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Complement inhibition: a therapeutic turning point in the treatment of recurrent myelitis in a patient with systemic lupus erythematosus

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Abstract
Systemic lupus erythematosus (SLE) and neuromyelitis optica spectrum disorder (NMOSD) are autoimmune diseases that have been reported to coexist. We describe the case of a 61-year-old woman with long-standing SLE and Sjögren's disease who developed recurrent longitudinally extensive transverse myelitis associated with concomitant NMOSD. Despite treatment with glucocorticoids, plasma exchange, and rituximab, she experienced multiple neurological relapses, with persistent positivity of anti-aquaporin-4 antibodies and magnetic resonance imaging findings consistent with NMOSD, while SLE remained clinically inactive. Therefore, we initiated treatment with an anti-C5 monoclonal antibody for relapse prevention. To our knowledge, this is the first reported case of a patient with coexisting SLE and NMOSD treated with an anti-C5 monoclonal antibody, remaining relapse-free throughout a 22-month follow-up period.

Introduction

The occurrence of neurological manifestations, particularly myelitis, in a patient with systemic lupus erythematosus (SLE) represents a diagnostic challenge. While this presentation may be attributable to neuropsychiatric lupus (NPSLE), it may also reflect the clinical manifestation of a concomitant neuromyelitis optica spectrum disorder (NMOSD). Although uncommon, the coexistence of these two conditions has been documented.

Here, we report the first case of a patient with SLE and concomitant NMOSD who was successfully treated with an anti-C5 monoclonal antibody, after recurrent episodes of myelitis and ineffective conventional therapy.

Case Report

The case of a 61-year-old Italian woman with a 33-year history of SLE and Sjögren's disease is described. The diagnosis was established in 1996 based on a combination of clinical features, including fatigue, weight loss, fever, lymphadenopathy, arthritis of the hands and feet, malar rash, and photosensitivity, and serological positivity for antinuclear antibodies (ANA) and anti-SSA. Cyclosporine (200 mg/day) was initially prescribed and discontinued in 2001. She was then maintained on hydroxychloroquine (400 mg/day), which provided sustained clinical benefit, enabling gradual reduction to 200 mg/day over the following years. In 2010, the patient developed acute-onset lower limb weakness and urinary retention, requiring hospitalization. Brain and spinal cord magnetic resonance imaging (MRI) revealed longitudinally extensive myelitis involving the cervicothoracic spinal cord. Cerebrospinal fluid analysis demonstrated ANA positivity and low-titer anti-neuromyelitis optica (NMO) antibody reactivity. She was treated with intravenous methylprednisolone (1 g/day for 6 consecutive days), followed by three monthly cycles of intravenous immunoglobulins (0.4 g/kg for 5 days) and physiotherapy, resulting in progressive recovery of independent ambulation; however, sphincter dysfunction persisted (1).

In July 2023, the hydroxychloroquine dose was increased to 300 mg/day due to a flare of hand arthritis. In September 2023, the patient developed progressive lower-limb paraparesis, paresthesias, and hypoesthesia involving the left lower limb and left gluteal region, along with left subscapular pain. Suspecting a recurrence of myelitis, she was rehospitalized. Neurological examination revealed muscle strength graded 3/5 in the left lower limb and 4/5 in the right lower limb, brisk deep tendon reflexes (more pronounced on the left), absence of the right Achilles reflex, and plantar responses that were indifferent on the left and in flexion on the right. She also reported superficial hypoesthesia involving the left hemibody up to the D2-D3 dermatome level. Spinal MRI demonstrated longitudinally extensive cervicothoracic myelitis, with spinal cord swelling from C7-D1 to D5-D6, and a centrally located T2- and STIR-hyperintense lesion with fusiform contrast enhancement, extending approximately 9.5 cm craniocaudally and up to 0.5 cm in diameter. Cerebrospinal fluid analysis showed positivity for anti-aquaporin-4 (AQP4) antibodies and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies. Serum testing confirmed anti-AQP4 positivity and elevated anti-Ro60 titers (126.0 UA/mL), while ANA, anti-dsDNA, and anti-MOG antibodies were negative. Interestingly, the autoantibody profile differed from the previous myelitis episode, which may partly reflect the impact of prior immunosuppressive therapy. However, the clinical significance of these changes remains uncertain, and caution is warranted when interpreting variations in antibody titers in the context of ongoing treatment. The recurrence of longitudinally extensive transverse myelitis (LETM) while SLE remained clinically inactive supported the diagnosis of coexisting NMOSD rather than lupus-associated myelitis. The patient was treated with intravenous methylprednisolone (1 g/day for five days), followed by six sessions of therapeutic plasma exchange and physiotherapy, resulting in progressive clinical and radiological improvement. In November 2023, maintenance therapy with rituximab (1000 mg, followed by a second infusion 14 days later) was initiated in consultation with the neurology team, resulting in improved ambulation with the aid of a crutch and amelioration of sphincter function. In February 2024, the patient developed sudden right lower-limb weakness without sensory deficits, raising suspicion of NMOSD relapse and prompting

rehospitalization. Brain and spinal cord MRI demonstrated an extensive cervicothoracic spinal cord lesion characterized by cord swelling and predominant central T2-weighted hyperintensity, without gadolinium enhancement on post-contrast T1-weighted sequences. Serological testing confirmed positivity for anti-AQP4, anti-ENA, and anti-SSA antibodies. Treatment consisted of intravenous methylprednisolone (1 g/day for 5 days), followed by seven plasma exchange sessions and an additional 250 mg methylprednisolone bolus, resulting in clinical and radiological improvement (Figure 1). Given the relapse, rituximab was considered ineffective, and the patient was maintained on biweekly plasma exchange while awaiting initiation of eculizumab, an anti-C5 monoclonal antibody, as recommended by the neurology team. In early July 2024, she developed low back pain, right subscapular pain, left lower-limb hypoesthesia, and right gluteal paresthesias. Suspecting another NMOSD flare, she was treated with intravenous methylprednisolone (1 g/day for five days) and two plasma exchange sessions. After discharge, biweekly plasma exchange was continued from mid-July to late August. In August 2024, eculizumab therapy (900 mg weekly for four weeks, followed by 1200 mg one week later, then 1200 mg every two weeks) was initiated after meningococcal vaccination and ciprofloxacin prophylaxis (500 mg/day for five days), as recommended by the infectious disease specialist. Infusions were administered in a day-hospital setting within the Neurology Department. The last eculizumab infusion was on February 5, 2025, and subsequently the treatment was switched to another anti-C5 monoclonal antibody (ravulizumab 3300 mg) for non-medical reasons, which the patient continues to receive every eight weeks. Throughout the 22-month period of complement inhibition, the patient experienced no further clinical relapses. Follow-up brain and spinal cord MRI performed in December 2025 demonstrated stable T2-hyperintense lesions in the white matter of both hemispheres, brainstem, and cerebral peduncles, as well as in the proximal dorsal spinal cord, with no evidence of contrast enhancement. At the most recent rheumatological evaluation (June 2026), the patient remained relapse-free with an Expanded Disability Status Scale score of 6.0 (2). She was able to deambulate with mild ataxic gait, with the assistance of a single crutch and continued to experience residual sphincter dysfunction (urinary incontinence and constipation).

Discussion

SLE is a chronic autoimmune connective tissue disease characterized by multisystem involvement and a broad spectrum of clinical manifestations. Neuropsychiatric involvement is common, with a reported prevalence ranging from 12% to 95% (3), reflecting heterogeneity related to study design, inclusion criteria, and attribution of neurological symptoms to SLE.

In 1999, the American College of Rheumatology (ACR) defined 19 neuropsychiatric syndromes associated with SLE, categorized into central (12 syndromes) and peripheral (7 syndromes) nervous system involvement. More recently, the 2019 European Alliance of Associations for Rheumatology (EULAR)/ACR classification criteria introduced a weighted, domain-based system that includes a dedicated neuropsychiatric domain (4). Unlike the 1999 ACR nomenclature, which aimed to describe the spectrum of NPSLE comprehensively, the EULAR/ACR criteria include only a limited number of manifestations, such as delirium, psychosis, and seizures, selected for their higher specificity for SLE and intended primarily for classification rather than clinical diagnosis. This distinction highlights a potential diagnostic gap in patients presenting with inflammatory demyelinating syndromes, such as those observed in NMOSD, which are not encompassed within the current neuropsychiatric SLE classification domain.

Myelitis represents a rare (1-2%) but potentially severe manifestation of central nervous system (CNS) involvement in SLE and may result in significant morbidity, including permanent neurological disability (5). Although the pathogenesis of lupus-associated myelitis remains incompletely understood, several mechanisms have been proposed, including immune-mediated vasculopathy, the presence of pathogenic autoantibodies, notably antiphospholipid antibodies (6), cytokine and chemokine dysregulation, oxidative stress, and alterations in neurotransmission (7). However, the

rarity and heterogeneity of this condition, as well as the potential overlap with other demyelinating disorders, limit definitive conclusions regarding a predominant pathogenic pathway.

Neurological manifestations in patients with SLE may also result from the coexistence of NMOSD, a group of chronic inflammatory demyelinating disorders of the CNS that primarily affect the optic nerves, spinal cord, and brainstem. First described by Devic in 1894 (8), NMOSD was initially considered a variant of multiple sclerosis, but is now recognized as a distinct entity following the identification of pathogenic anti-AQP4 antibodies and anti-MOG antibodies, its characteristic relapsing course, and specific MRI features, including LETM and distinctive brain lesions (9).

NMOSD frequently coexists with systemic autoimmune diseases, most commonly Sjögren's disease and SLE (10, 11), both of which were present in our patient. The nature of this association remains incompletely understood. Current evidence supports the hypothesis that NMOSD and rheumatic diseases represent coexisting conditions in individuals with a shared predisposition to autoimmunity. Two main mechanisms have been proposed: shared genetic and/or environmental risk factors, and a pathogenic role of systemic autoimmune diseases in facilitating NMOSD development, for example, through blood-brain barrier disruption allowing circulating anti-AQP4 antibodies to access the CNS (12). Importantly, the concurrence of NMOSD and SLE should be regarded as a coexistence rather than a complication (10).

A comprehensive literature search was performed on PubMed using the search terms: ("systemic lupus erythematosus" OR "SLE") AND ("neuromyelitis optica spectrum disorder" OR "NMOSD") AND ("LETM"). The first report describing the association between SLE and NMOSD dates back to 1976, involving a young woman who developed paraparesis, urinary incontinence, and retrobulbar neuritis, with a subsequent diagnosis of SLE (13). Since then, approximately 50 cases have been reported, predominantly involving female patients in whom SLE preceded the onset of NMOSD-related neurological manifestations. Most cases were seropositive for AQP4-IgG or anti-MOG antibodies, and treatment of acute attacks generally relied on high-dose glucocorticoids and therapeutic apheresis, while maintenance therapy included immunosuppressive agents such as mycophenolate mofetil, cyclophosphamide, azathioprine, or rituximab. Notably, none of the published cases reported the use of complement inhibitors as part of their therapeutic strategy.

In patients with SLE who develop acute or recurrent neurological events, the possibility of coexisting NMOSD should always be considered (14). Early recognition and prompt initiation of appropriate therapy are crucial to prevent irreversible neurological damage. Treatment strategies for NMOSD include both management of acute attacks and long-term relapse prevention. Acute attacks are typically treated with high-dose intravenous glucocorticoids (methylprednisolone 1 g/day for 3-5 days), followed by an oral taper, while therapeutic apheresis is reserved for severe or glucocorticoid-refractory cases (15). For relapse prevention, conventional immunosuppressive therapies include azathioprine, mycophenolate mofetil, and rituximab (15). In 2019, three targeted therapies were approved for NMOSD: inebilizumab (anti-CD19), eculizumab (complement C5 inhibitor) (16), and satralizumab (anti-IL-6 receptor), all of which have demonstrated significant efficacy in reducing relapse risk.

We report the case of a woman with long-standing SLE who developed an initial episode of transverse myelitis after 19 years of disease remission, followed 13 years later by LETM fulfilling diagnostic criteria for NMOSD (Figure 2). In retrospect, the initial episode of LETM in 2010, despite low-titer anti-NMO antibody positivity, may have represented the first manifestation of NMOSD rather than SLE-associated myelitis, as it occurred in the absence of disease activity. Notably, neurological relapses occurred while SLE remained clinically inactive, supporting the diagnosis of coexisting NMOSD rather than lupus-related myelitis. The rationale for selecting complement C5 inhibition over other approved targeted therapies (such as satralizumab or inebilizumab) relies on both immunopathogenic mechanisms and clinical urgency. In AQP4-IgG-positive NMOSD, antibodies binding to AQP4 channels on astrocytic foot processes activate the classical complement cascade, leading to C5 cleavage and membrane attack complex (MAC) formation, which drives astrocyte injury and secondary demyelination (16). Following relapse under rituximab, further B-cell depletion

(inebilizumab) was deemed mechanistically redundant and unpromising. Also, switching to terminal complement inhibition was preferred over IL-6 receptor blockade (satralizumab) due to its immediate pharmacodynamic onset, rapidly arresting MAC-mediated destruction, and high relapse-free survival rates (17-19).

Conclusions

This case highlights the importance of considering NMOSD in patients with SLE who develop inflammatory myelitis, even after prolonged periods of disease remission and in the absence of active systemic manifestations. The occurrence of recurrent LETM while SLE remained clinically inactive strongly supports the concept of NMOSD as a coexisting autoimmune condition rather than a manifestation of NPSLE.

To our knowledge, this is the first reported case of a patient with concomitant SLE and NMOSD successfully treated with a complement C5 inhibitor for relapse prevention. This observation suggests that targeted NMOSD therapies, including complement inhibition, may represent an effective treatment strategy in selected patients with overlapping autoimmune diseases.

Given the lack of specific guidelines for the management of patients with coexisting NMOSD and SLE, this case underscores the need for a high index of suspicion, careful diagnostic reassessment of neurological events, and an individualized therapeutic approach. Close multidisciplinary collaboration between neurologists and rheumatologists is essential to ensure timely diagnosis and optimal long-term management, with the ultimate goal of preventing irreversible neurological disability.

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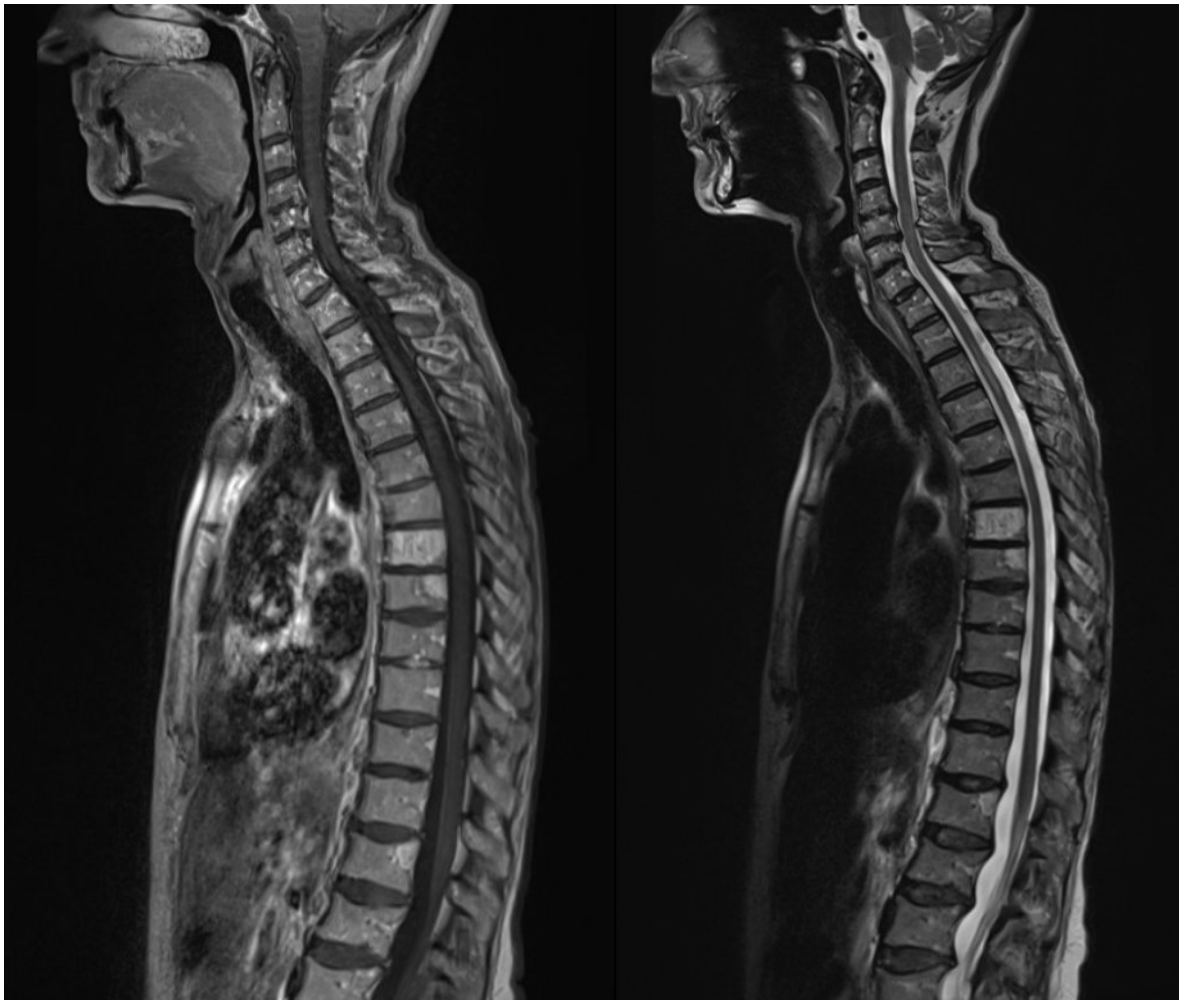


Figure 1. T2-weighted (left) and post-contrast T1-weighted (right) magnetic resonance imaging showing transverse myelitis from D2 to D4 (obtained in March 2024 after intravenous methylprednisolone and during plasma exchange).

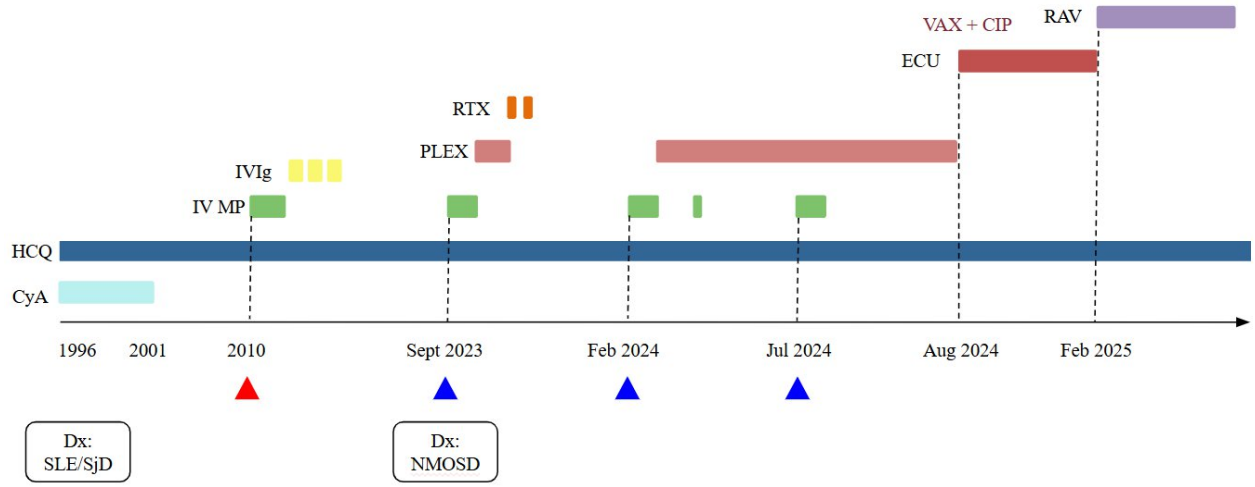


Figure 2. Clinical timeline and treatments. Red triangle indicates the first myelitis attack; blue triangles indicate subsequent attacks. Abbreviations: CIP, ciprofloxacin; CyA, cyclosporine A; Dx, diagnosis; ECU, eculizumab; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; NMOSD, neuromyelitis optica spectrum disorder; PLEX, plasma exchange; RAV, ravulizumab; RTX, rituximab; SjD, Sjögren's disease; SLE, systemic lupus erythematosus; VAX, meningococcal vaccine.