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Reversible Cerebral Vasculopathy, Transverse Myelitis, and Active Systemic Lupus Erythematosus in an Aquaporin-4 Antibody–Positive Patient

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Organ-specific and nonorgan-specific autoimmune diseases commonly coexist with aquaporin-4 antibody (AQP4-IgG)–positive neuromyelitis optica spectrum disorder (NMOSD). We report an unusual case in which a young woman with known systemic lupus erythematosus (SLE) was discovered to be AQP4-IgG seropositive when she developed simultaneous severe longitudinally extensive transverse myelitis, reversible intracranial vasculopathy, cutaneous vasculitis, and myocarditis. We discuss the pathogenic mechanisms that may underlie systemic and CNS disease activity in these coexisting diseases.

Case Description

A 27-year-old woman with a 10-year history of SLE treated with mycophenolate mofetil and hydroxychloroquine was transferred to our facility for rapidly progressive sensorimotor paraparesis with areflexia, a thoracic sensory level (T6–T8), and urinary retention that developed over 36 hours. Her symptoms started 6 days earlier with fever, headache, nausea, vomiting, back spasms, and pruritic skin eruptions involving the right cheek, left shoulder, upper back, and lower abdomen.

Spinal MRI showed extensive T2 hyperintensity involving the entire spinal cord from the conus to the lower medulla (figure, A.a–e). CSF analysis showed lymphocytic pleocytosis (152 nucleated cells per microliter with 85% lymphocytes, 8.5% neutrophils, 5.2% monocytes, and 1.3% eosinophils), hypoglycorrhachia of 29 mg/dL, elevated CSF protein of 299 mg/dL, negative oligoclonal bands, and elevated CSF IgG index of 1.94. Laboratory testing showed elevated inflammatory markers (C-reactive protein 25.2 mg/dL and erythrocyte sedimentation rate 19 mm/h), low complement levels (C3 47 mg/dL, C4 13 mg/dL), and positive titers for antinuclear antibodies, anti-Ro (SS-A), and DNA double-stranded antibodies (>12 U, >8 U and 305 IU/mL, respectively), as well as elevated cardiac markers (troponin T 157 ng/L, creatinine kinase 1,387 U/L, and N-terminal-pro hormone BNP8198 pg/mL). Serum AQP4-IgG was positive at a titer of >1:100,000; myelin oligodendrocyte glycoprotein and antiphospholipid antibodies were negative. Transthoracic echocardiogram demonstrated reduced left ventricular ejection fraction of 49%, and skin biopsy of the rash demonstrated leukocytoclastic vasculitis (figure, E.a and b). Brain MRI demonstrated scattered, nonenhancing T2 hyperintensities in the deep subcortical white matter, brainstem, and cerebellum and a punctate periventricular infarct (figure, B.a and b). MRI brain angiogram (MRA) on day 3 of admission showed segmental narrowing and dilation involving small and medium sized vessels (figure, C.a and b).

A diagnosis of NMOSD with AQP4-IgG and SLE-related CNS vasculopathy and/or vasculitis was made. Treatment with IV methylprednisolone, plasma exchange, and one cycle of IV

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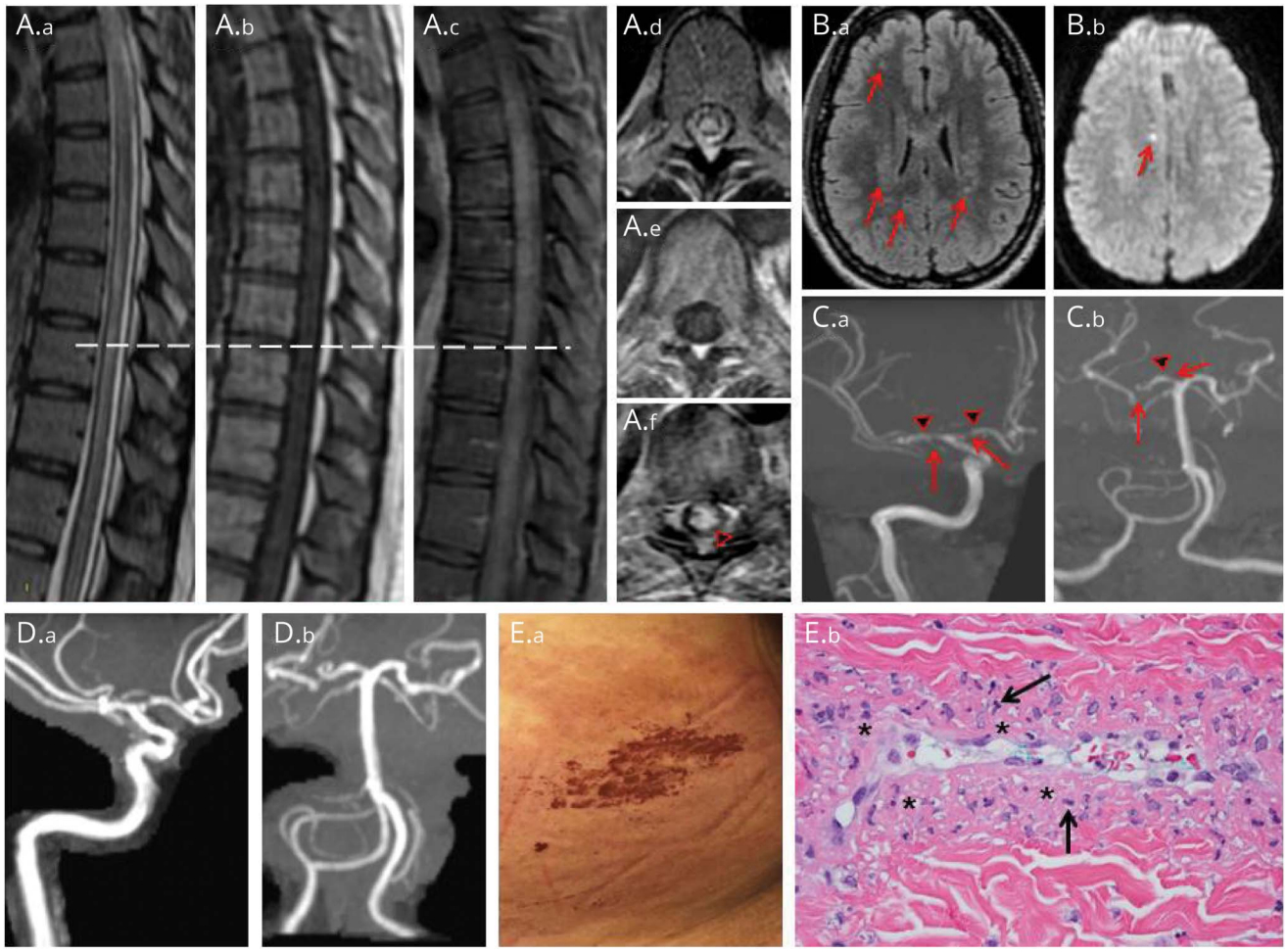
Figure Simultaneous Transverse Myelitis, Reversible Cerebral Vasculopathy, and Cutaneous Vasculitis



(A.a) Sagittal T2-weighted fast spin echo (FSE) MRI of the thoracic spine demonstrating extensive T2 hyperintensity of the entire thoracic cord and involving the cervical cord (image not shown). (A.b) Sagittal T1-weighted MRI spine without gadolinium contrast. (A.c) Sagittal T1-weighted MRI spine with gadolinium contrast demonstrating mild and diffuse thoracic cord enhancement. (A.d) Axial T2-weighted FSE, (A.e) axial T1-weighted precontrast and (A.f) postcontrast thoracic spine images all taken at the same level (white line) demonstrating centrally located T2 hyperintense and enhancing lesions (arrowhead). (B.a) Fluid-attenuated inversion recovery MRI of the brain demonstrating scattered, nonenhancing T2 hyperintensities in the deep subcortical white matter (arrows). (B.b) Diffusion-weighted imaging reveals a punctate right periventricular focus of diffusion restriction (arrow), with corresponding correlate on apparent diffusion coefficient imaging (not shown). (C.a and C.b) MRI brain angiogram (MRA) on day 3 of admission showing segmental narrowing (arrows) and dilation (arrowheads) involving the right M1 middle cerebral artery (C.a), right A1 anterior cerebral artery (C.a), and right P1 posterior cerebral artery (C.b). (D.a and D.b) repeat MRA on day 12 of admission showing significant improvement in the appearance of the intracranial vasculature. (E.a) Patient's photograph depicting an erosive skin rash in the left paraumbilical region. (E.b) Skin biopsy of the rash demonstrating leukocytoclastic vasculitis with perivascular neutrophilic (arrows) and histiocytic dermal inflammation with marked fibrin deposition (asterixes) surrounding thin-walled superficial vessels (hematoxylin-eosin; original magnification ×400).

cyclophosphamide was initiated. On day 12 of admission, the patient developed severe thunderclap headache and repeated MRA showed significant improvement in the appearance of the intracranial vasculature (figure, D.a and b), suggesting reversible vasoconstriction rather than vasculitis as the likely mechanism. The patient was transitioned to oral mycophenolate mofetil and IV rituximab. At the 6-month follow-up, the patient showed significantly improved quadriparesis with good grip strength and antigravity movement in lower extremities.

Discussion

NMOSD is a rare but well-documented and potentially devastating coincident disease in patients with SLE.[1] A high prevalence of AQP4-IgG had previously been demonstrated in patients with connective tissue disease and clinical signs of NMOSD.[2] More recently, Asgari et al.[3] examined the prevalence of AQP4-IgG in a prospective cohort of 208 patients with SLE and reported AQP4-IgG in only 2 of 30 patients with neuropsychiatric SLE (NPSLE), both of whom had myelitis. These findings demonstrate that AQP4-IgG retain a high specificity for NMOSD in the setting of SLE, suggesting 2 distinct but overlapping disease entities.

The simultaneous occurrence of active SLE, AQP4-NMOSD, and CNS vasculopathy in our case is intriguing and raises important questions as to whether common disease mechanisms exist. Interestingly, Birnbaum et al. had described a

subset of patients with SLE-myelitis and similar presentation of flaccidity-hyporeflexia, inflammatory prodrome, and urinary retention in the setting of active SLE. However, unlike in our case, most of these were AQP4-IgG seronegative.[4] Serum-derived autoantibodies are central in the pathogenesis of AQP4-NMOSD and thought to mediate several pathologic manifestations in NPSLE.[5] Furthermore, complement activation is a critical mediator of tissue damage in both SLE and AQP4-NMOSD.[6] Notably, production of proinflammatory cytokines, immune complex formation, and vascular injury in NPSLE can lead to disruption of the blood-brain barrier (BBB) and facilitate CNS entry of pathogenic autoantibodies.[7]

To our knowledge, this is the first reported case of AQP4-IgG positive NMOSD with reversible cerebral vasculopathy in the setting of active SLE. Systemic inflammation, complement activation, and increased permeability of the BBB are important mechanisms in NPSLE and may be contributing factors to both vascular injury and NMOSD. A better understanding of the pathogenic mechanisms involved will be instrumental in developing future preventative and therapeutic strategies.

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Amir A. Mbonde, MBChB	Mayo Clinic, Arizona	Conceptualized and drafted the figure, literature review, and revised the manuscript for intellectual content
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