



Longitudinally Extensive Transverse Myelitis

The borderline of neuromyelitis optica and systemic lupus erythematosus.

By Lakshmi Leishangthem, MD; Pooja SirDeshpande, MD; Saman Zafar, MD; Ylec Mariana Cardenas, MD; Aparna Prabhu, MD; and David Roby, MD



Case

Clinical Presentation

A right-handed African-American woman, age 61, presented with multiple comorbidities including a 22-year history of well-controlled systemic lupus erythematosus (SLE); rheumatoid arthritis, treated with chronic prednisone therapy; Sjögren's syndrome; gout; low-grade mucosa-associated lymphoid tissue (MALT) lymphoma of left parotid gland status postresection; and hepatitis C. Ms. A came to the emergency depart-

ment with acute onset of constrictive, band-like sensations around her chest associated with paresthesia and numbness in her trunk and bilateral lower extremities and subsequent development of urinary incontinence. On examination, she was found to have mild weakness of bilateral lower extremities, loss of sensation to all modalities below the T4 level, and sensory ataxia leading to an unsteady gait. Her visual acuity, color vision, and pupillary light reaction were intact bilaterally. Ms. A's brain MRI had findings of mild patchy signal abnormalities in cerebral white matter that were consistent with small vessel ischemic changes. Cervical, thoracic, and lumbar spine MRI findings included an expansive T2 hyperintense signal measuring 5.8 cm from T2 to T5, consistent with longitudinally extensive transverse myelitis (LETM) (Figure). Postcontrast imaging findings of abnormal enhancement at the T3 to T4 level were present.



Figure 1. MRI cervical and thoracic spine showing a T2 to T5 longitudinally extensive hyperintense lesion consistent with the diagnosis of neuromyelitis optica.



Differential Diagnosis

Our working differential diagnosis included a primary or metastatic neoplasm because of Ms. A's history of MALT lymphoma, a demyelinating or inflammatory lesion because of her history of autoimmune disease, or an infectious process because of her chronic immune suppression with steroid use and anti-tumor necrosis factor- α (TNF- α) agents.

Diagnostic Studies

Ms. A's blood analysis findings included erythrocyte sedimentation rate (ESR) of 44, antinuclear antibody (ANA) titer of 1:2560 with a speckled pattern suggestive of SLE, normal complement 3 (C3) levels (116 mg/dL, normal range 90-180 mg/dL) but low complement 4 (C4) levels (14 mg/dL, normal range 16-47 mg/dL), and a negative viral panel for hepatitis C, varicella zoster, and herpes simplex. Liver function, coagulation profile, renal function, urine and C-reactive protein (CRP) test results were unremarkable. She underwent lumbar puncture and cerebrospinal fluid (CSF) analysis, with unremarkable findings (white blood cell count 0, red blood cell count 44, glucose 73, protein 37.4).

Ms. A had a CT of her chest, abdomen, and pelvis to rule out any primary neoplasm or infection, including tuberculosis, given that she was previously treated with anti-TNF- α for rheumatoid arthritis. An ocular coherence tomography (OCT) showed no evidence of retinal nerve fiber layer thinning, ruling out optic neuritis (ON).

Treatment and Follow-Up

Ms. A was started on pulse methylprednisone treatment that continued for 3 days when her CSF antibody study results were found negative for oligoclonal bands and positive for aquaporin-4 (AQP4) antibody confirming the diagnosis of neuromyelitis optica (NMO). She was then treated with 2 doses of 1,000 mg rituximab intravenously and had significant improvement of her symptoms after the second dose. She is receiving maintenance therapy with prednisone and mycophenolate and is doing well without no flare-ups to date.

Discussion

Diagnosis

A severely disabling, autoimmune demyelinating disorder of the central nervous system that selectively targets optic nerves and spinal cord, NMO is characterized by LETM that involves 3 or more vertebral segments and recurrent episodes of ON.¹⁻³ Until 2004, NMO was considered a variant of multiple sclerosis (MS). The groundbreaking discovery of AQP4 autoantibody (AQP4-Ab) showed instead that NMO has a distinct autoantibody-mediated astrocytopathy, and the presence of this AQP4-Ab confirms diagnosis of NMO with 100% specificity.¹⁻³



CLINICAL GEMS

Presence of AQP4-Ab confirms NMO with 100% specificity.

The absence of AQP4-Ab and presence of CSF-specific oligoclonal bands suggests MS when the clinical presentation and imaging findings meet the revised McDonald 2017 criteria that require dissemination in space and time.⁴ The lesions of MS are typically cerebellar, periventricular, and cortical/juxtacortical, involving the corpus callosum; in contrast, lesions of NMO typically involve the dorsal brainstem (area postrema), periependymal region in the diencephalon, hemispheric white matter, and areas adjacent to the lateral ventricles. It is important to differentiate NMO from MS and other demyelinating conditions because both treatments and prognoses differ.

Both organ-specific and nonorgan-specific autoimmune disorders (eg, SLE, rheumatoid arthritis, antiphospholipid antibody syndrome, Sjögren's syndrome, myasthenia gravis, celiac disease, ulcerative colitis, autoimmune hypothyroidism, psoriasis, scleroderma, chronic inflammatory demyelinating polyneuropathy, paraneoplastic disorders, insulin-dependent diabetes mellitus, and autoimmune encephalitis) are associated with NMO in up to 20% to 30% of patients.⁵ Identification of AQP4-Ab as a biomarker for NMO allows the disease to be differentiated from other autoimmune diseases. Although neuropsychologic complications of lupus may occur in up to 60% of patients, LETM is uncommon and has been reported in only 1% to 2% of patients with SLE in some large case series.^{5,6} Multidisciplinary, longitudinal care coordination that includes neurology, rheumatology, and physical and rehabilitation medicine is required to ensure proper identification of this small subset of patients with NMO and SLE and to enhance early recognition of NMO for patients presenting with a first central nervous system (CNS) event, especially LETM.

Epidemiology

Although the acute presentation of transverse myelitis in a patient with SLE may deter further workup for other coexisting autoimmune conditions, SLE-related myelitis is rare and frequently presents as acute transverse myelitis (ATM) rather than LETM.⁶ The onset of ATM may be acute or subacute, with symptoms including weakness in the lower extremities, paresthesia, sphincter disturbances, and sensory level dysfunction at the thoracic segments.⁷ The main clinical features of NMO consist of ON and LETM.^{1,7}

There are an estimated 4,000 people with NMO in the US and approximately 250,000 people worldwide.⁵



The prognosis of NMO, which presents with a monophasic or relapsing form is poor compared with SLE myelitis.⁵⁻⁸ A small subset of patients with NMO (20%-30%) can have coexisting autoimmune diseases like lupus, Sjögren's syndrome, and rheumatoid arthritis. Our case reiterates the strong association of NMO with other systemic autoimmune disorders. In a patient with an autoimmune disorder presenting with myelitis, early testing for NMO can help with prognostication and treatment optimization.

Although 50% to 60% of patients with SLE develop neurologic complications ranging from mild headache and vision changes to acute psychosis, seizures, and stroke, transverse myelitis has been reported in only 1% to 2% of patients with lupus.^{5,7} Although the prevalence of LETM in patients with SLE is unknown, a recent systematic review of the literature between 1966 and 2008 included 22 published cases of SLE with LETM.⁹



CLINICAL GEMS

Other autoimmune disease occurs in 20% to 30% of patients with NMO and 13% to 15% of patients with SLE have NMO but LETM is rare in patients with SLE (1%-2%).

Comorbid SLE and NMO is rare and the exact prevalence of NMO in patients with SLE is unknown. In a recent meta-analysis of 104 cases of people with SLE who also had demyelinating syndromes (DS), NMO was present in 13.5% (14/104) of patients. The initial presentation in 71.4% (10/14) of these patients was LETM.¹⁰

Pathophysiology

There is increasing evidence that LETM in NMO is characterized by antibody-mediated neutrophilic degranulation and chemotactic damage. There is likely a pathogenic role of the NMO immunoglobulin G (IgG) antibody in mediating a humorally mediated spinal cord microangiopathy.¹⁰⁻¹³

Treatment

Patients with established NMO or relapsing NMO spectrum disorder are typically treated with immunosuppressive therapies that suppress B cells or antibody production, most commonly azathioprine, rituximab, or mycophenolate.¹⁴⁻¹⁷ Rituximab, a monoclonal antibody against the protein CD20, depletes mature and precursor B cells, reduces disease activity, and prevents disability.¹⁸⁻²²

Although cyclophosphamide and methotrexate are commonly employed therapies for autoimmune disease that may also favorably affect NMO, there may be other



CLINICAL GEMS

For patients with NMO and SLE, early initiation of antibody and B-cell-targeted therapies (eg, IVIG, rituximab, PLEX, or intravenous pulse steroids with cyclophosphamide) may mitigate further episodes of ON or myelitis.

therapeutic issues making collaborative team-based care appropriate, especially for patients with severe systemic manifestations, evidence of vasculitis, or inadequate response to immunosuppression.

Aquaporin-4 autoantibody seropositive LETM is associated with a high risk (>60%) of neurologic relapse within 1 year, making timing and selection of immunosuppressive therapy in patients with comorbid NMO and SLE crucial.^{5,6,14} The cornerstone of treatment for autoimmune transverse myelitis is concomitant high-dose corticosteroids with intensive immunosuppressive therapy (eg, cyclophosphamide). Aggressive, early treatment is crucial for a favorable response.⁶

Studies and existing guidelines indicate that patients with DS and SLE should receive either high-dose methylprednisolone pulses (500-1000 mg daily for 3 or 5 days) with cyclophosphamide pulses (500 mg every 2 weeks for 3 months or monthly doses of 750 mg/m² body surface for 3-6 months according to severity and clinical response) or rituximab (1,000 mg intravenously once every 2 weeks for 2 doses, repeated every 6 months or 375 mg/m² once weekly for 4 weeks, repeated every 6 months) as first-line prophylactic therapy for NMO. Mycophenolate mofetil (1-3 g/d), mitoxantrone (12 mg/m² every 3 months), methotrexate or cyclophosphamide (7-25 mg/kg monthly for 6 months) are considered second-line therapy.

Monoclonal antibody therapies that interfere with TNF- α function, including infliximab, adalimumab, or etanercept and immunomodulatory agents (ie, interferon- β) should be avoided because they may provoke a demyelinating process.¹⁸

Prognosis

Recent studies reported that if a patient has a DS secondary to SLE, it could be life-threatening or lead to severe disability in a high proportion of affected patients; those with NMO have the worst prognosis.^{14,16} The major cause of disability is LETM followed by ON. By itself, NMO has very poor clinical outcomes with most patients having irreversible, severe neurologic disability. Research suggests that the presence of NMO-IgG antibodies may be associated with an increased risk (> 60%) of relapse of LETM and

**CLINICAL GEMS**

SLE may present with different demyelinating syndromes including LETM; when associated with NMO, the prognosis is less favorable. Autoantibody to NMO (IgG) can be a valuable prognostic tool.

development of ON.^{5,6,14} In a prospective study, risk of developing recurrent myelitis or new-onset ON in patients with an isolated LETM was more than 50% among those who were NMO-IgG seropositive, compared with 0% in those who were NMO-IgG seronegative.¹⁴ An early search for AQP4-Ab should always be performed in patients with SLE who have signs of demyelination to identify those with NMO who are at high risk for relapse and worse prognosis.^{9,10,23-25}

Controlled studies and development of a standardized registry for patients with SLE that includes LETM and NMO could help to develop an effective treatment strategy and targeted management plan for this debilitating illness. ■

1. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006;66:1485-1489.
2. O'Riordan JL, Gallagher HL, Thompson AJ, et al. Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. *J Neuro Neurosurg Psychiatry*. 1996;60:382-387.
3. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364(9451):2106-2112.
4. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
5. Iyer A, Elson L, Appleton R, et al. A review of the current literature and a guide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica. *Autoimmunity*. 2014;47(3):154-161.
6. Kovacs B, Lafferty TL, Brent LH, et al. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of literature. *Ann Rheum Dis*. 2000;59:120-124.
7. Kitley JL, Leite MI, George JS, et al. The differential diagnosis of longitudinally extensive transverse myelitis. *Mult Scler*. 2012;18(3):271-285.
8. Tellez-Zenteno JF, Remes-Troche JM, Negrete-Pulido RO, et al. Longitudinal myelitis associated with systemic lupus erythematosus: clinical features and magnetic resonance imaging of six cases. *Lupus*. 2001;10:851-856.
9. White C, Leonard B, Patel A. Longitudinally extensive transverse myelitis: a catastrophic presentation of a flare-up of systemic lupus erythematosus. *CMAJ*. 2012;184(3):197-200.
10. Piga M, Chessa E, Peltz MT, et al. Demyelinating syndrome in SLE encompasses different subtypes: do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis. *Autoimmun Rev*. 2017;16(3):244-252.
11. Wingerchuk DM. Evidence for humoral autoimmunity in neuromyelitis optica. *Neural Res*. 2006;28(3):348-353.
12. Kovacs K, Kalluri SR, Boza-Serrano A, et al. Change in autoantibody and cytokine responses during the evolution of neuromyelitis optica in patients with systemic lupus erythematosus: a preliminary study. *Mult Scler*. 2016;22(9):1192-1201.
13. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain*. 2002;125:1450-1461.
14. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol*. 2006;59(3):566-569.
15. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: clinical features, immunopathogenesis and treatment. *Clin Exp Immunol*. 2014;176(2):149-164.
16. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. *Mult Scler*. 2012;18(1):5-10.
17. Minagar A, Sheremata WA. Treatment of Devic's disease with methotrexate and prednisone. *Int JMS Care*. 2000;2:43-49.
18. Bosch X, Saiz A, Ramos-Casals M, et al. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol*. 2011;7(3):165-172.
19. Scott TF, Frohman EM, De Seze J, et al. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis. *Neurology*. 2011;77:2128-2134.
20. Adawi M, Bisharat B, Bowirrat A. Systemic lupus erythematosus (SLE) complicated by neuromyelitis optica (NMO - Devic's disease): clinic-pathological report and review of the literature. *Clin Med Insights Case Rep*. 2014;7:41-47.

21. Damato V, Evoli A, Iorio R. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. *JAMA Neurol*. 2016;73(11):1342-1348.
22. Huang LK, Chung CC, Chen BZ, et al. Systemic lupus erythematosus presented as extensive longitudinal myelitis. *Acta Neurol Taiwan*. 2013;22(2):67-71.
23. Nardone R, Fitzgerald RT, Bailey A, et al. Longitudinally extensive transverse myelitis in systemic lupus erythematosus: case report and review of the literature. *Clin Neurol Neurosurg*. 2015;129:57-61.
24. Jain RS, Kumar S, Mathur T, et al. Longitudinally extensive transverse myelitis: a retrospective analysis of sixty-four patients at tertiary care center of North-West India. *Clin Neurol Neurosurg*. 2016;148:5-12.
25. Jarius S, Jacobi C, de Seze J, et al. Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. *Mult Scler*. 2011;17(9):1067-1073.

Lakshmi Leishangthem, MD

Neurology Resident
Department of Neurology
Albert Einstein Medical Center
Philadelphia, PA

Pooja SirDeshpande, MD

Research Fellow
Department of Neurology
Yale School of Medicine,
New Haven, CT

Saman Zafar, MD

Neurology Resident
Department of Neurology,
Albert Einstein Medical Center,
Philadelphia, PA

Ylec Mariana Cardenas, MD

Neurology Resident
Department of Neurology
Albert Einstein Medical Center
Philadelphia, PA

Aparna Prabhu, MD

Associate Program Director
Department of Neurology
Albert Einstein Medical Center
Philadelphia, PA

David Roby, MD

Program Director
Department of Neurology
Albert Einstein Medical Center,
Philadelphia, PA