis, Writing – original draft,

Methodology. AM: Methodology, Writing – original draft, Conceptualization, Visualization. SC: Visualization, Writing – original draft, Data curation. FR: Visualization, Writing – original draft, Conceptualization, Methodology. PG: Conceptualization, Visualization, Writing – original draft, Validation. MP: Conceptualization, Visualization, Writing – original draft, Data curation, Formal analysis, Methodology.

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## Conflict of interest

AM received a travel grant from Novartis, Sanofi-Genzyme, and Biogen. MP received a travel grant from Novartis, Genzyme, Biogen, Teva, Almirall and Sanofi-Genzyme; he has been a consultant for Sanofi-Genzyme, Novartis., Biogen. FR serves as an advisory board member of Biogen-Idec and has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva and Bayer Schering Pharma. PG reports grants and personal fees from Novartis, grants and personal fees from Almirall, grants and personal fees from Biogen Idec, grants and personal fees from Sanofi Genzyme, grants and personal fees from Teva, grants and personal fees from Merck Serono, grants from University of Padova, grants from Italian Ministry of Public Health, grants from Veneto Region of Italy, grants from Italian Association for Multiple Sclerosis, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1432360/full#supplementary-material

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# Case report: Intralesional secukinumab injection for pediatric nail psoriasis: does it have to be a positive outcome?

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Recent studies have shown that local injection of secukinumab can achieve positive therapeutic effects when applied in the treatment of nail psoriasis. At present, there have been no other studies on the use of biological agents in the treatment of pediatric nail psoriasis. Three children were included in the study to evaluate the efficacy and safety of periungual injection and long-term injection of secukinumab in the treatment of nail psoriasis in children. It was found that local injection did not achieve a remarkable therapeutic effect. The nail lesions were improved continuously by subcutaneous injection once a month.

KEYWORDS

**intralesional injection, secukinumab, nail psoriasis, pediatric, psoriasis**

## Introduction

Nail psoriasis is a type of psoriasis with particularly serious health consequences. Up to 50% of psoriasis patients and up to 80% of psoriatic arthritis (PSA) patients experience recurring nail psoriasis (1). The incidence rate of nail changes in children with psoriasis varies from 17% to 39.2%, depending on the study (2). At present, the pathogenesis of nail psoriasis is not clear (3). Treatment of nail psoriasis includes local treatment, systemic treatment and physical therapy, but all of them have the characteristics of long cycle and uncertain curative effect. However, biologics can now provide new options for the treatment of nail psoriasis (3). In previous studies, some researchers applied secukinumab to 8 cases of adult nail psoriasis by local injection and have achieved good outcomes (4, 5). Our aim was to determine whether periungual injection of secukinumab can produce therapeutic effects equal to those of subcutaneous injection in children suffering from nail psoriasis, as well as to evaluate the therapeutic effects of long-term application.

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## Methods

The legal guardians of all three patients agreed to the use of local injection of secukinumab in the treatment of their children's nail psoriasis. The pilot therapy protocol was approved by the local ethics committee (20210302KYKTKS002) and the informed consent to use their photographs was obtained from the legal guardians of all three patients. In order to reduce pain, nitrous oxide was used in conjunction with finger nerve block before the injection. In order to establish a proper control for this study, we used the right hand of each patient as the treatment group and the left hand of each patient as the control group. Injection method: The needle was inserted from the two sides of the proximal nail fold (2mm distance) (2 points), as well as on both sides of the anterior nail plate (2 points). (Figures 1E, 2E) 30mg Secukinumab was injected into each fingernail. (Figure 1) 150mg/1mL Secukinumab was injected into the right hand each of each patient. The patients were injected once every 2 weeks for 3 months. Then the treatment was changed to subcutaneous injection, of 150 mg, once a month for 9 months. The patients were followed up for a long time, and it's been no less than two years now. Case 1: the patient was a seven-year-old female with continuous thickening and deformation of the fingernails and toenails that had been present for six months. The patient had developed erythema and scales had appeared on her scalp, Auspitz (+). The patient was eventually diagnosed with nail psoriasis and psoriasis vulgaris. Patient has no family history of psoriasis. The scalp lesions improved after the administration of adalimumab, but the condition of the child's fingernails did not improve. Adalimumab had been discontinued for 2 months prior to this treatment. The patient had nail psoriasis severity index (NAPSI) baseline scores of 40 for the right hand and 39 for the left hand prior to local injection (Figure 1).

Case 2: the patient was a four-year-old male with thickening and deformation of the fingernails and toenails that had been occurring for two years prior to admission. He had periungual erythema and scaling that had been visible for one year prior to his admission and upon further dermatological examination, multiple fingernails on both hands were found to be rough, deformed, and containing hyperkeratosis, with erythema around the left thumb nails, which also showed desquamation. Histopathological examination showed hyperkeratosis, and abscess formed by neutrophil aggregation was seen in the upper part of nail matrix. Fungal fluorescence detection was negative. The patient was eventually diagnosed with nail psoriasis and psoriasis vulgaris. Patient has no family history of psoriasis. He used to take multivitamin orally and use calcipotriol externally, but the treatment effect was not good. The NAPSI scores of the patient were determined to be 40 in both the left and right hand prior to local injection. (Figure 2).

Case 3: the patient was an eight-year-old male whose fingernails had begun to thicken and had become deformed one year prior to his admission. The toenails of the patient showed similar thickness and deformation. The patient had developed erythema with scales on his scalp approximately six months prior to his admission.




FIGURE 1
Case 1: **(A)** Baseline nail condition; **(B)** In the third month, a total of 5 local injections were completed, and the improvement rate of the two groups was similar; **(C)** In the sixth month, the patient's nails continued to improve after three times of subcutaneous injection once a month; **(D)** The therapeutic effect of patients' fingernails continued after 12 months. **(E)** injection site.

Further dermatological examination showed thickening and deformation of the fingernails, periungual erythema, and scaly erythema on the scalp and ears, Auspitz (+). Glucocorticoid ointment such as fluticasone propionate was used topically, but the effect was not good. Patient has no family history of psoriasis. The patient had NAPSI baseline scores of 37 for the right hand and 35 for the left hand prior to local injection. (Figure 3).

All three patients underwent fungal microscopy to exclude onychomycosis. After a comprehensive physical examination, eczema (atopic dermatitis), alopecia areata, lichen planus and other skin diseases were excluded.



FIGURE 2
Case 2: **(A)** Baseline nail condition; **(B)** In the third month, nail improvement after 5 local injections; **(C)** In the sixth month, after three subcutaneous injections; **(D)** The therapeutic effect of patients' fingernails continued after 12 months. **(E)** injection site.




FIGURE 3
Case 3: **(A)** Baseline nail condition; **(B)** In the third month, a total of 5 local injections were completed; **(C)** In the sixth month, the patient 's nails continued to improve after three times of subcutaneous injection once a month; **(D)** The therapeutic effect of patients' fingernails continued after 12 months. **(E)** injection site.

## Results

Among the three patients, the efficacy of the perionychium injection was assessed by comparing the NAPSI scores of the right hand (treatment) with those of the left hand (control). We analyzed the improvement rate of NAPSI score in 3 patients at 3, 6, and 12 months. (Table 1). There was no remarkable difference in the NAPSI scores between the treatment group and the control group. However, all of the patients showed improvement. Moreover, we found that psoriasis vulgaris lesions in other parts of the patient were also improved during local injection.Three months post-injection, the treatment regimen was changed to subcutaneous injection and the patients continued to improve. All three patients were treated with subcutaneous injection of secukinumab for more than 2 year and followed up. The clinical effect has been maintained.

## Discussion

The treatment of nail psoriasis can be complicated (2, 6). According to existing literature, local injection of triamcinolone acetonide or methotrexate can achieve excellent therapeutic effects (7). At present, biologic agents are a first-line treatment for moderate or severe psoriasis (8). In addition, the use of secukinumab has been extended to children aged two years and above (9). It has been reported that significant therapeutic effects can be achieved with local injection of secukinumab, when they are used in the treatment of nail psoriasis (4, 5).

TABLE 1 NAPSI score and improvement rate.

| | Age/Gender | Baseline NAPSI score | | 3rd moth (NAPSI score/ improvement rate) | | 6th moth (NAPSI score/ improvement rate) | | 12th moth (NAPSI score/ improvement rate | |
|---|---|---|---|---|---|---|---|---|---|
| | | left | right | left | right | left | right | left | right |
| Case1 | 8/female | 39 | 40 | 28 (28.2%) | 27 (32.5%) | 8 (79.4%) | 7 (82.5%) | 3 (92.3%) | 3 (94.9%) |
| Case2 | 4/male | 40 | 40 | 16 (60%) | 13 (67.5%) | 11 (72.5%) | 11 (72.5%) | 5 (87.5%) | 5 (87.5%) |
| Case3 | 8/male | 35 | 37 | 19 (45.7%) | 17 (54.1%) | 8 (77.1%) | 8 (78.4%) | 4 (88.6%) | 4 (89.2%) |

In order to observe any therapeutic effects achieved by local injection of secukinumab in children, three children were selected for secukinumab injection in the perionychium. According to the previous literature, the subcutaneous injection of Secukinumab in the treatment of nail psoriasis can achieve significant clinical efficacy at 16 weeks, and the local blood concentration of nail injection is high, so we set the time node at 12 weeks (10). After clinical observation, the symptoms of the treatment group and the control group were improved in the three patients at 3 months after local injection. In addition to intramatricial injection, our study added two periungual injection points at the front of nail, aiming to increase the periungual drug concentration in addition to the treatment of nail matrix based on the premise of patient benefit, so as to improve the treatment effect. But it didn't have the effect we expected. Local injection didn't have an advantage over control side treatment. (Table 1). The results of this study indicate that the local use of secukinumab can cause an immune system response in children suffering from nail psoriasis, leading to similar improvement rates in both the control and treatment groups. Furthermore, post-subcutaneous injection appeared to cause a continuous improvement of symptoms. Local injection around the nail itself can be painful and increase the cost of treatment, so this procedure is not ideal for children (7). The patients that were selected for this study were children with higher NAPSI scores than those employed in previous studies (5). The results were similar to those of previous studies involving the periungual injection of triamcinolone acetonide and methotrexate, in that for severe nail psoriasis, no remarkable difference was shown between local injection and subcutaneous injection of secukinumab, but both were shown to remarkablely improve nail psoriasis symptoms. This study has certain limitations, the number of cases studied is small, and this study is self-controlled, and no strict randomized double-blind randomized controlled study has been conducted.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Shandong First Medical University Affiliated Dermatology Hospital Medical Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

XW: Conceptualization, Data curation, Writing – original draft. YS: Conceptualization, Data curation, Software, Supervision, Writing – original draft. WX: Formal analysis, Validation, Writing – original draft. HL: Conceptualization, Funding acquisition, Software, Writing – original draft. GL: Data curation, Project administration, Resources, Supervision, Writing – review & editing.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1435141/full#supplementary-material

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# Case report: Recurring potassium channel complex autoimmunity-related neuropathic pain

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Voltage-gated potassium channel (VGKC) complex autoimmunity associated with nerve hyperexcitability is an uncommon clinical spectrum. It is mostly characterized by limbic encephalitis, continuous neuromyotonia, and dysautonomia. Pain, however, has rarely been reported as the first symptom. The present study describes a case of persistent neuropathic pain as the only symptom associated with a positive serum contactin-associated protein-like 2 (CASPR2) auto-antibody in a 41-year-old female patient. Her pain was completely relieved with steroids and intravenous immunoglobulin (IVIG) therapy. Nevertheless, the pain recurred 1 year later, consistent with an immunofluorescence titer of the CASPR2 antibody. Our case shows that neuropathic pain may occur as the first and only manifestation of a VGKC complex autoimmunity disorder. VGKC antibody titers might be an indication of pain severity. Steroids coupled with IVIG are effective, but relapse may still occur.

KEYWORDS

**voltage-gated potassium channel, neuropathic pain, contactin-associated protein-like 2, recurrence, antibody titer**

## Introduction

Neuronal voltage-gated potassium channel (VGKC) complex hyperexcitability may be caused by an autoimmune process, causing consequences for the central nervous system, peripheral nervous system, and autonomic nervous system. This autoimmune involvement can manifest in severe forms such as limbic encephalitis, which involves inflammation of the limbic system, and Morvan syndrome, characterized by severe insomnia and neuromyotonia.

It was initially described by Isaacs in 1961, with peripheral features in two patients such as persistent muscle twitching and spontaneous motor potential on needle electromyography (1). However, autoantibodies targeting neuronal contactin-associated protein-like 2 (CASPR2) were not discovered until 1999 (2). Historical reports (3, 4) indicate a broad clinical spectrum associated with CASPR2 antibodies, a component of VGKC complexes. Common clinical presentations include cognitive disturbances (26%), seizures (24%), and peripheral nerve hyperexcitability (21%) (3). The heterogeneity of these disorders contributes to the complexity of clinical symptoms. Notably, pain as an initial and sole symptom is exceedingly rare, complicating the diagnosis which typically requires the use of immunofluorescence for the antibody testing. As part of our report, we provide a description of the entire 3-year follow-up period, including diagnosis, treatment, and recurrence, so that a better understanding of this disease may be formed.

## Case report

A 41-year-old Asian female was admitted to our Pain Management Ward for the first time complaining of persistent pain in her lower limbs bilaterally for more than 6 months. It was characterized by persistent lancinating pain that worsened with cold temperatures. Her past medical history comprised of depression only. There was no record of carcinoma or any other hereditary disease in her family. Her pain had already been treated in multiple hospitals prior to this hospitalization. All hematological tests, including routine blood tests, C-reactive protein, erythrocyte sedimentation rate, liver function tests, kidney function, creatine kinase, and tumor markers, were normal. A magnetic resonance imaging (MRI) of the brain, a total spinal cord MRI, an ambulatory electroencephalogram (EEG) for 24 h, a cognitive functioning scale assessment, a pelvic MRI, and a muscle biopsy were also normal. Her only symptom of neuropathic pain, which lacked any corresponding positive test, combined with a history of depression led to a misdiagnosis. As a result, her pain was erroneously attributed to somatization disorder as a result of depression. Furthermore, the patient underwent several ineffective treatments, including antidepressant medication such as quetiapine fumarate or venlafaxine, and cognitive behavioral therapy.

However, her condition deteriorated. The medication she was taking for depression had no effect on her neuropathic pain symptom. During her stay in our hospital, her muscle tone, strength, reflexes, and sensation to all modalities were all normal upon neurological examination. A needle electromyography (EMG) examination of the patient's lower limbs including both distal and proximal muscles, such as the quadriceps femoris, gastrocnemius, and small foot muscles, was conducted by an experienced neurophysiologist, along with sensory and motor nerve conduction examinations. Her examinations and laboratory results were all within normal limits. Pregabalin and oxycodone hydrochloride extended-release tablets were prescribed initially. Her numerical rating scale (NRS) score (5) decreased from 8 points to 6 points, demonstrating a partial alleviation of her neuropathic pain. Coincidentally, during one of our regular morning rounds, we noticed brief muscle twitching in both of her legs, lasting only a few seconds. Considering her neuropathic pain and twitching movement, we performed a lumbar puncture. The cerebrospinal fluid (CSF) was clear, with a protein concentration of 530 mg/L and a chloride concentration of 118 mg/L. Her other CSF examinations, including biochemical tests, immunoglobulin G tests, and cytological tests were normal. Additionally, serum and CSF were tested for antibodies against CASPR2 and leucine-rich glioma-inactivated protein 1 (LGI1). Only CASPR2 antibodies were positive in serum (antibody titer 1:100, Figure 1A).

Following this, she received 5 days of intravenous immunoglobulin (IVIG) therapy ($0.4 mg \cdot kg^{-1} \cdot d^{-1}$) (6, 7). However, there was not much improvement in her condition. Consequently, $500 mg \cdot d^{-1}$ methylprednisolone (7) was added sequentially to the IVIG therapy. The combination regimen resulted in better clinical relief of the intractable neuropathic pain prior to discharge, with her NRS score decreasing to 1 point. Similarly, her CASPR2 antibody levels also decreased in serum (Figure 1B). Prior to her discharge, a positron emission tomography-computed tomography (PET-CT) scan was performed to exclude the possibility of tumors.

She was followed up with on a regular basis. On medical advice, she gradually reduced her steroid use. Over a span of 6 months, she had completely recovered and was not on any treatment. Unfortunately, 1 year after her discharge, she complained of recurrent neuropathic pain. Approximately 20 days after the recurrence of her pain, she was referred to our hospital again with an NRS score of approximately 5 points. Based on the first result, we only tested for CASPR2 antibodies in serum. CASPR2 antibodies were again detected in serum (antibody titer 1:10, Figure 1C). Similar to her first hospitalization, she was treated symptomatically with pregabalin and oxycodone hydrochloride extended-release tablets. However, this did not successfully alleviate her pain. Consequently, a combination of IVIG and a high dose of methylprednisolone was administered as part of immune therapy. This relieved her pain, evidenced by an NRS score of 1 point. Moreover, a routine chest computed tomography scan was performed during her second hospitalization, which ultimately revealed lung carcinoma. Subsequently, she underwent surgical removal of the lung tumor as part of her cancer treatment. As of now, 2 years after her second discharge, the symptoms have not recurred.

## Discussion

VGKCs are widely present in the neuronal membranes of the central and peripheral nervous systems and are involved in determining the resting potential of cell membranes, controlling excitation thresholds, regulating action potential waveforms and frequency, and repolarizing depolarized membranes (6, 8). In humans, there are at least eight members of this family, which range from Kv 1.1 to Kv 1.8 (9). LGI1 and CASPR2 are two defined target antigens associated with Kv 1 (10). Between them, CASPR2 is more related to pain (30%-60%) (11) and low long-term quality of life (12). The incidence of potassium channel complex autoimmunity diseases is low, particularly when neuropathic pain

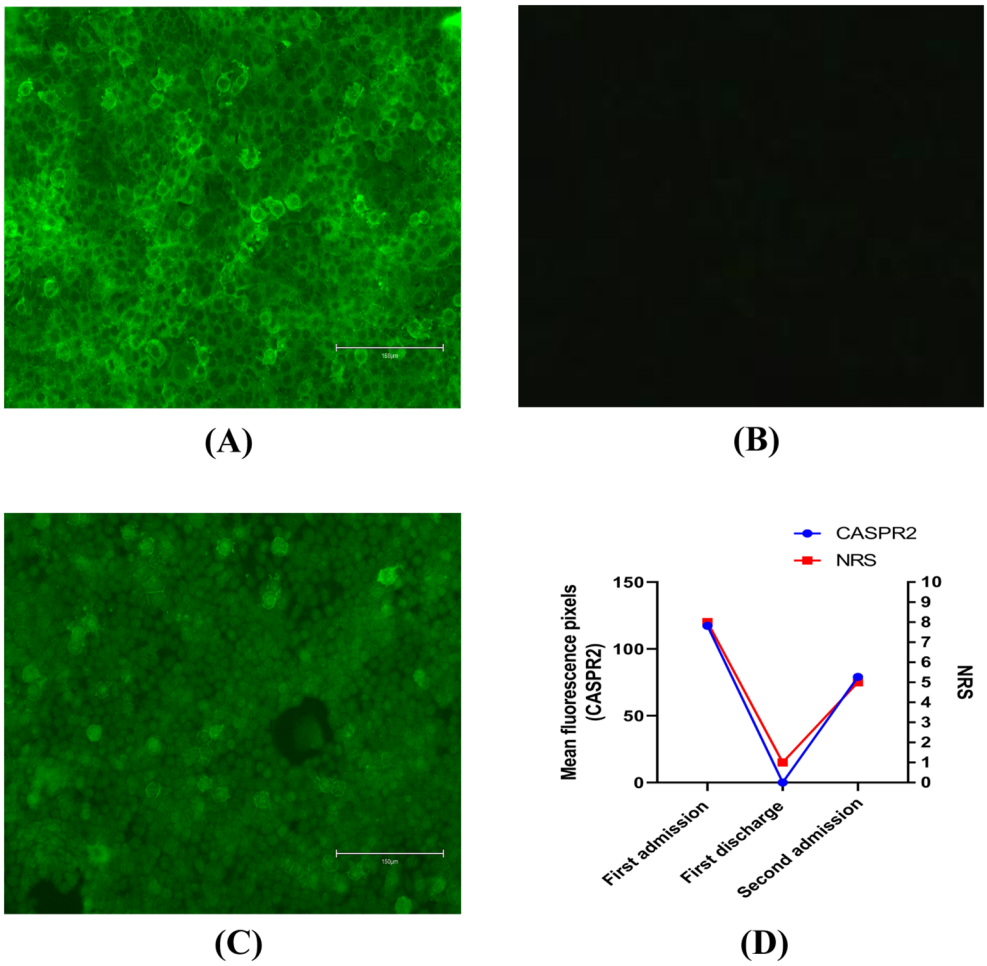



FIGURE 1
**(A)** CASPR2 antibodies were assessed by immunofluorescence in serum on first admission. Bar: 150μm. **(B)** CASPR2 antibodies were assessed by immunofluorescence in serum at first discharge. Bar: 150μm. **(C)** CASPR2 antibodies were assessed by immunofluorescence in serum on second admission. Bar: 150μm. **(D)** Changes in antibody titers of CASPR2 and numerical rating scale. All the titers were end-point titrations. Further dilutions were also performed. However, antigen-antibody reactions could also be identified by immunofluorescence after further dilutions. CASPR2, contactin-associated protein-like 2; NRS, numerical rating scale.

is the first and only symptom. The fact that we have a complete consultation and follow-up process, including the recurrence and re-admission in our case, makes this report valuable.

The clinical spectrum of CASPR2 antibodies is broad. The complexity and variability in the symptoms caused by CASPR2 antibodies often lead to diagnostic challenges, as evidenced in this case where neuropathic pain in the lower limbs was the primary complaint and all routine tests returned negative, including needle electromyography, sensory and motor nerve conduction studies, and PET-CT scans. However, we briefly observed suspicious muscle twitching in both lower limbs on one occasion for a few seconds. As a result, we suspected that our patient had a potassium channel complex autoimmunity-related disease with pain as its first and only manifestation, as a few subtle manifestations were not evident. Our report serves as a reminder that potassium channel complex autoimmunity-related disease might be one of the reasons for unknown pain. It is often a missed diagnosis or is misdiagnosed as fibromyalgia (6%) or psychogenic causes (13%) (10).

As far as treatment is concerned, pain relief should be prioritized over immune therapy (6). Carbamazepine and phenytoin have been shown to be effective as symptomatic therapy (13). Additionally, pregabalin and gabapentin are equally beneficial (14, 15). Nevertheless, nearly 70% of patients with pain require multiple medications, of which 30% require narcotics. In our case, pregabalin and extended-release oxycodone hydrochloride tablets were combined. Considering the side effects of carbamazepine, such as leukopenia, toxic epidermal necrolysis, and Stevens–Johnson syndrome, carbamazepine was not our first choice. However, immune therapy is often necessary and effective. The available options included plasma exchange, IVIG, steroids, and oral immunosuppression. We prescribed IVIG as the first immune therapy for our patient. However, as demonstrated by previous studies (16), it was not immediately effective on its own. Consequently, we added a high dose of methylprednisolone sequentially as part of a combination therapy. Our experiences were consistent with those reported in previous studies (6). We recommend the use of IVIG as an alternative therapy for potassium channel

complex autoimmunity disorders, although oral steroids can be administered concurrently or sequentially.

Regarding prognosis, the literature has reported a 25% relapse rate, some of which recurred up to 7 years after the first episode (3). Relapse was defined as a recurrence of symptoms after a complete or partial recovery, with sustained improvement for at least 2 months. According to previous studies, delayed diagnosis, inadequate initial treatment, and poor response to immunotherapy were associated with increased morbidity (17). In our case, the relapse had the same manifestations as the first episode and responded well to the same therapy, but it is also important to remember that CASRP2 antibodies may affect different parts of the nervous system compared to the initial episode. CASPR2-IgG was significantly associated with the occurrence of pain (4). Moreover, our case supports the use of CASRP2 antibody titer as a disease monitor, especially for pain severity. It also correlated with the patient's NRS scores (Figure 1D). CASPR2 is a synaptic protein involved in both synapse development and maintenance. Dawes et al. (18) demonstrated Caspr2-IgG-induced mechanical pain-related hypersensitivity in mice and confirmed its pathogenicity in driving pain-related behavior, which is related to increased DRG soma excitability due to impaired Kv 1 channel function. They also showed that the CASPR2 antibody drove primary afferent excitability and pain (18), which was confirmed in our case.

Regarding comorbidity, potassium channel complex autoimmunity-related disease may be a manifestation of a paraneoplastic state by cross-reaction (4). However, the finding that patients with tumors had a similar progressive disease course as those without tumors was controversial (2). We highly recommend excluding malignancy, and PET-CT imaging should be conducted when it is highly suspected. Previous studies have reported that occult malignancies should be followed for a period of 5 years (19). In our case, no evidence of malignancy was apparent on PET-CT at first. Nevertheless, a chest CT scan during her second episode ultimately revealed lung carcinoma. Even in suspected paraneoplastic cases such as this, peripheral neuropathic pain can also be a sign of potassium channel complex autoimmunity-related disease.

Our case report provides a description of the complete 3-year follow-up period of one case of recurring potassium channel complex autoimmunity-related neuropathic pain. It is often erroneously attributed to somatization disorder as neuropathic pain might be the first and only manifestation. In addition, the antibody titers might also be an indication of pain severity. We found a correlation between CASPR2 antibody fluorescence intensity and NRS score. There are also several limitations. First, it would have been better to perform a skin biopsy during hospitalization as she had already had a muscle biopsy. Second, CSF was not tested for antibodies on her second admission. Only serum was tested due to the result on her first admission.

## Conclusion

Herein, we describe a case with recurring neuropathic pain as the first and only manifestation of a potassium channel complex autoimmunity-related disease. The heterogeneity of the disease's clinical presentation might lead to a misdiagnosis. Furthermore, this case also emphasizes that the antibody titer of CASRP2 could be a monitor of pain severity and an indicator of a paraneoplastic state.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by The First Affiliated Hospital of Nanjing Medical University's Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

Y-QZ: Writing – original draft. X-QZ: Writing – original draft. MY: Writing – original draft. SH: Data curation, Writing – original draft. Z-YW: Data curation, Writing – original draft. J-JY: Writing – review & editing. Y-BP: Writing – review & editing. X-KZ: Writing – review & editing.

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# Hemophagocytic lymphohistiocytosis caused by multiple infections during primary chemotherapy for pediatric acute lymphoblastic leukemia: a case report

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory disorder that occurs as a consequence of immune dysregulation. HLH can be primary (familial or non-familial) or secondary to infection, autoimmune disease or malignancy. Malignancy-associated HLH is often accompanied by hematologic and lymphoid neoplasms. This report describes the case of a 3-year-old girl with an initial diagnosis of acute lymphoblastic leukemia who subsequently developed HLH during primary chemotherapy. She was admitted with a pulmonary infection, and initial blood tests showed thrombocytopenia and anemia. Whole-exome sequencing of gene and whole transcriptome RNA sequencing data indicated mutations of *UNC13D*. The hospital course was complicated by multiple infections, altered mental status and acute respiratory distress syndrome. HLH secondary to multiple infections that achieved remission following targeted therapy with ruxolitinib, in conjunction with corticosteroids and other complementary treatments. This report provides a synopsis of the diagnostic and treatment procedures implemented in this case.

KEYWORDS

**hemophagocytic lymphohistiocytosis, pediatric acute lymphoblastic leukemia, multiple infections, *UNC13D*, ruxolitinib**

# 1 Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory disorder that is caused by immune dysregulation. HLH is diagnosed using the standard molecular or clinicopathologic criteria proposed by Henter et al. in 2004 (Supplementary Table 1), whereby five out of eight points need to be met (1). HLH may be primary (familial or non-familial) or secondary. Primary HLH is often observed in childhood in association with a number of genetically heterogeneous disorders and is typically triggered by common infections. Secondary HLH is typically linked to an infection, malignancy, or autoimmune disease, without any explicit genetic predisposition toward HLH. In instances where HLH or a syndrome mimicking HLH transpires in the context of a rheumatologic or autoinflammatory disease, it is frequently termed as macrophage activation syndrome (MAS) (2). Therein, malignancy-associated HLH may be triggered by malignancy or by chemotherapy and is typically associated with lymphoid neoplasms, leukemias and occasionally with solid tumors. In chemotherapy-associated HLH, the initiating triggers include direct cytotoxic effects, secondary infection, or the hyperinflammatory state caused by the treatment (3).

The patient described in this report was a 3-year-old girl who was diagnosed initially with acute lymphoblastic leukemia and subsequently developed HLH following primary chemotherapy. The condition of HLH demonstrated improvement following a targeted treatment with ruxolitinib, in conjunction with corticosteroids, several broad-spectrum antimicrobials, tracheal intubation, ventilator-assisted ventilation, and immunoglobulin therapy. This report summarizes the diagnostic process and treatments used in this case.

# 2 Case presentation

The patient was a 3-year-old girl who was hospitalized with fever and cough. Routine blood tests at a local clinic suggested leukocytosis, moderate anemia, and thrombocytopenia. She was then transferred to our hospital, where a bone marrow puncture was performed. The initial bone marrow examination shows that both primary lymphocytes and naive lymphocytes are at 52%, and the minimal residual disease (MRD) shows that abnormal naive B lymphocytes accounted for 61.9% (Supplementary Table 2).The results of initial bone marrow examination,MRD and immunophenotyping studies indicated acute B-cell lymphoblastic leukemia (common B-ALL).

The VDLD (vincristine 1.5mg/m$^2$, daunorubicin 30mg/m$^2$, L-asparaginase 2500U/m$^2$, and dexamethasone 6mg/m$^2$) chemotherapy regimen was started on day 8 after admission. Two administrations of intrathecal injection, comprising cytarabine (30mg), methotrexate (12mg), and dexamethasone (5mg), were executed as a prophylactic measure against central leukemia. The patient experienced recurrent fever during the hospital course. Her body temperature fluctuated between 37°C and 39°C but gradually increased, peaking at 39.5°C. The cerebrospinal fluid cultures and cytology were negative. Blood culture results suggested *C. tropicalis* infection. Blood metagenomic next-generation sequencing revealed 104 specific reads of human herpes virus type 5 and 239 specific reads of *C. tropicalis*. High-throughput sequencing of bronchoscopic alveolar lavage fluid also identified *C. tropicalis*, *P. jirovecii*, and human metapneumovirus (Table 1). The third vincristine and daunorubicin chemotherapy were discontinued in view of severe infections, and dexamethasone treatment continued. The fever persisted despite treatment with broad-spectrum antibacterial including vancomycin, meropenem, imipenem, tigecycline and oral trimethoprim/sulfamethoxazole (TMP/SMX), antifungal (caspofungin and fluconazole), and antiviral (ganciclovir) therapy.

One month after admission, she developed tachypnea of sudden onset with tachycardia, altered mental status, and cyanosis with an increase in temperature to 40°C. Physical examination revealed hepatosplenomegaly (liver 3 cm, spleen 1.5 cm below the costal margin). Blood tests revealed severe trilineage cytopenia with neutropenia. Soluble CD25 and ferritin levels were increased (sCD25, 10,065 U/L; ferritin, 4070 μg/L). Flow cytometry showed decreased natural killer (NK) cell activity (Table 2). Bone marrow biopsy revealed histiocytes with hemophagocytic activity (Figure 1A). Whole-exome gene sequencing data for the patient and her father indicated mutations of *UNC13D* (Figure 1B). Specifically as follows: the patient shows a mutation at position 370, where the normal base sequence is altered. The shaded area indicates the mutation position, which likely represents a heterozygous mutation (Figure 1Bi). The father's sequencing also shows the same variant in the same position (highlighted area), suggesting that he may be a carrier of this mutation (Figure 1Bii). The mother's sequencing does not appear to show the mutation at this position, implying that she does not carry this particular mutation in the *UNC13D* gene (Figure 1Biii). The site information regarding the *UNC13D* gene mutation is as follows:1) The *UNC13D* gene mutation site information from her father as shown in Supplementary Table 3: UNC13D: NM_199242.2: c.1201_1202delinsAA (p.Ser401Asn); 2) The site information of UNC13D gene mutation of the patient included the result of whole-exome sequencing indicated that 'c.1201_1202delinsAA p.Ser401Asn' in Supplementary Table 4.

Besides, whole transcriptome RNA sequencing was also performed on the patient. The result of whole transcriptome

TABLE 1 Summary of the pathogene findings in our patient.

| Pathogene | Sample | Method | The number of sequence |
|---|---|---|---|
| Human herpesvirus 5 | Blood | NGS | 104 |
| Candida tropicalis | Blood | NGS | 239 |
| | BALF | NGS | 37804 |
| Pneumocystis jirovecii | BALF | NGS | 947 |
| Human metapneumovirus | BALF | NGS | 12415 |

NGS, next-generation sequencing; BALF, bronchoscopic alveolar lavage fluid.

TABLE 2 Summary of the laboratory findings in the patient.

| | Unit | Normal Range | Before HLH | HLH | HLH-treated |
|---|---|---|---|---|---|
| Ferritin | ng/ml | 13-150 | 933 | 4070 | 2090 |
| Triglycerides | mmol/L | 0.56-1.7 | 1.01 | 3.69 | 1.66 |
| Fibrinogen | g/L | 2-4 | 1.49 | 0.36 | 1.66 |
| NK cell activity | % | ≥15.11 | NA | 15.20 | 14.92 |
| Souble CD25 | U/ml | 223-710 | NA | 10065 | 1121 |
| Hemoglobin | g/L | ≥110 | 77 | 49 | 106 |
| Platelets | *10^9/L | 100-300 | 8 | 1 | 207 |
| WBC | *10^9/L | 4.4-11.9 | 0.91 | 0.16 | 5.77 |
| Neutrophils | *10^9/L | 1.2-7 | 0.18 | 0.00 | 3.03 |
| IL-6 | pg/ml | ≤5.04 | NA | 219.89 | 2.61 |
| IL-10 | pg/ml | ≤5.00 | NA | 13.84 | 4.24 |
| G test | pg/ml | NA | >600 | 331 | 178.55 |

HLH, Hemophagocytic lymphohistiocytosis; NK, natural killer; WBC, white blood cell; IL, Interleukin; NA, No available; G test, 1,3-β-D-glucan test.

RNA sequencing indicated that 'NM_199242.3:exon14:c.1201_1202 delinsAA:p.S401N' in Supplementary Table 5. Next, we also detected expression of HLH-related markers such as CD107a, the degranulation function of which was decreased in NK cells (ΔCD107a 9%, normal >10%) and normal in cytotoxic T lymphocytes (ΔMFI 4.8%, normal ≥2.8%). CT scan showed exudative lesions in both lungs and brain magnetic resonance showed white matter lesions (Figure 1C). The patient was diagnosed with HLH based on the HLH-2004 diagnostic criteria. Endotracheal intubation and mechanical ventilation were initiated to manage respiratory distress. Intravenous methylprednisolone (initial 2mg/kg, peak at 10 mg/kg), immunoglobulin, intravenous TMP/SMX (0.18g per dose, twice a day) and ruxolitinib (5mg, every12h) were administered daily for 8 days. During this period, dexamethasone was tapered, and discontinuated in 3 days. Her fever, altered mental status and dyspnea improved, and her HLH biomarker levels gradually decreased (sCD25 to 1121 U/L; ferritin to 2090 μg/L) (Table 2).

When the patient's condition had stabilized, she received the third intrathecal injection and bridging chemotherapy (blinatumomab for 28 days) for her B-ALL and the follow-up bone marrow examination shows that both primary lymphocytes and naive lymphocytes are at 0%, and the follow-up MRD is negative, indicating that the patient has achieved complete remission (CR) (Supplementary Table 2). She eventually improved and remained stable. The timeline in Figure 2 includes key events throughout the disease course of the patient.

## 3 Discussion

HLH is a syndrome describing patients with severe systemic hyper-inflammation, caused by immune dysregulation with abnormal or impaired function of NK cells and cytotoxic T lymphocytes and characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in the bone marrow, liver, and lymph nodes. Critical HLH patients can also develop rash, hepatitis, disseminated intravascular coagulation, acute liver failure, central nervous system (CNS) involvement, multiorgan failure and death. The high mortality rate makes prompt recognition and treatment of this hyperinflammatory syndrome essential (2).

Survival rates of 56% following the acute phase and 36% at 5 years have been reported for pediatric patients with HLH (4). Infection, malignancy (particularly lymphoma), autoimmune disease, and genetic defects are known to be common etiologies of pediatric HLH (5). According to the latest consensus recommendations, HLH associated with malignancy can manifest initially as a consequence of the malignant disease, referred to as malignancy-triggered HLH, or can occur in the context of myelosuppression induced by chemotherapy, known as chemotherapy-associated HLH. Malignancy-triggered HLH occurs most frequently in patients with T-cell or NK-cell lymphoma or leukemia, diffuse large B-cell lymphoma, or Hodgkin lymphoma (6). Reports on B-ALL-related HLH are rare. Martinez-Romera et al. reported two cases of HLH that developed during the maintenance phase of chemotherapy for ALL (7). In 2008, O'Brien et al. reported nine cases of B-ALL-associated HLH, four of which were fatal (8). Our report describes a rare case of B-ALL-associated HLH during primary chemotherapy. The patient achieved CR in HLH following treatment with ruxolitinib and methylprednisolone.

Owing to a paucity of clinical trials, the recommended management for HLH includes steroids (dexamethasone), immunosuppression (e.g., etoposide or ciclosporin), and intrathecal therapy (e.g., methotrexate or steroids). Rituximab might be beneficial for Epstein–Barr virus-related HLH. Additional therapies including alemtuzumab, anti-thymocyte globulin, interferon-gamma blockers, and salvage therapy are also used to treat HLH (9). Treatment varies according to type of HLH. For primary HLH, the HLH-94 and HLH-2004 protocols are mostly

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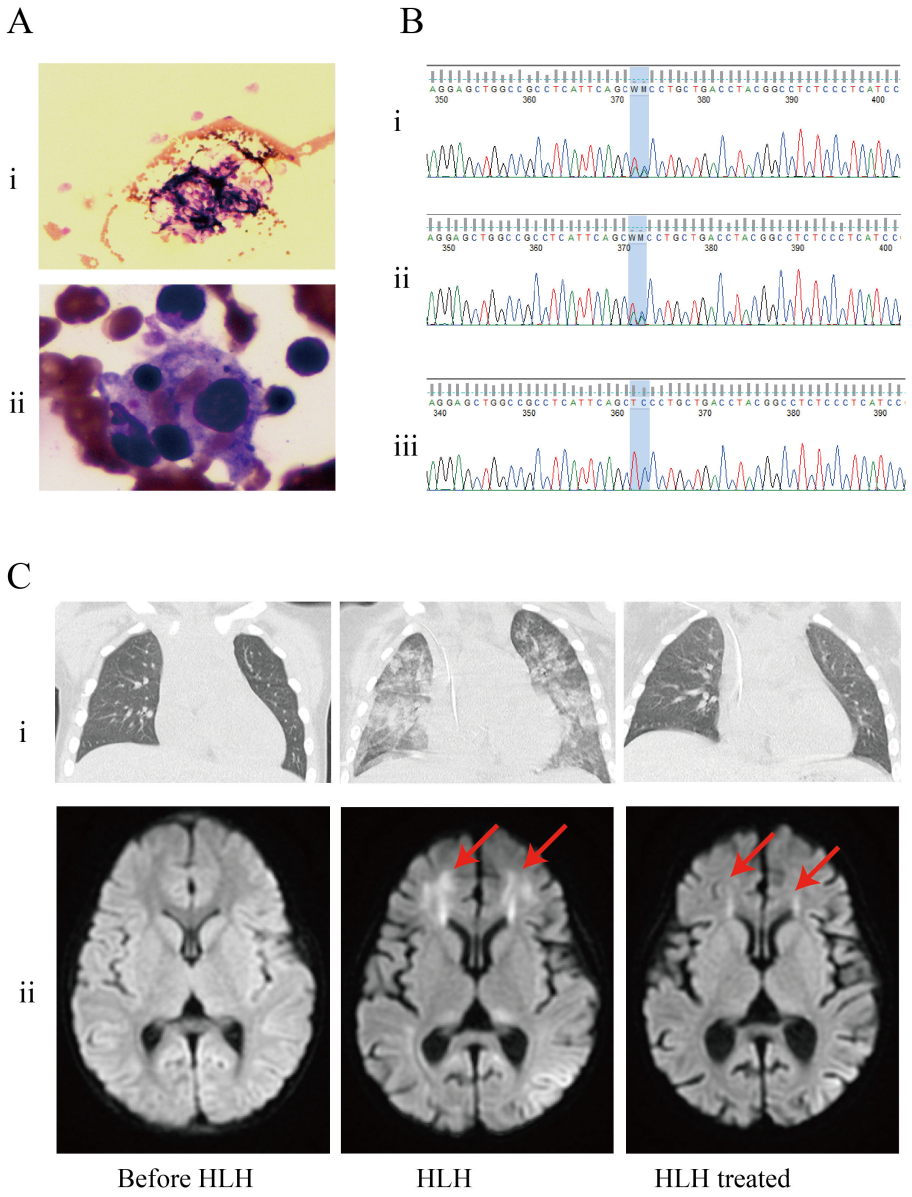



FIGURE 1
Patients examination results. **(A)** Bone marrow biopsy found histiocytes phagocytosing blood cells. (i) Histiocytes phagocytosed blood cells (arrow); (ii) Hemophagocytic cells underwent phagocytosis (arrow). **(B)** Results of whole-exome sequencing: the genetic analysis identified that the patient and her father had heterozygous mutations in UNC13D. (i) patient; (ii) father; (iii) mother. **(C)** The results of imaging examinations were as follows, (i) CT scan showed exudative lesions in both lungs; (ii) brain magnetic resonance imaging (MRI): a T2–weighted sequence showing abnormal white matter signal (arrow).

used (10, 11). Notably, a cure can only be obtained via allogeneic hematopoietic stem cell transplantation, in which the defective immune system is replaced with a healthy one (12). Treatment of secondary HLH always starts with targeting of the underlying trigger using agents to combat infection, malignancy, or autoimmune disease. However, in some cases, it may also be necessary to treat the associated hyperinflammation. Various agents have been used to treat hyperinflammation, including dexamethasone and, in the most severe cases, etoposide (13). Agents that block the effects of individual cytokine have also been employed. This approach is particularly appealing for patients in whom HLH is triggered by infection and administration of cytotoxic or other immunosuppressive agents that could compromise clearance of the inciting pathogen (14, 15). Despite use of currently available therapies, many patients with HLH succumb to the disease. To improve HLH patient outcomes, studies have focused on the use of novel cytokine-directed therapies to dampen hyperinflammation.

Many of the cytokines that are elevated in HLH, including interferon-gamma, interleukin (IL)-2, IL-6, IL-10, IL-12, and granulocyte macrophage-colony stimulating factor, signal through a pathway that involves the Janus kinases and signal transducers and activators of transcription. Ruxolitinib, as a strong Janus kinase inhibitor, can exert an anti-hyperinflammatory effect in HLH by

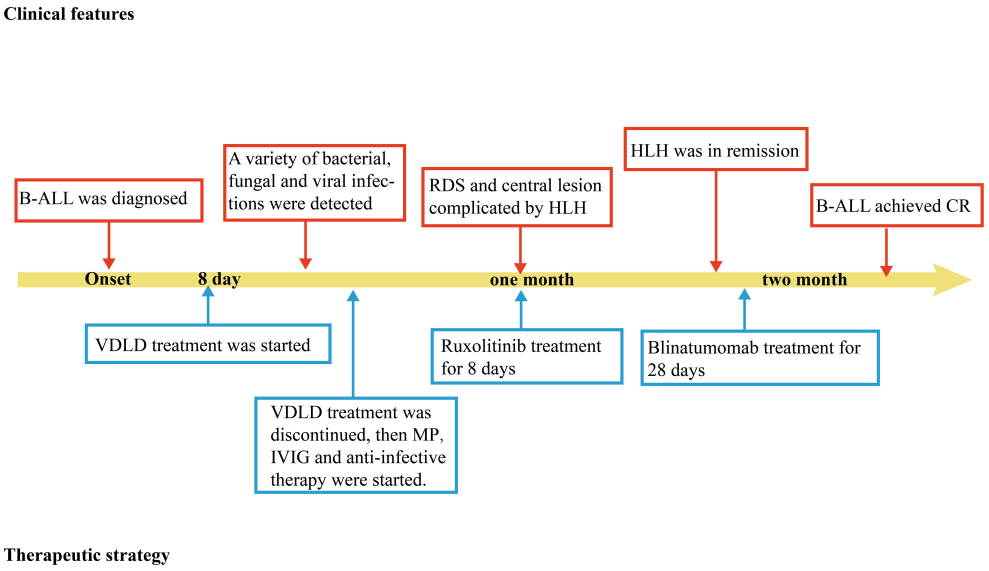



FIGURE 2
Timeline depicting the disease course of the patient. The timeline illustrates the different events in the course of the patient's treatment and disease progression. MP, methylprednisolone; B-ALL, B-cell acute lymphoblastic leukemia; IVIG, intravenous immunoglobin; RDS, respiratory distress syndrome. HLH, Hemophagocytic lymphohistiocytosis; CR, complete remission.

blocking multiple cytokines. Compared with intensive chemotherapy, ruxolitinib has low toxicity and is well tolerated (16). Zhang et al. used ruxolitinib to treat 12 pediatric patients with newly diagnosed secondary HLH. Ten patients experienced a favorable response at 28 days, with eight exhibiting a CR. Among these eight, seven maintained the CR for more than 6 months (17). In 2022, Zhang et al. continued to treat 52 pediatric HLH patients with ruxolitinib monotherapy, the results indicated that 22 patients achieving CR, 9 patients achieving partial remission (PR), and 5 patients showing HLH improvement. Notably, 3 out of the 4 primary HLH patients achieved CR after ruxolitinib monotherapy (18). These results indicated the potential effectiveness of ruxolitinib as a first-line treatment for pediatric HLH. Nonetheless, the ideal dosage and timing of ruxolitinib administration still require definitive determination. Furthermore, there is a need for comprehensive studies that investigate treatment plans incorporating ruxolitinib and other HLH-targeted agents for infants and young children diagnosed with HLH. These studies are essential to gain a more profound understanding of the efficacy and safety of ruxolitinib in such contexts.

It is worth noting that the patient developed transient altered mental status when her HLH was at its most severe. Craniocerebral magnetic resonance scans obtained at this time indicated acute White matter injury. Following the administration of ruxolitinib for targeted treatment of HLH, the patient regained normal consciousness. Significant absorption of the white matter lesion was evident in the subsequent plain magnetic resonance imaging. The patient was diagnosed with CNS involvement secondary to HLH (CNS-HLH) according to the latest diagnostic criteria. CNS-HLH can be familial, non-familial, or isolated. The severity of CNS-HLH varies widely but usually heralds a poor prognosis, and treatment of refractory CNS-HLH is challenging (19). The standard treatment for CNS-HLH is a combination of methotrexate and dexamethasone intrathecal injection (20). Nonetheless, the majority of patients suffering from CNS-HLH are not suitable candidates for intrathecal injection when their condition is critical. Furthermore, the CNS-HLH can potentially benefit from the HLH-94 and HLH-2004 protocols, or from innovative cytokine-directed therapies specifically designed to target HLH (21). There has been a case report suggesting that Lazarus is effective for non-familial CNS-HLH (9). Indeed, the absence of a specifically developed pharmaceutical treatment for CNS-HLH significantly complicates the management of this condition.

Previous studies demonstrated that ruxolitinib reversed CNS inflammation and prolonged survival in murine models of HLH (22). Results of another animal experiments indicated that ruxolitinib could penetrate the blood brain barrier of mice and reduce CNS involvement in the Rab27a-/- mice (an animal model of HLH) (23). However, these findings haven't been confirmed in human patients. Ge J et al. considered that ruxolitinib is probably not an ideal drug for CNS involvement in primary HLH according their latest clinical research results. In this study, all pediatric HLH patients with CNS involvement received intrathecal therapy and ruxolitinib treatment. The results indicated two patients with CNS-HLH died, two patients achieved PR and four patients with CNS involvement relapsed after achieving CR (24). In fact, CNS symptoms have been regarded as a predictor of mortality in children with HLH (25). Firstly, their subjects were primary HLH patients with CNS symptoms, who had a high likelihood of progression to refractory or recurrent HLH and a poor clinical prognosis in the research conducted by Ge J. Seconldy, these CNS-HLH patients were also administered intrathecal injections, which is considered the standard treatment for CNS-HLH. Despite this, there was no significant enhancement in the patients' prognosis,

suggesting that the treatment of these CNS-HLH patients is extremely difficult. Thus, we do not consider this result sufficient to indicate that ruxolitinib may not be effective for treating CNS-HLH. In our case, the patient's CNS symptoms were attributed to acute neuroinflammatory caused by HLH. Ruxolitinib delivered across the Blood-Brain Barrier to exert the potent anti-inflammatory effect as a potential mechanism for ameliorating the CNS-HLH The effectiveness of ruxolitinib in treating refractory HLH necessitates further empirical evidence, particularly in cases involving CNS, which requires additional investigation.

Anakinra, one of cytokine-directed therapies, is first-line recommended for the treatment of HLH for adults and children in all ages according to the studies from western countries (26, 27). However, anakinra is recommended as grade B in Chinese guidelines for diagnosing and treating HLH due to the limited evidence reported within China. This rationale elucidates why anakinra is not regarded as the preferred therapeutic option for HLH in the current case. Additionally, dexamethasone is recognized as the preferred corticosteroid for HLH treatment, especially in CNS-HLH treatment based on previous research evidence. However, in the present case, we used methylprednisolone instead of dexamethasone for the treatment of CNS-HLH for several reasons: firstly, the chemical structure of methylprednisolone is characterized by the presence of eight hydrogen bonds and three methyl groups, which confer advantageous lipid solubility and facilitate its passage across the blood-brain barrier. Compared to dexamethasone, which contains a fluoride side chain, methylprednisolone exhibits enhanced lipid solubility, potentially resulting in superior permeability through the blood-brain barrier (28); secondly, previous research has demonstrated that dexamethasone, a long-acting glucocorticoid, exhibits potent and prolonged pharmacological effects, including significant immunosuppressive properties. Consequently, its use is associated with an increased risk of secondary severe bacterial infections and opportunistic infections, such as tuberculosis, herpes zoster, and Pneumocystis carinii pneumonia, particularly during the treatment of HLH (29). Methylprednisolone is classified as a medium-acting glucocorticoid with a shorter half-life compared to that of dexamethasone, which indicated its immunosuppressive effect was less pronounced compared to that of dexamethasone. Thus, we consider that methylprednisolone demonstrates a lower propensity for inducing severe adverse effects compared to dexamethasone; Lastly, an modified HLH-04 regimen from Beijing Children's Hospital involved substituting dexamethasone with methylprednisolone to mitigate the incidence and mortality of chemotherapy-related complications in the treatment of pediatric HLH.The improved protocol reduced the intensity of chemotherapy, with overall efficacy no worse than the standard HLH-04 regimen, and significantly reduced the rate of chemotherapy-related myelosuppression, fungal infection and mortality. The results indicated that there was no statistically significant difference in treatment outcomes following substituting dexamethasone with methylprednisolone for CNS -HLH patients. This lack of significant difference did not impact the long-term prognosis of pediatric HLH with CNS involvement (30). According to the above, comparing to dexamethasone, methylprednisolone can exert comparable effect with fewer severe adverse effects in pediatric CNS-HLH.

Finally, the patient's genetic test report revealed a heterozygous mutation in the *UNC13D* gene, implying a familial predisposition toward HLH. A total of 12 causative genes were identified between 1999 and 2018 (13). Familial Hemophagocytic Lymphohistiocytosis (FHL) is a rare autosomal recessive disorder caused by mutations in *PRF1* (resulting in FHL2), the UNC13 homologue D gene (*UNC13D*, resulting in FHL3), the synapse fusion protein 11 gene (*STX11*, resulting in FHL4), or synapse fusion protein caused by mutations in the binding protein 2 gene (*STXBP2*, resulting in FHL5) and usually occurs in infancy (31). The latest data indicate that *PRF1* and *UNC13D* mutations are quite common (32–34). According to the ClinVar database, there are currently more than 300 *UNC13D* mutations confirmed to be associated with FHL. Although genetic mutations in the FHL subtype vary, they all lead to impaired function of NK cells and T cells (35). They are correlated in granulose-mediated cytotoxic pathways, interfering with perforin-mediated cytotoxic functions, thereby blocking the mechanism that triggers apoptosis or activates induction of apoptosis. Cytotoxic T cells and NK cells cannot effectively kill target cells, so the immune response is overactivated and the inflammatory state persists, causing HLH. The patient and her father had a simple heterozygous *UNC13D* mutation, and whether this mutation can cause HLH is controversial. In fact, whole transcriptome RNA sequencing data for the patient also indicated mutations of *UNC13D*. Next, We also detected expression of HLH-related markers such as CD107a, the degranulation function of which was decreased in NK cells. Combined with the aforementioned results, the diagnosis of primary HLH could not be completely ruled out. Further functional examination should be conducted on the patient's father.

## 4 Conclusion

HLH requires early diagnosis and should be considered in patients with ALL who present with pancytopenia. CNS involvement associated with HLH should not be ignored, and magnetic resonance imaging of the brain can identify CNS-HLH early. Infection and inflammation tend to be noticed and treated promptly, but HLH is harder to diagnose in a timely manner because of its rarity and the low likelihood of testing for immune system dysregulation and impaired activation. HLH-related biomarkers need further investigation. Genetic testing should be performed in all patients with HLH. The role of HLH-related heterozygous gene mutations should be emphasized. More prospective evidence is needed regarding the timing, dose, and efficacy of ruxolitinib therapy in HLH and CNS-HLH. Diagnostic vigilance and prompt treatment are essential in the management of HLH.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YA: Writing – original draft, Resources, Investigation, Formal analysis, Data curation, Supervision. YH: Writing – review & editing, Supervision, Data curation. XZ: Writing – review & editing, Supervision, Data curation. JL: Writing – review & editing, Supervision, Data curation. QZ: Writing – review & editing, Data curation. SW: Writing – review & editing, Data curation. YF: Writing – review & editing, Validation, Supervision, Conceptualization, Data curation. JZ: Writing – review & editing, Validation, Supervision, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1438378/full#supplementary-material

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# Myasthenia gravis complicated by pure red cell aplasia with clonal large granular lymphocytosis in the absence of thymoma: a rare case report and literature review

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In 2013, a young woman during her early pregnancy was repeatedly hospitalized due to respiratory and swallowing difficulties. The pregnancy was terminated due to recurrent severe lung infections. She was later diagnosed with myasthenia gravis (MG) based on positive acetylcholine receptor antibodies. Her muscle weakness was subsequently well-controlled with pyridostigmine bromide, azathioprine, and prednisone. Notably, in the seventh year after her MG diagnosis (2021), the patient developed severe anemia (hemoglobin: 44 g/L). Bone marrow analysis revealed a rare combination of pure red cell aplasia (PRCA) with clonal expansion of large granular cells. Further examinations excluded thymoma. Considering the possibility of drug-induced PRCA, azathioprine was replaced with tacrolimus. Remarkably, the anemia resolved within 1 month, and her MG remained well-controlled. It is well-established that abnormal thymic hyperplasia within thymomas can alter the distribution and function of peripheral T lymphocytes, leading to the development of autoimmune diseases such as MG and PRCA. In this unique case without thymoma, we discussed the mechanisms and associations of PRCA with MG, medication, and clonal large granular T cells. This unique case highlights the unprecedented association of MG and PRCA without thymoma, underscoring the complexity of the disease spectrum. The patient's subsequent successful delivery in June 2023 adds another dimension to the multifaceted clinical course, warranting attention and exploration into potential connections between these conditions.

KEYWORDS

**pure red cell aplasia, myasthenia gravis, thymomas, large granular cells, autoimmune disorders**

# 1 Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigue caused by impaired neuromuscular transmission. It primarily affects voluntary muscles, including those involved in breathing and swallowing. PRCA is a rare hematologic condition marked by a severe reduction or absence of erythroid precursors in the bone marrow, leading to anemia. Both MG and PRCA could be closely associated with thymoma, respectively. Reports indicated that approximately 10% of MG patients and 5%–13% of PRCA patients exhibited thymoma (1, 2). The intricate relationship between MG and PRCA has been well-documented, with both conditions frequently associated with thymoma (3–6). In the current literature, most reported cases of concurrent MG and PRCA are associated with thymoma. Besides our case, only three other cases without thymoma have been reported. Furthermore, a case with concurrent clonal large granular lymphocyte proliferation is unprecedented.

In this report, we present a case of concurrent MG and PRCA without an associated thymoma. We describe the clinical course, diagnostic workup, and treatment. We also discuss potential mechanisms between MG and PRCA, including the role of clonal large granular lymphocytes (LGL), immunosuppressive therapy, and autoimmune connections. Studying such rare cases is essential. Firstly, they present unique diagnostic and therapeutic challenges, highlighting the need for a multidisciplinary approach. Secondly, understanding the potential link between these autoimmune conditions could provide insights into their pathophysiology and improve patient management. Lastly, documenting and analyzing these cases can raise awareness and aid in the early recognition and treatment of similar presentations in clinical practice.

# 2 Case presentation

## 2.1 Diagnosis and treatment of myasthenia gravis

In April 2013, a young pregnant woman at 3 months' gestation was admitted to a local hospital with complaints of respiratory distress, dysphagia, and coughing while drinking. Cerebrospinal fluid (CSF) analysis indicated cell–protein dissociation, raising suspicion of Fisher syndrome (FS). Despite receiving high-dose intravenous immunoglobulin treatment, her condition did not improve and relapsed.

In August 2013, she was admitted to our neurology department with worsening dysphagia. Neurological examination revealed the following: symmetrical nasolabial folds, normal strength for showing teeth and puffing cheeks, symmetrical forehead wrinkles, and strong eyelid closure without lagophthalmos. Muscle strength was grade 3 in both lower limbs and grade 5 in both upper limbs. The finger-to-nose and heel-to-shin tests were performed accurately bilaterally, but she could not perform tandem walking or the Romberg test. Ocular movements were full without lagophthalmos or gaze palsy, and no diplopia was elicited. She had strong and coordinated chewing, with no impairments in lip and teeth coordination. Thyroid hormone levels were within normal limits, and the autoantibodies were negative.

Owing to her critical condition and a history of repeated radiation exposure, prompt induction of labor was applied in September 2013 (34 weeks gestation). Over the next year, the patient experienced multiple severe respiratory infections, including tuberculous pleurisy, necessitating interventions such as tracheostomy, mechanical ventilation, antimicrobial and anti-tuberculosis treatments (isoniazid, rifampicin, pyrazinamide, and ethambutol), and bromhexine. Despite these measures, symptoms of muscle weakness, including respiratory distress, dysphagia, and speech weakness, persisted without improvement.

In August 2014, the patient underwent additional investigations at a higher-level hospital, revealing elevated acetylcholine receptor antibodies (AChR-Ab) (this information is from the medical records; the original data are not available) and electromyography (EMG) findings showing no abnormalities in motor conduction velocity (MCV) and F waves. Repetitive nerve stimulation (RNS) showed a decremental response, consistent with the diagnosis of oropharyngeal or generalized MG. Additionally, CSF protein levels and cell counts were normal on two separate occasions, thereby ruling out FS. Chest computed tomography (CT) revealed no thymoma. The patient had a negative neostigmine test result. Because of poor response to monotherapy with pyridostigmine bromide, she was treated with oral azathioprine 150 mg once daily and prednisone 15 mg in addition to pyridostigmine bromide, resulting in good control of symptoms, with noticeable alleviation of respiratory distress, dysphagia, and speech weakness. The patient could engage in light physical labor without recurrence of severe pulmonary infections.

## 2.2 Onset of pure red cell aplasia

Until 3 November 2021, the patient was readmitted to our hospital's gastroenterology department with complaints of dizziness, fatigue, and dark stools, without respiratory or swallowing difficulties. Neurological examination revealed no ptosis or facial muscle weakness. However, there was evidence of limb muscle weakness and dysphagia, with symptoms exhibiting a diurnal variation, being milder in the morning and worsening by evening, and exacerbating with exertion. The patient exhibited no symptoms of acute abdomen, such as abdominal pain, acid reflux, heartburn, vomiting, or diarrhea. Abdominal examination revealed no tenderness, rebound tenderness, or abdominal muscle rigidity, and Murphy's sign was negative. Gastrointestinal endoscopy revealed no evidence of bleeding or tumors. The fecal occult blood test was negative and both transaminase and bilirubin levels were within normal limits. Laboratory tests revealed red blood cells (RBCs) $1.4 \times 10^{12}$/L, hemoglobin (HGB) 44 g/L, mean corpuscular volume (MCV) 103.6 fL, reticulocytes (RET) $0.0024 \times 10^{12}$/L, and erythropoietin (EPO) level 3,739 mIU/L. Bone marrow smear indicated reasonable hematopoiesis with almost no erythroid series. Upon transfer to our department for further diagnosis and treatment, bone marrow biopsy revealed a hematopoietic-to-adipose tissue ratio of approximately 0.6:1, a granulocyte–erythrocyte ratio of approximately 10:1, reduced erythropoiesis, and overall diminished bone marrow hyperplasia

primarily characterized by decreased erythropoiesis. Ferritin remained elevated at 3,119.16 ng/mL. Folate and vitamin B12 were normal, and the Coombs test was negative. Paroxysmal nocturnal hemoglobinuria (PNH) testing was negative. Viral markers (hepatitis B virus, hepatitis C virus, cytomegalovirus, human immunodeficiency virus, Epstein–Barr virus, and parvovirus B19) were negative. The common autoimmune disease-related antibodies, such as those associated with rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, polymyositis, and primary biliary cirrhosis, were all negative. Flow cytometry of bone marrow and peripheral blood revealed a few large granular lymphocyte (LGL) cells: 9.2% in the bone marrow expressing cluster of differentiation (CD) 2, CD3, CD7, CD8, T-cell receptor (TCR) α/β, TCRγ/δ, and partially expressing CD57; 5% in peripheral blood expressing CD2, CD3, CD7, CD8, TCRα/β, and TCRγ/δ. Peripheral blood gene testing showed positive TCRγ gene rearrangement, with no mutations in STAT3 and STAT5b genes. Based on the comprehensive examination results, the diagnosis of pure red cell aplasia (PRCA) with concomitant clonal expansion of large granular T cells was established. Gastrointestinal bleeding and hemorrhagic anemia were ruled out. Repeat AChR-Ab showed a significant increase (a result of 3.91 nmol/L; normal range, <0.45 nmol/L), while the anti-muscle-specific kinase antibodies (MuSK-Ab), anti-connexin antibody (Titin-Ab), receptor lanny alkali-resistant calcium release antibodies (RyR-Ab), and anti-low density lipoprotein receptor-associated protein 4 antibody (LRP4-Ab) were normal. Repeat EMG showed negative RNS.

## 2.3 Outcome and follow up

Upon considering a diagnosis of PRCA, azathioprine was discontinued, and the patient underwent treatment with a regimen comprising RBC transfusion, tacrolimus, and prednisone.

Three months later, a blood analysis revealed normalized hemoglobin levels. She continued to adhere to a daily oral tacrolimus at 1.5 mg without visiting hematologists further. In October 2022, the patient became pregnant again. Throughout the pregnancy, she experienced no recurrence of MG or severe anemia. However, because of a COVID-19 infection, she had to undergo a cesarean section at 37 weeks and 4 days. The newborn was healthy, and both mother and child were discharged shortly thereafter. The patient's summarized diagnostic and treatment course from 2013 to 2023 is depicted in Figure 1, while the trend of hemoglobin levels can be seen in the line graph in Figure 2.

# 3 Discussion

MG tends to worsen during pregnancy in approximately 30%–40% of female patients, especially during the first 3 months of pregnancy or postpartum (7). The patient in this case developed symptoms of MG at 3 months into pregnancy, and it is possible that pregnancy induced and exacerbated the MG symptoms. Because of the passage of time, it is unknown whether the patient had symptoms of MG, such as weakness or ptosis, before pregnancy. Approximately 8%–15% of MG patients have thymomas, and some may also have other associated conditions (8–13) such as PRCA, neuromyotonia, polymyositis, graft-versus-host disease (GVHD), and pseudo-obstruction, achalasia, among others. Secondary PRCA can have various causes (14–16), including autoimmune diseases, lymphoproliferative disorders, hematologic or solid tumors (such as thymomas), immune deficiencies, ABO-incompatible hematopoietic stem cell transplantation, viral or bacterial infections, and medications (e.g., recombinant human erythropoietin, immunosuppressive drugs, antibiotics, and antiviral drugs). A search of the PubMed database revealed over 100 reports of concurrent MG, PRCA, and thymoma. However, reports of MG with PRCA in the absence of a thymoma are extremely rare. Aside from the case reported in this paper, only three similar cases have been identified (17–19). Their medical history and treatment outcomes are summarized in Table 1.

The rare case we are reporting occurred during a 7-year course of azathioprine treatment for the diagnosis of MG, and PRCA

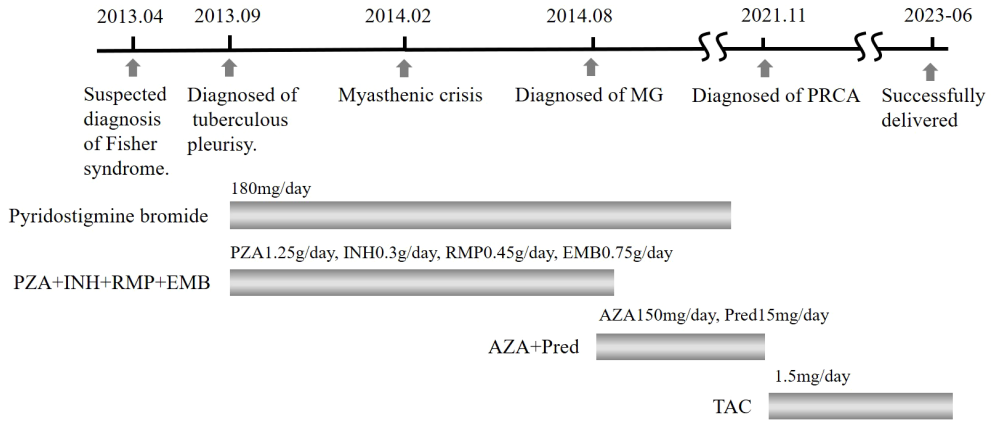



FIGURE 1
Timeline of primary diagnosis and pharmacological interventions. PZA, pyrazinamide; INH, isoniazid; RMP, rifampicin; EMB, ethambutol; AZA, azathioprine; Pred, prednisone; TAC, tacrolimus.

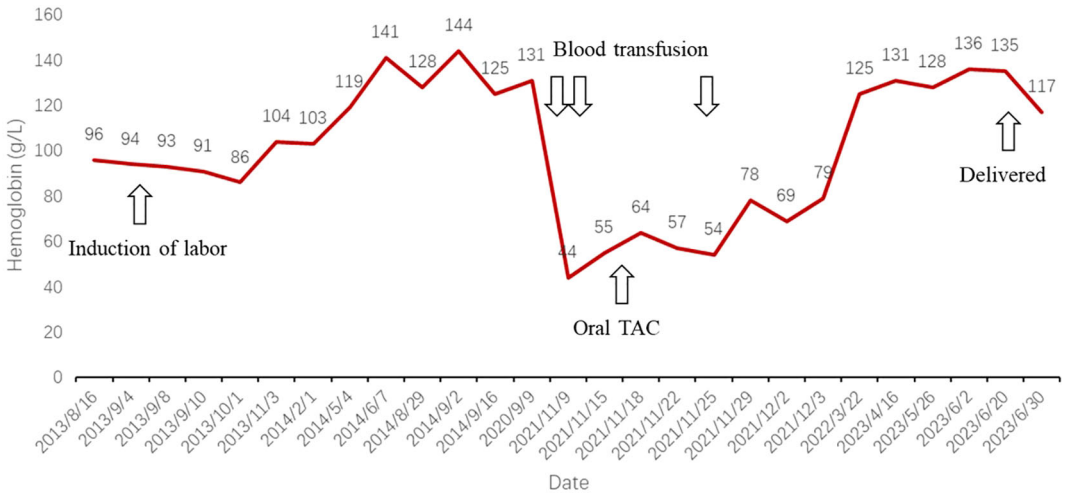



FIGURE 2
Line graph depicting trends in hemoglobin levels, significant events, and therapeutic interventions. TAC, tacrolimus.

developed as a complication. Phenotypically atypical large granular lymphocytes with T-cell receptor (TCR) gene rearrangement were observed in bone marrow and peripheral blood flow cytometry. Several potential mechanisms for the development of PRCA in this case are proposed. First, we hypothesize that the onset of PRCA may be associated with the clonal proliferation of large granular lymphocytes. In a cohort of 47 PRCA patients at Mayo Clinic, LGL leukemia was the most common associated condition, with approximately 19% of patients being diagnosed with LGL leukemia (20). Even though this patient did not meet the criteria for a diagnosis of T-cell large granular lymphocytic leukemia (T-LGLL), clonal T-LGL cells were indeed present. The potential mechanism involves cytotoxic T-LGL cells whose surface TCR recognizes antigens presented by class I human leukocyte antigen (HLA-I) on red cell precursors, leading to the activation of their cytotoxic signals. Under normal circumstances, this cytotoxic signal is counteracted by inhibitory signals produced when HLA-I molecules on the surface of red cell precursors interact with their inhibitory receptors. However, during the differentiation process of red cell precursors, the expression of HLA-I class molecules is physiologically downregulated (21). The patient was not evaluated with bone marrow and peripheral blood flow cytometry when initially diagnosed with MG; thus, it is unknown when these clonal T-LGL cells first appeared.

Second, the occurrence of PRCA may be drug-induced. The patient had been on azathioprine treatment for MG for an extended period before the development of PRCA. There have been multiple cases reported where PRCA occurred after kidney transplantation or in patients with Crohn's disease treated with azathioprine (22–26). It is believed that this might be related to the azathioprine metabolite 6-thioguanine (6TGN), which inhibits DNA synthesis and exerts direct cytotoxicity on erythroid precursor cells, especially in patients with reduced activity of thiopurine methyltransferase (27). The timing of bone marrow toxicity varies widely, from a few days to 11 years, with a higher incidence in the first 8 weeks (23). Therefore, the role of azathioprine as a contributing factor cannot be ruled out in this case. In addition, it has been reported that anti-tuberculosis drugs such as isoniazid and rifampicin may also lead to the occurrence of PRCA (17, 28–30). In such cases, hemoglobin levels typically recovered gradually after discontinuation of the drugs (30). Mizobuchi et al. speculated that T cell-mediated immune responses may be associated with the secondary development of PRCA (6). Proposed mechanisms include direct cytotoxic effects or metabolic interference impacting erythropoiesis, as well as immune-mediated inhibition of bone marrow erythroid progenitor cells (31, 32). The patient in this case underwent anti-tuberculosis treatment from September 2013 to August 2014, which included isoniazid and rifampicin. However, severe anemia occurred in November 2021, suggesting that it may not be related to these agents.

Most published cases of MG complicated by PRCA are associated with thymoma, and the pathophysiological mechanisms underlying the association of thymoma with autoimmune diseases or paraneoplastic syndromes remain unclear. Some researchers have reviewed the pathological and clinical features of 42 thymoma patients with paraneoplastic syndromes and speculated that the coexistence of thymoma with PRCA, MG, and other autoimmune diseases may be related to the generation, migration, and subsequent interaction of autoantigen-specific T cells with B lymphocytes outside the thymus (33). As for patients without thymoma, there may be an immunological connection between MG and PRCA. Reports indicate that patients with both MG and PRCA typically develop PRCA several years after the onset of MG, with only 1 out of 11 cases in a series where PRCA occurred before the onset of MG (34). This implies that MG may initiate a mechanism resulting in the onset of PRCA. Within the thymus, immature T cells undergo differentiation, clonal selection, and proliferation before being released into the circulation. When associated with thymomas, aberrant thymopoiesis within thymomas can modify the peripheral T-cell repertoire, potentially leading to the generation of autoantigens and the development of thymoma-associated autoimmune diseases (35). However, this patient did not present with a thymoma, necessitating further clinical observation and mechanistic research in similar cases to elucidate the connection between MG and PRCA.

TABLE 1 The characteristics of four cases with MG combined with PRCA without thymoma.

| | Sex/ age | Pre-existing condition | Sequence of onset | Parvovirus B19 | AChR-Ab | Hemoglobin | Reticulocyte | Coombs test | PNH clone | Hematopoietic ingredients | Autoimmune antibodies | Thymoma | Bone marrow | Treatments | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aquilina et al. | M/65 | Inexistence | PRCA preceded MG | IgM positive | Positive | 6 g/dL | $7\times10^9$/L | Negative | Negative | Normal | Negative | Thymic cyst (based on PET-CT and histopathology) | Hypercellular marrow, reduction of erythroid precursor, myeloid hyperplasia | Packed cell blood transfusions, pyridostigmine, intravenous Ig | Remission |
| Nakamura et al. | F/47 | SLE, isoniazid | MG preceded PRCA | IgM, IgG, and DNA all negative | Positive | 5.8 g/dL | $1\times10^9$/L | NA | NA | Normal | Negative | Inexistence | Reduction of erythroid precursor, normal myeloid cells, and megakaryocytes | Pyridostigmine bromide, mizoribine, red blood cell transfusion, cyclosporine A, tacrolimus, | Remission |
| Mohri et al. | F/37 | Hodgkin's lymphoma, chemotherapy | Simultaneously | NA | Positive | NA | NA | NA | NA | NA | NA | Inexistence | Reduction of erythroid precursor | steroid, and pyridostigmine | Died of pneumonia |
| Our case | F/17 | Pregnancy | MG preceded PRCA | DNA negative | Positive | 4.4 g/dL | $2.4\times10^9$/L | Negative | Negative | Elevated ferritin levels | Negative | Inexistence | Overall diminished bone marrow hyperplasia primarily characterized by decreased erythropoiesis | Pyridostigmine bromide, azathioprine, red blood cell transfusion, tacrolimus, and prednisone | Remission, successful conception, and childbirth |

PNH, paroxysmal nocturnal hemoglobinuria; PET-CT, positron emission tomography–computed tomography; SLE, systemic lupus erythematosus; NA, not available.



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After more than 8 years, the patient became pregnant again and successfully delivered, despite long-term treatment with tacrolimus and prednisone. This pregnancy did not exacerbate MG symptoms, aligning with current clinical experience (1). Authoritative consensus recommends treatment of MG during pregnancy primarily with pyridostigmine and glucocorticoids, with minimal impact from immunosuppressive therapy on fertility (1). In this case, combination immunosuppressive therapy was necessary due to concurrent PRCA. Tacrolimus is widely used to prevent rejection following solid organ transplantation. Although pregnancies in organ transplant recipients are considered high risk, more than 14,000 such pregnancies have been reported (36). While pregnancy can affect the whole blood concentration of tacrolimus, it does not impact its free concentration (36); thus, dose adjustments are not necessary during pregnancy. Our patient experienced a smooth pregnancy and delivered a healthy newborn, suggesting minimal fetal side effects from tacrolimus. This case provides valuable clinical insights, although further observations are warranted.

MG could potentially trigger other autoimmune disorders, such as PRCA in the case described here. Immunosuppressive agents may also contribute to the development of PRCA, necessitating close monitoring of blood parameters during treatment. In this rare case, the coexistence of MG and PRCA, along with an increase in clonal LGLs, warrants continued surveillance to determine whether the disease undergoes further evolution under well-controlled MG and PRCA conditions.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by the ethics committee of Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

LD: Data curation, Writing – original draft, Writing – review & editing. YL: Data curation, Writing – original draft. QZ: Conceptualization, Writing – review & editing. FX: Conceptualization, Supervision, Writing – review & editing.

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# Case Report: Successful treatment of severe Guillain-Barré syndrome with paralytic ileus as a presenting symptom by intensive immunotherapy

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Involvement of the intestinal autonomic nerves in Guillain-Barré syndrome (GBS) can lead to paralytic ileus, a condition commonly observed in severe cases during later stages of the disease. Cases with paralytic ileus as a presenting symptom are very rare. We report a case of a 35-year-old male patient who was admitted to the hospital with acute abdominal pain persisting for 12 hours. Abdominal CT suggested small bowel obstruction, for which routine conventional pharmacological treatment were ineffective. Subsequently, the patient presented with multiple sets of cranial nerve paralysis, bilateral symmetrical delayed paralysis, distal limb numbness, respiratory failure, urinary retention, shock, and electrophysiology, suggesting axonal-type multifocal peripheral nerve damage. Notably, blood antiganglioside tests showed IgG positivity for anti-sulfatide antibodies, anti-GD1a antibodies, and anti-GT1a antibodies. The patient was administered plasma exchange combined with intravenous immunoglobulin, and symptoms gradually improved. The patient resumed independent ambulation within two months and returned to normal status at one year, with no recurrence of symptoms. Given that paralytic ileus can precede other neurological abnormalities in patients with GBS, early detection and individualized treatment are critical to reduce the risk of death and promote recovery. Here, we demonstrate that intensive immunotherapy is a viable therapeutic approach that can be clinically adopted for such conditions.

KEYWORDS

**ileus, Guillain-Barré syndrome, intensive immunotherapy, case report, GBS**

## Introduction

Guillain-Barré syndrome (GBS) is an autoimmune peripheral neuropathy characterized by acute flaccid paralysis. It affects individuals of all age groups worldwide. Despite standard immunotherapies, approximately 5% of those affected succumb to the condition, and an additional 20% are unable to walk independently one year after disease onset (1). Approximately 20% of people with GBS experience respiratory failure requiring mechanical ventilation (2), which poses a severe threat to human health.

Autonomic dysfunction has been reported in more than half of patients with GBS, primarily affecting the cardiovascular system, urinary tract, and intestines. Paralytic ileus is a rare occurrence typically observed in severe cases during the later stages of the disease (3). However, in rare circumstances, paralytic ileus can manifest as the initial and sole presentation of GBS in the early stages of the disease (4). Moreover, patients with GBS who have comorbid autonomic dysfunction experience a higher mortality rate and slower neurological recovery, requiring meticulous medical attention (5, 6), and the treatment of such patients remains challenging, especially in severe cases.

The pathophysiology of GBS is complex, with distinct mechanisms potentially underlying the demyelinating and axonal subtypes. Anti-ganglioside antibodies, particularly anti-GM1 and anti-GD1a antibodies, are closely related to the pathogenesis of the axonal form of GBS (acute motor axonal neuropathy, AMAN; acute motor and sensory axonal neuropathy, AMSAN). Although the pathological hallmark of the demyelinating form of GBS (acute inflammatory demyelinating poly neuropathy, AIDP) is the phagocytosis of myelin by macrophages, the relationship between autoantibodies to AIDP has not been fully clarified (7, 8). Notably, the pathophysiological mechanisms underlying GBS are still being elucidated, with both T cells and B cells likely implicated in its pathogenesis (9). The complexity of the mechanisms indicates that there is room for improvement in therapeutic strategies.

## Case presentation

A 35-year-old man was admitted to the emergency department with abdominal pain and distension for 12 hours without other clinical manifestations. The patient was transferred to the general surgery department, where abdominal CT suggested a small bowel obstruction (Figure 1). Upon examination, he had a temperature of 36.7°C, heart rate of 85 bpm, blood pressure of 125/75 mmHg, and respiratory rate of 12 breaths/min. The patient's abdomen was slightly distended, and pressure pain was noted around the umbilicus, with no significant rebound pain, and diminished bowel sounds. The electrocardiogram was normal, and no significant abnormalities were found in arterial blood gas analysis, complete blood count, coagulation profile, D-dimer, liver and kidney function tests, electrolytes, cardiac enzymes, or tumor markers, revealing no evidence of electrolyte imbalances, inflammatory acute abdomen (such as appendicitis, cholecystitis, or pancreatitis), intestinal mucosal ischemia or necrosis, or intra-abdominal infections—common causes of ileus, and the patient's ileus showed no response to treatments such as paraffin oil enema and catharsis, gastrointestinal decompression, antibiotics, proton pump inhibitors, or somatostatin therapy. The patient denied a history of antecedent infection, and the other medical histories were unremarkable. On the third day of admission, the patient had bilateral eyelid ptosis, hoarseness, limited tongue extension, neck weakness, a Medical Research Council of the Extremities (MRC) grade of 4/5, and a negative Babinski's sign. No significant abnormalities on the brain MRI scan were observed on day 3, and the etiology of the patient's symptoms remained undetermined. On the fourth day of admission, the patient experienced the loss of deep tendon reflection in all four limbs, with an MRC grade of 2/5, accompanied by loss of tactile and pain sensation in the distal limbs, respiratory failure requiring mechanical ventilation, shock requiring pressurization, and urinary retention requiring catheterization. After an urgent multidisciplinary consultation, the

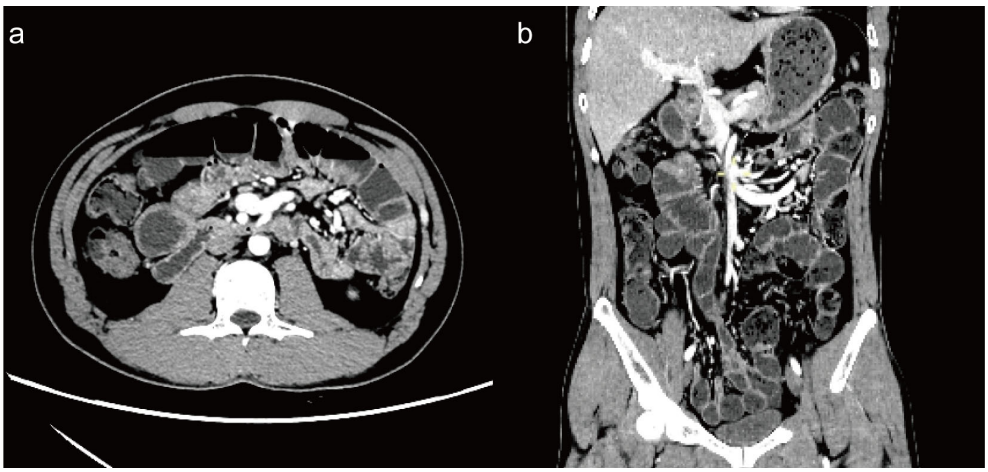



FIGURE 1
Enhanced CT of the abdomen [**(a)** axial view; **(b)** coronal view] shows multiple small bowel and colon bowel dilatations, mild to moderate enhancement of the bowel wall, and multiple air-liquid planes, with no evidence of obstruction points.

patient was clinically diagnosed with GBS with an mEGOS score of 9 (10) and transferred to the Neuro ICU for plasma exchange (PE) (40 ml/kg/qod). A lumbar puncture was performed on the same day, revealing that the cerebrospinal fluid routine and biochemical tests were within normal ranges.

The patient's condition did not improve after receiving the initial PE, and it continued to progress. On the sixth day of admission, the patient became lethargic, was unable to open his eyes, had fixation of both eyeballs, and had an MRC grade of 1/5 in the extremities and a Hughes score of 5. Electromyography (EMG) performed on day 6 suggested bilateral symmetrical axonal-type motor-sensory poly peripheral neuropathy with a peroneal nerve-sparing pattern, lack of F-waves, disappearance of bilateral blink reflexes, and the EMG results supporting the diagnosis of GBS. The patient then received three additional PEs (40 ml/kg/qod). After four PE sessions, the patient regained alertness, eye movement returned, and limb muscle strength was achieved with an MRC grade of 3/5. However, he consistently had persistent poor gastrointestinal emptying, respiratory weakness, and exposure to life-threatening conditions. The patient was provided a course of intravenous immunoglobulin (IVIG), as it is possible for individual patients to benefit from intensive treatment early in the disease before irreversible neurologic damage occurs.

A repeat lumbar puncture was performed on day 12 of admission; the CSF routine and biochemical test findings were still in the normal range. Notably, immunoblotting assays revealed positive results for serum anti-sulfatide IgG, anti-GD1a IgG, and anti-GT1a IgG, whereas cerebrospinal fluid tests were negative. On day 16, the patient resumed urination, anal exhaust, and defecation, and enteral nutrition was administered. Based on the patient's medical history, auxiliary examinations, and response to treatment, we concluded that the paralytic ileus was of GBS origin. However, the patient's respiratory function improved slowly and repeated weaning tests failed. On the 17th day of admission, a tracheotomy was performed. By the 34th day, the patient was successfully weaned off the ventilator, and a repeat EMG examination was conducted, revealing that the amplitudes of the compound muscle action potential and sensory nerve action potential were significantly higher than before. Moreover, the F-wave latencies of the bilateral median, ulnar, and tibial nerves were all within normal ranges, with an occurrence rate of 100%. The blink reflex also returned to normal. The tracheostomy tube was removed on the 41st day. He resumed independent walking on the 60th day but required assistance getting up from a squat, which he could perform without assistance at the 8th month. After one year, the patient could run, albeit not as well as before the onset of the disease (Figure 2).

## Discussion

Our patient initially presented with symptoms unsuggestive of GBS, such as abdominal pain and distension (11). However, the patient subsequently developed a typical cluster of GBS symptoms, including symmetrical delayed paralysis, numbness of the extremities at the ends, cranial nerve involvement, urinary retention, shock, and respiratory failure. The diagnosis of GBS was confirmed based on electrophysiological studies, the presence of positive anti-ganglionic antibodies, the effectiveness of immunotherapy, the absence of any other explanatory etiologies, and a unidirectional course of the disease.

Ileus occurs in approximately 16% of patients with GBS (3, 12). However, this figure may be overestimated owing to the lack of uniform diagnostic criteria and difficulty distinguishing GBS-induced ileus from confounding factors, such as critical illness, electrolyte disturbances, immobility, and medications (e.g., anesthetics) (3, 13). Paralytic ileus is thought to be caused by GBS damage to the gastrointestinal autonomic nerves. Autopsy results confirm autonomic demyelination is present in patients with GBS (14), resulting from an immune response to the autonomic nerves (15). Spectral analysis of heart rate variability revealed a marked shift in sympathovagal balance to sympathetic dominance at the height of GBS disease (16), and similar alterations have been observed in Miller Fisher syndrome (17). Sympathetic dominance may also be present in

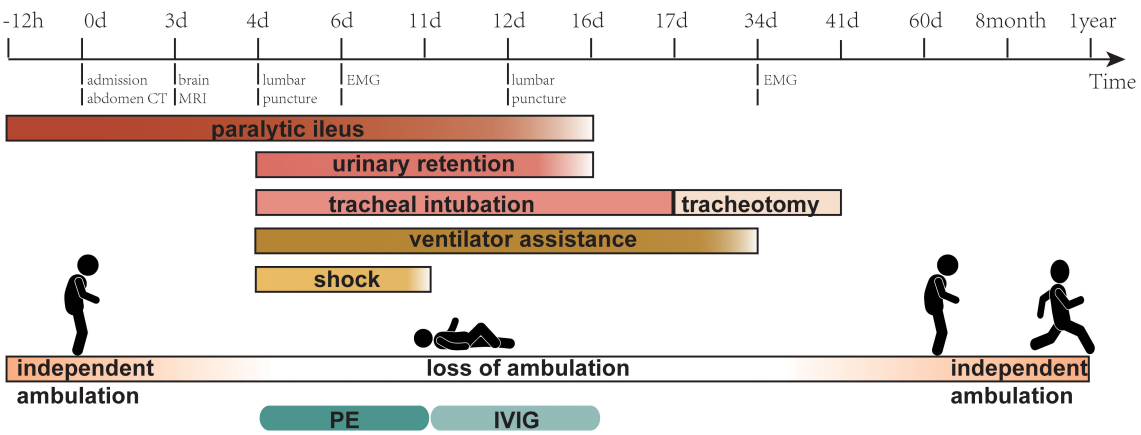



FIGURE 2
Timeline showing the main relevant events in the case. MRI, magnetic resonance imaging; EMG, electromyogram; PE, plasma exchange; IVIG, intravenous immunoglobulin.

the autonomic nervous system of the gastrointestinal tract during the acute phase of GBS, leading to slow gastrointestinal motility and potentially ileus (13).

Gangliosides are widely present in tissue cells and are particularly abundant in nerve cell myelin membranes, axon membranes, neuromuscular junctions, and nodes of Ranvier. Antibody binding to gangliosides in these regions may lead to disturbances in axon-glia interactions, disorders in ion channel regulation, and trigger axonal degeneration (18, 19). This process can destabilize cytoskeletal structures and impede nerve conduction (8, 18). Antibodies against gangliosides are occasionally associated with clinical signs suggestive of selective nerve damage. Our patient tested positive for blood anti-GT1a, anti-GD1a, and anti-sulfatide antibodies. Anti-GT1a antibodies have been associated with somnolence, ataxia, extraocular muscle paralysis, oropharyngeal involvement, medullary paralysis, decreased tendon reflexes, and pharyngeal and cervical brachial weakness (20, 21). Anti-GD1a antibodies have been implicated in the pathogenesis of AMAN and AMSAN and have been associated with distal dominant weakness, neck weakness, and cranial nerve injury (21). Neuropathic manifestations of anti-sulfatide antibodies are highly heterogeneous and have previously been reported to be associated with sensory axonal neuropathies with small fibers, ataxia, and pain (22). Our patient's clinical presentation is consistent with those reported in previous studies.

The observation that our patient's condition continued to deteriorate after the initial PE is a commonly observed phenomenon and is considered a natural progression of the disease. At least 25% of patients experience a decline during or shortly after treatment with IVIG or PE. This phenomenon is not attributed to drug resistance, as the patient's medical status would have continued to worsen in the absence of treatment (23). Following a brief exacerbation of symptoms, the patient gradually experienced recovery.

Although studies in Western countries have shown no significant difference between PE combined with IVIG and PE treatment alone, the sample size in these studies may not have been large enough to rule out a small beneficial effect of combination therapy (24). In addition, previous studies did not include a sufficient number of participants with axonal GBS to determine whether they responded differently to treatment compared to those with AIDP (25). Geography appears to influence the GBS electrophysiologic subtypes, with axonal subtypes being higher in Asian countries than in Europe and the United States of America (26). An observational study based in Japan found that intensive immunotherapy was superior to a single course of Propecia in serious patients (mEGOS ≥ 7 points on admission) (27). However, a randomized controlled trial conducted in the Netherlands demonstrated the ineffectiveness of a second course of IVIG (28). Differences in studies did not exclude correlations with different electrophysiological characteristics, since pathogenic mechanisms of axonal and demyelinating types could differ (7, 8). Moreover, patients with GBS have high heterogeneity, and intensified immunotherapy shows potential benefits for patients with treatment-related fluctuations and severe cases (27, 29, 30). Additionally, the mechanisms of PE and IVIG therapy are distinct. PE functions by removing circulating autoantibodies, whereas IVIG therapy neutralizes autoantibodies, inhibits complement activation, suppresses the formation of membrane attack complexes, and acts by blocking antibody production. According to preliminary evidence, PE combined with IVIG shows significant efficacy in severe pediatric cases, indicating a potential synergistic effect (30). Our patient was classified as AMSAN according to the electrodiagnostic criteria summarized by Uncini (31); his mEGOS score on day 4 of admission was 9. He gradually improved after receiving intensive immunotherapy without any significant side effects. Lee et al. reported a similarly severe case of GBS that started with ileus, followed by severe delayed paralysis and respiratory failure. The patient recovered his muscle strength after one course of IVIG, but poor gastric emptying persisted, and enteral nutritional support was unavailable. He ultimately died from a severe infection (32). In contrast, relatively mild cases of GBS presenting with ileus have been reported to respond well to IVIG (4, 33, 34). Although we do not know the outcome of PE or IVIG treatment alone in our patient, to our knowledge, this is the only reported case of severe GBS starting with paralytic ileus that has been successfully treated. More evidence and trials are required to establish a treatment plan.

## Conclusion

Clinical practitioners should consider the possibility of GBS when encountering acute abdominal pain or paralytic ileus to avoid misdiagnosis or underdiagnosis, especially during non-specialty visits. Early diagnosis and timely individualized treatment are essential to improve patient prognosis.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the studies involving humans because the authors confirmed that this study did not require a review board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

LL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original

draft, Writing – review & editing. LC: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. JL: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. YD: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. CC: Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. DC: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. YL: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. HZ: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. LZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1435817/full#supplementary-material

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