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Case Report

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Sero-negative neuromyelitis optica spectrum disorder as a presenting feature of systemic lupus erythematosus: A rare case report

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune demyelinating that predominantly affects the optic nerves and spinal cord. While AQP4-IgG seropositivity remains the diagnostic hallmark, a subset of patients presents as seronegative NMOSD, fulfilling clinical and radiological criteria in the absence of detectable antibodies. Notably, NMOSD can occur independently or coexist with other autoimmune diseases, including systemic lupus erythematosus (SLE). It is critical to differentiate NMOSD from neuropsychiatric lupus, as the treatment strategies differ significantly.

Case summary: We present a case of a 25-year-old woman with no prior history of autoimmune disease who initially presented with acute urinary retention. She subsequently developed altered mental status, bilateral lower limb weakness, and brainstem symptoms such as ptosis, involuntary facial movements, and nystagmus. Magnetic resonance imaging of the brain and spine revealed longitudinally extensive transverse myelitis (LETM), indicative of NMOSD. Serological testing revealed positive ANA, high anti-dsDNA, low complement levels, and pancytopenia, fulfilling the 2019 ACR/EULAR criteria for SLE. However, the AQP4 antibodies were negative. After treatment with intravenous methylprednisolone and five cycles of plasma exchange, the patient's neurological condition improved significantly.

Conclusion: This case highlights that NMOSD may be the initial manifestation of SLE, even in the absence of AQP4 antibodies. A high index of suspicion for NMOSD is warranted when LETM or unexplained brainstem symptoms are present, allowing for timely diagnosis and initiation of appropriate therapy.

Keywords: neuromyelitis optica spectrum disorder, systemic lupus erythematosus, central nervous system, neuropsychiatric lupus, aquaporin-4

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect nearly every organ system. Clinical manifestations range from mild (e.g., skin rashes and arthralgia) to severe, multi-organ involvement. Neuropsychiatric systemic lupus erythematosus (NPSLE) refers to neurological manifestations of SLE, typically presenting with seizures, psychosis, stroke, or chronic headaches. However, spinal cord involvement such as transverse myelitis is relatively rare and often indicates severe disease activity [1].

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune condition primarily targeting the optic nerves and spinal cord. It is frequently associated with antibodies against aquaporin-4 (AQP4) and is typically characterized by longitudinally extensive transverse myelitis (LETM) and recurrent optic neuritis [2, 3]. While NMOSD is classically associated with AQP4 antibodies, a subset of patients present with seronegative NMOSD, fulfilling the clinical and radiological criteria despite the absence of detectable antibodies. These seronegative cases pose a diagnostic challenge and require careful clinical correlation, especially when overlapping with other autoimmune conditions . Although SLE and NMOSD share immunological features such as complement activation and B-cell dysregulation, their coexistence remains rare. In seronegative cases, NMOSD may represent the first clinical manifestation of SLE, and may be misclassified as neuropsychiatric lupus if not properly recognized [4, 5].

This case report discusses a rare instance where NMOSD served as the initial manifestation of underlying SLE. The case underscores the importance of distinguishing NMOSD from central nervous system lupus for timely and accurate treatment.

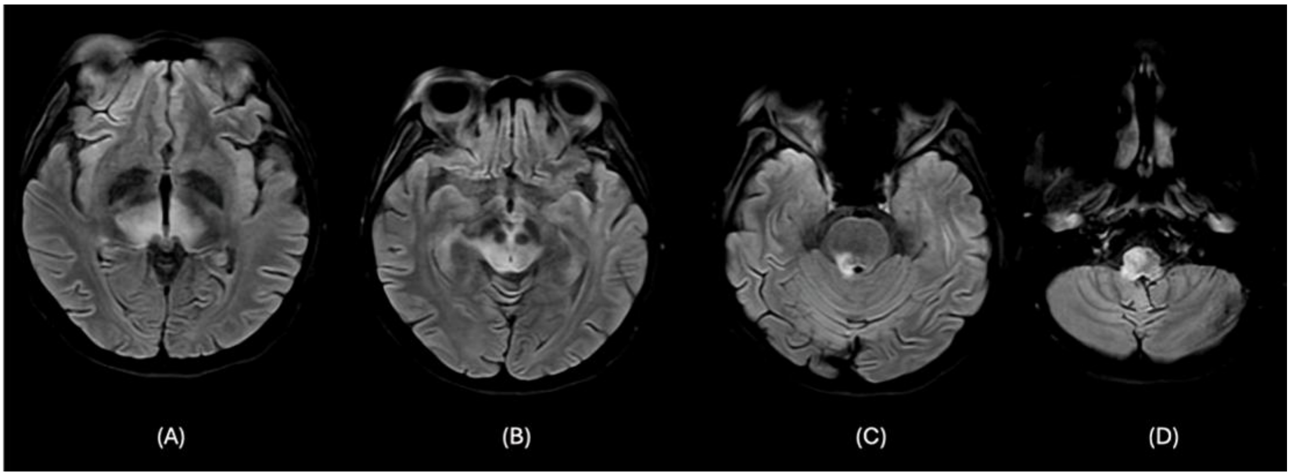

Figure 1. Axial FLAIR MRI brain sequence demonstrating hyperintense signal abnormalities in a patient with NMOSD: (A) bilateral thalamic and dorsal midbrain involvement, (B) hyperintensity in the periaqueductal region and upper pons, (C) signal changes in the pontine tegmentum and surrounding brainstem structures, & (D) extension of signal abnormalities into the medulla oblongata and inferior cerebellar peduncles (Reprinted with permission of the patient)

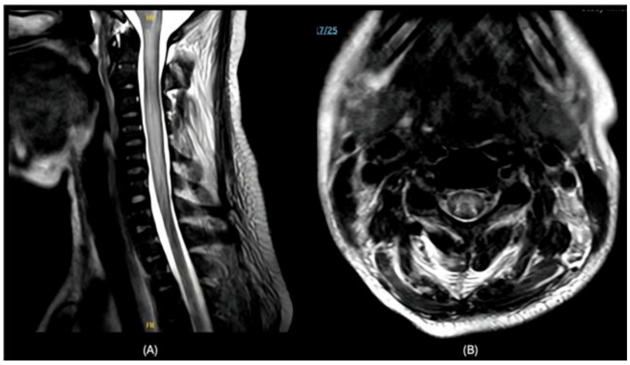

Figure 2. T2-weighted MRI of the cervical spine in a patient with AQP-4 antibody-positive NMOSD: (A) sagittal T2-weighted image demonstrates LETM with intramedullary T2 hyperintensity and cord expansion, spanning more than three contiguous vertebral segments & (B) corresponding axial T2-weighted image shows a central gray matter hyperintensity with involvement of both anterior and posterior horns, forming the characteristic "H-sign" (Reprinted with permission of the patient)

CASE PRESENTATION

A 25-year-old woman with no previous history of autoimmune disease presented with acute urinary retention, initially suspected to be due to recurrent urinary tract infections. She was discharged with a long-term urinary catheter. Subsequently, she developed significant neurological and systemic symptoms including headache, confusion, vomiting, progressive bilateral lower limb weakness and numbness, which left her bedridden for two weeks. She also reported prolonged low-grade fever, oral ulcers, hair loss, and generalized joint pain.

On examination, she exhibited brainstem signs including bilateral ptosis, intermittent orolingual dyskinesia, and vertical nystagmus. Motor examination revealed upper and lower limb strength of at least 3/5, hypertonia in the lower limbs, upgoing plantar reflexes, and intermittent tonic spams in both legs.

Laboratory investigations showed pancytopenia: white blood cell count of 3.7×10^9/L, hemoglobin level of 7.0 g/dL, and platelet count of 40×10^9/L. Peripheral blood film revealed normochromic normocytic anemia with teardrop and cigar-shaped cells, along with neutropenia and thrombocytopenia with giant platelets—features suggestive of SLE-associated cytopenia. Serological tests showed an ANA titer of 1:180, positive anti-dsDNA (68 IU/mL), and low complement levels (C3: 0.34 g/L, C4: 0.04 g/L). Anti-histone antibodies were borderline positive, while serumAQP4 antibodies was negative. Cerebrospinal fluid analysis was not performed due to personal preference. Occasionally, patients without detectable serum AQP4-IgG are later found to be sero-positive despite the presence of florid neuro-imaging features. There may be technical explanations in some cases, but antibody levels also increase with clinical relapse.

Brain MRI findings were suggestive of NMOSD and possible autoimmune encephalitis (**Figure 1**). Spinal MRI demonstrated LETM in the cervical cord, supporting a diagnosis of NMOSD (**Figure 2**) [2, 6]. MRI brain and whole spine demonstrated abnormal signal intensity seen at the bilateral thalami, peri-aqueductal grey matter, dorsal midbrain, pons and medulla. These abnormal signals demonstrate hypointense signal on T1W and hyperintense on T2W and FLAIR and were characteristic of areas with high expression of AQP4, an astrocyte protein targeted by the disease antibodies. MRI whole spine also showed longitudinal extensive transverse myelitis extending from the cranio-cervical junction to T1 level involving the central part of the cord. The preferential involvement of the central grey matter, also known as the "H-sign" can also be appreciated. These findings are consistent with the international consensus diagnostic criteria for NMOSD, which describe typical brain lesions in the thalami, hypothalamus, peri-aqueductal grey matter, and dorsal brainstem (particularly the area postrema), as well as spinal cord lesions extending over three or more vertebral segments with central grey matter predominance and T1 hypo-intensity [6]. The combined imaging findings of the brain and spinal cord were characteristic of NMOSD.

Based on the 2019 ACR/EULAR classification criteria, she fulfilled both clinical and immunological domains for SLE [7], including mucocutaneous, musculoskeletal, and hematologic features. Despite being AQP4-seronegative, her clinical presentation and neuroimaging findings strongly supported a diagnosis of NMOSD, raising the possibility of overlapping autoimmune disease. According to the 2015 international consensus diagnostic criteria, a diagnosis of seronegative NMOSD requires at least two core clinical characteristics, with dissemination in space, fulfillment of MRI requirements, a negative AQP4-IgG test, and exclusion of alternative diagnoses [8]. In her case, she exhibited acute myelitis (in the form of LETM) and acute brainstem syndrome (manifesting as ptosis, vertical nystagmus, and orolingual dyskinesia), thereby meeting the required core clinical features for seronegative NMOSD. The combination of these neurological syndromes in distinct anatomical regions, alongside characteristic MRI findings and a negative AQP4-IgG, confirms the diagnosis of seronegative NMOSD co-existing with SLE.

She was treated with 1 gm of intravenous methylprednisolone followed by five cycles of plasma exchange. She then proceeded with 6 cycles of cyclophosphamide (EURO-Lupus regime). Post-treatment, the patient regained full consciousness, and her fever, nystagmus, ptosis, and orofacial dyskinesia resolved. Her motor strength improved significantly, with hip strength rated at 4+ and complete restoration of knee, ankle, and foot movements (5/5). A repeat serum AQP4-IgG assessment will be considered if she were to have another relapse.

DISCUSSION AND CONCLUSIONS

SLE is an autoimmune disease with a wide range of clinical manifestations, including neuropsychiatric involvement (NPSLE), which typically presents as seizures, psychosis, or cerebrovascular events. Spinal cord involvement, such as longitudinal extensive transverse myelitis, is uncommon and should prompt evaluation for alternative diagnoses like NMOSD [1, 2].

In this case, the patient presented with acute urinary retention, progressive lower limb weakness, and brainstem features. MRI revealed LETM, and despite being AQP4-seronegative, her clinical picture aligned with seronegative NMOSD while also fulfilling the ACR/EULAR criteria for SLE [7].

This clinical overlap has been reported in several other cases. For example, a 27-year-old Indian woman with SLE developed urinary retention, paraparesis, and AQP4-positive LETM, and responded well to dexamethasone and rituximab [9]. Another case involved a 41-year-old woman with established SLE who developed AQP4-positive NMOSD presenting with similar myelitis, managed with satralizumab, plasmapheresis, and corticosteroids [10]. Similarly, a 44-year-old woman with chronic cutaneous lupus presented with a brainstem syndrome including nausea, vomiting, vertigo, and cranial nerve involvement; MRI showed lesions in the area postrema, and she tested positive for AQP4 antibodies. She was treated successfully with intravenous methylprednisolone and rituximab [11]. Another case described a 24-year-old woman with longstanding SLE who developed LETM and optic neuritis, with pseudo-athetosis and vision loss. Despite receiving high-dose corticosteroids and cyclophosphamide, she only improved after plasmapheresis and was maintained on rituximab [11]. Lastly, a 42-year-old woman with SLE presented with optic neuritis and upper limb weakness, with MRI showing chiasmatic neuritis and chronic spinal cord lesions. She was AQP4-positive and required plasmapheresis after incomplete steroid response [11].

While most reported cases involve AQP4-positive NMOSD coexisting with SLE, our case represents a rare but important variant—AQP4-seronegative NMOSD presenting as the first manifestation of SLE. Emerging evidence demonstrates that NMOSD frequently overlaps with SLE, and that its clinical and radiological phenotype remains largely consistent regardless of antibody status [13]. Importantly, seronegative NMOSD behaves similarly to classical NMOSD and may be misclassified as neuropsychiatric lupus (NPSLE) potentially delaying early immunotherapy during a period of heightened relapse risk [13]. In our patient, despite AQP4 sero-negativity, classical NMOSD features were evident on MRI, including LETM with H-sign and brainstem involvement, and she responded well to IV methylprednisolone, plasma exchange, and cyclophosphamide. This presentation is consistent with comparative studies demonstrating no major differences in clinical, imaging, or laboratory features between AQP4-seropositive and AQP4-seronegative NMOSD, aside from a later age of onset and more frequent optic nerve involvement in seropositive disease, supporting the view that seronegative NMOSD represents a clinically valid phenotype rather than a distinct entity [14]. Real-world cohort data from Taiwan further reinforce this concept, demonstrating that patients with AQP4-seronegative NMOSD exhibit comparable clinical severity, relapse patterns, and core syndromic presentations to seropositive disease, underscoring the primacy of clinical–radiological phenotype over antibody status in diagnostic decision-making [15].

This case therefore highlights the diagnostic challenge of distinguishing seronegative NMOSD from neuropsychiatric lupus (NPSLE), however the features like LETM, brainstem syndromes, and classical MRI patterns strongly support the diagnosis of seronegative NMOSD coexisting with SLE rather than a manifestation of NPSLE. In line with recent consensus guidelines, this case reinforces that AQP4-IgG negativity should not delay NMOSD diagnosis or treatment when core clinical and radiological features are present and alternative etiologies have been carefully excluded [16]. Importantly, the case reinforces that AQP4-negative status should not delay NMOSD diagnosis or treatment. Early recognition and humoral-targeted immunotherapy remain critical to prevent permanent neurologic damage. To our knowledge, this is the first reported Malaysian case of AQP4-seronegative NMOSD presenting with new-onset SLE, highlighting the need for high clinical suspicion even in seronegative contexts.

NMOSD is thought to be caused by autoantibodies directed against AQP-4, a water channel protein on astrocytes. These antibodies activate the complement system, resulting in astrocyte injury, demyelination, and central nervous system inflammation [3]. Both NMOSD and SLE are associated with humoral immune dysfunction, including B-cell hyperactivity, complement activation, and type I interferon involvement [4, 5].

Differentiating NMOSD from NPSLE is critical, as the underlying mechanisms and treatment differ. NPSLE generally presents with vague neuropsychiatric symptoms such as mood changes, headaches, seizures, or features of vasculitis. In contrast, NMOSD is characterized by:

(1) LETM affecting three or more vertebral segments,

(2) bilateral optic neuritis, and

(3) brainstem or area postrema syndromes [6].

MRI findings in NMOSD typically involve central cord and brainstem lesions, whereas NPSLE more often shows cortical infarcts or diffuse white matter changes related to vasculitis or thrombotic events [6]. In our case, the presence of brainstem symptoms (ptosis, nystagmus, and dyskinesia), LETM on spinal imaging, and a rapid clinical response to high-dose steroids and plasma exchange are more consistent with NMOSD. Furthermore, the absence of seizures, psychosis, or infarct-like MRI lesions which are typical of NPSLE further supports the diagnosis of NMOSD over NPSLE

The 2019 ACR/EULAR SLE classification criteria do not specifically recognize NMOSD or LETM as distinct neuropsychiatric manifestations of lupus. Instead, they list broader terms such as "psychosis" or "mononeuritis multiplex" [7]. This lack of specificity may contribute to diagnostic confusion, where true cases of NMOSD particularly the seronegative forms are misclassified as NPSLE, potentially delaying appropriate and targeted treatment. In our case, despite this diagnostic gap, the clinical presentation, MRI findings, and therapeutic response supported a distinct diagnosis of NMOSD overlapping with SLE, rather than a primary neuropsychiatric lupus manifestation.

Early identification and treatment of NMOSD are crucial, particularly in AQP4-negative cases. Management includes

(1) **acute phase:** high-dose corticosteroids and plasmapheresis and

(2) **maintenance therapy:** immunosuppressants such as rituximab, azathioprine, mycophenolate mofetil, or targeted biologics like eculizumab or inebilizumab [8].

Our patient responded well to early intervention which included high-dose intravenous methylprednisolone and plasma exchange. These treatments align with the standard acute-phase management of NMOSD, aimed at halting active demyelination and reducing neurological damage. This approach is in line with recent advances in NMOSD management, which highlight the value of starting immunotherapy early to address both the acute inflammatory attack and the prevention of future relapses, while long-term treatment has increasingly shifted toward B-cell–targeted therapies and biologics rather than nonspecific immunosuppression [12].

In view of her underlying SLE, which was newly diagnosed during this episode, cyclophosphamide was introduced as part of long-term immunosuppressive therapy to control both CNS and systemic disease activity.

While she fulfilled the 2019 ACR/EULAR criteria for SLE, her presentation marked by LETM, brainstem signs, and a rapid response to plasma exchange was more consistent with NMOSD than classical neuropsychiatric lupus (NPSLE). Importantly, the absence of hallmark NPSLE features such as seizures, psychosis, or infarct-like lesions on MRI further supported this distinction.

Although AQP4 antibodies were negative, the presence of central cord lesions with an H-sign, brainstem involvement, and typical clinical course align with a diagnosis of AQP4-seronegative NMOSD. Simultaneously, her hematological manifestations and systemic features confirmed an underlying diagnosis of SLE. Therefore, this case is best interpreted as a coexisting presentation of seronegative NMOSD and new-onset SLE, representing two distinct but immunologically linked autoimmune diseases.

This case underscores the need to consider NMOSD as a potential early manifestation of SLE, even in AQP4-seronegative patients. Differentiating NMOSD from NPSLE. is critical, as both require distinct diagnostic and therapeutic approaches. The patient's significant clinical improvement after corticosteroids and plasma exchange emphasizes the necessity of early recognition and intervention. Clinicians should maintain a high level of suspicion for NMOSD in SLE patients presenting with LETM or unexplained brainstem symptoms and begin appropriate treatment without waiting for antibody confirmation.

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