

Optic neuritis and recurrent myelitis in a woman with systemic lupus erythematosus

Julius Birnbaum* and Douglas Kerr

SUMMARY

Background A 38-year-old woman with systemic lupus erythematosus presented with headaches and bilateral hearing loss. Brain MRI was initially suggestive of small-vessel disease developing in the context of neuropsychiatric systemic lupus erythematosus. Several months later, the patient developed optic neuritis, followed by recurrent attacks of myelitis.

Investigations MRI of the spine revealed multifocal regions of myelitis affecting the cervical spine. Serological evaluation revealed the presence of neuromyelitis optica-IgG antibodies. MRI of the brain was nondiagnostic for multiple sclerosis.

Diagnosis Recurrent myelitis and optic neuritis, occurring in the context of neuromyelitis optica (also known as Devic's syndrome).

Management The patient had recurrent attacks of myelitis despite treatment with pulse cyclophosphamide. After initiation of rituximab, the patient experienced symptomatic improvement and had no further attacks of optico-spinal disease.

KEYWORDS multiple sclerosis, myelitis, neuromyelitis optica, optic neuritis, systemic lupus erythematosus

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify conditions to be considered in the differential diagnosis of white matter lesions in patients with systemic lupus erythematosus.
- 2 List clinical features seen in subacute sclerosing panencephalitis.
- 3 Describe presenting features of multiple sclerosis.
- 4 Describe diagnostic features of neuromyelitis optica.
- 5 Identify the most effective treatment for neuromyelitis optica.

Competing interests

The authors, the Associate Publisher R Ashton and the CME questions author D Lie declared no competing interests.

THE CASE

A 38-year-old African-American woman, with a 2-year history of systemic lupus erythematosus (SLE), was referred for evaluation of recurrent episodes of myelitis and optic neuritis (ON). The patient's course of SLE was previously characterized by antinuclear antibody positivity, anti-dsDNA antibody positivity, polyarthritis, and malar rash with photosensitivity; her symptoms were controlled with hydroxychloroquine treatment. The patient experienced subacute onset of right ear otalgia and a "throbbing", temporal headache. She concomitantly developed bilateral sensorineural hearing loss. At the time of these symptoms (designated as month 0), MRI of the brain revealed a cystic lesion in the left frontal lobe,

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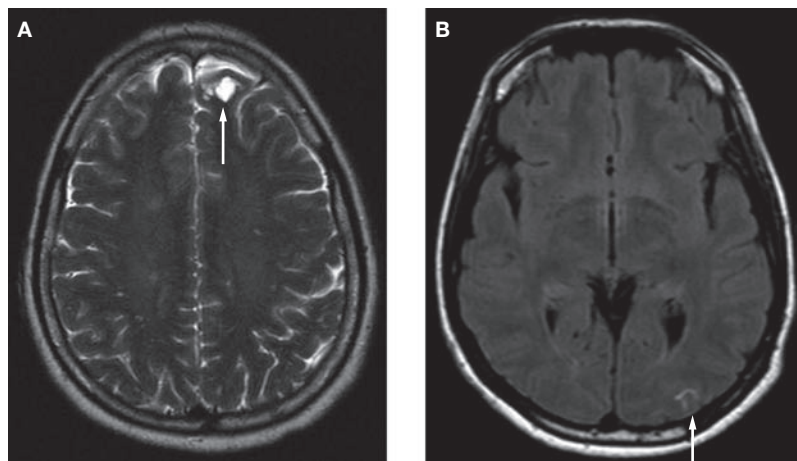


Figure 1 Axial MRI of the brain performed upon onset of headaches and sensorineural hearing loss. (A) T2-weighted sequence revealing cystic encephalomalacia in left frontal lobe (arrow). (B) Post-gadolinium T1-weighted sequence revealing pial enhancement in left occipital lobe (arrow).



Figure 2 Sagittal T2-weighted MRI of spine, performed 19 months after initial hearing loss and headache, shows multifocal, hyperintense lesions at C5–C6 and C7–T1 (arrows).

which was believed to reflect cystic encephalomalacia resulting from ischemia or vasculitis (Figure 1A). Post-gadolinium T1 images revealed pial enhancement in the left occipital lobe (Figure 1B). There was no change in the patient's medication regimen.

The patient developed left ON during month 3, characterized by 1 week of subjectively worsening visual acuity, retro-orbital pain that worsened with eye movement, a left afferent papillary defect, and normal fundoscopic examination. A lumbar puncture revealed 20 white blood cells/ μ l (80% lymphocytes), normal total protein level (40 mg/dl), normal glucose level (49 mg/dl), and no oligoclonal bands. Despite treatment with 125 mg methylprednisolone sodium succinate for 5 days, the patient was left with visual acuity less than 20/400.

During month 5 the patient developed progressive paraparesis, and neurological examination revealed mild weakness (UK Medical Research Council grade [4+/5]) in her proximal lower extremities.¹ MRI performed at another facility reportedly revealed multifocal regions of T2 hyperintense signal in the cervical cord (C2–C3, C4–C5, and from C5–C6). The patient was treated with monthly cyclophosphamide (1000 mg/m²) for 6 months, with some subjective strength improvement in her lower extremities.

From month 17 to month 20, the patient developed difficulty buttoning objects and typing. A spinal cord MRI, performed at month 19, revealed multifocal regions of T2 hyperintensity in the spinal cord, generally spanning less than 3 vertebral segments, with a new 1.5 cm signal from C7–T1 (Figure 2). A follow-up MRI of the brain performed at month 19 revealed bilateral, hyperintense T2 signals in the white matter of the corona radiata (Figure 3). Evolution of the patient's brain lesions was believed to be possibly consistent with multiple sclerosis (MS). Previous regions of pial enhancement had resolved.

At month 20, there were no other symptoms of active SLE: there was no rash, photosensitivity, alopecia, oral or genital ulcers, shortness of breath, sicca symptoms, or hematuria. The patient had never been pregnant, and there was no reported history of venous or arterial thrombotic events. She was referred to our institution for further evaluation.

General physical examination at month 20 was unremarkable. Neurological examination showed a left afferent papillary defect, with left optic disc pallor, and ability to detect only gross hand movements in the left eye. There was bilaterally impaired, rapid successive movement in both hands, with normal power. There was

also mildly increased tone and weakness in the left leg (power of UK Medical Research Council grade [4+/5], unchanged from previous examinations), and normal power in the right leg. Reflexes were increased more in the left lower extremities than in the right lower extremities; bilateral Babinski reflexes were observed. There was decreased proprioception in the left foot, with mild left hemiparetic gait.

Laboratory results from tests performed at month 20 are shown in Table 1. Serological evaluation of neuromyelitis optica (NMO)-IgG antibody was positive. Given that the NMO-IgG antibody positivity occurred in the context of recurrent myelitis and ON, the diagnosis of NMO (also known as Devic's syndrome) was suspected. The patient was started on a regimen of 1 g rituximab, to be given at weeks 0, 2, 26, and 28 in the upcoming year, with follow-up MRI of the spine and brain recommended at 6–12 months. After two doses, the patient has reported decreased numbness in her lower extremities and improved dexterity in her hands.

DISCUSSION OF DIAGNOSIS

ON and myelitis can occur as manifestations of "idiopathic" demyelinating syndromes (i.e. NMO and MS), as well as of systemic rheumatic syndromes. Knowledge of the distinguishing clinical and radiographic features is crucial for an accurate diagnosis.

Slow viruses

Slow viruses, particularly subacute sclerosing panencephalitis (SSPE) and progressive multifocal leukoencephalopathy (PML), need to be considered as culprit etiologies of white-matter lesions in patients with SLE; however, the core clinical features seen in these infections were not present in this patient. Myelitis is not usually associated with SSPE or PML: SSPE is characterized by a subacute, progressive encephalopathy occurring with stimulus-sensitive myoclonus and other movement disorders, and PML is also associated with visual deterioration and field deficits, as well as other parietal findings.

Multiple sclerosis

MS can affect white-matter tracts in the spinal cord, optic nerve, brainstem and cerebellum.² ON is the presenting syndrome of MS in 15–20% of cases;³ however, several features of

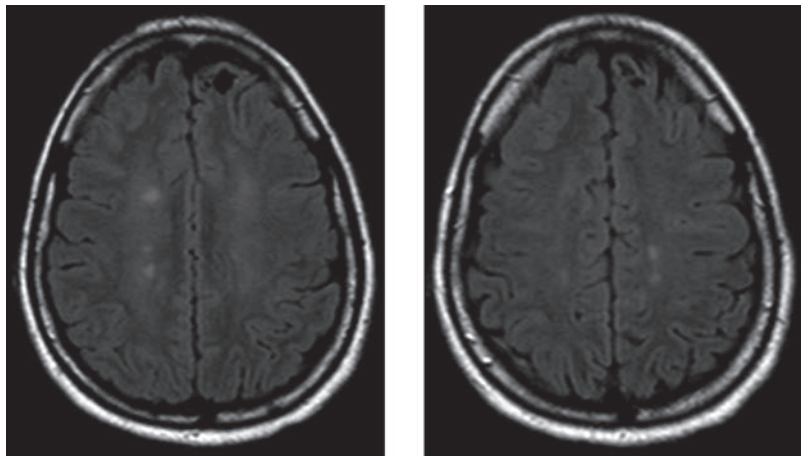


Figure 3 Axial T2-weighted MRI of brain, performed in the month before referral, shows bilateral, hyperintense, white-matter lesions in corona radiata.

this patient's ON are unusual in cases of MS. At clinical nadir, the patient was unable to perceive light illumination in the affected eye, improvement after 1 month was minimal, and the patient was left with acuity less than 20/400. The lack of significant improvement in vision after 5 weeks indicates a diagnosis other than idiopathic ON or ON associated with MS.⁴ Furthermore, at the time of the ON attack, the patient underwent brain MRI (Figure 1) that demonstrated cystic encephalomalacia in the left frontal lobe with pial enhancement. The European Magnetic Resonance Network in Multiple Sclerosis includes pial or gyral enhancement, as well as stigmata of previous ischemic episodes (cystic encephalomalacia), as radiographic "red flags" suggestive of diagnoses other than MS.⁵

On follow-up examinations, the patient had brain lesions thought to be suggestive of MS; however, lesions caused by small-vessel disease are frequently seen in patients with SLE and can be difficult to distinguish from MS. Rigid application of the Barkhof criteria illustrated that the patient's MRI was nondiagnostic for MS—there were less than nine lesions seen on the T2-weighted sequence, no juxtacortical lesions, no lesions in the periventricular white matter, and no infratentorial lesions.⁶ Other features that are indicative of a diagnosis other than MS include cerebrospinal fluid findings of moderate pleocytosis, as well as absent oligoclonal bands. In MS, oligoclonal bands are seen in 85–95% of patients,⁷ and moderate pleocytosis is uncommon. The constellation of

Table 1 Laboratory results from tests performed 20 months after initial hearing loss and headache.

Variable (units)	Value (normal range)
Hemoglobin (g/dl)	12.8 (12.0–15.0)
Hematocrit (%)	37.2 (36.0–46.0)
White-cell count (cells/ μ l)	8.6 (4,500–11,000)
Neutrophils (%)	77.7 (40.0–70.0)
Lymphocytes (%)	17.5 (24.0–44.0)
Platelet count (cells/ μ l)	286,000 (150,000–350,000)
Mean corpuscular volume (fl)	86.9 (80.0–100.0)
Prothrombin time (s)	1.0 (0.9–1.1)
Partial thromboplastin time (s)	24.9 (23.5–34.0)
Glucose (mg/dl)	80 (60–99)
Sodium (mEq/l)	138 (135–148)
Potassium (mEq/l)	3.8 (3.5–5.1)
Chloride (mEq/l)	106 (96–109)
Bicarbonate (mEq/l)	26 (21–31)
Urea nitrogen (mg/dl)	7 (7–22)
Creatinine (mg/dl)	0.5 (0.5–1.2)
Albumin (g/dl)	3.8 (3.5–5.3)
Calcium (mg/dl)	9.2 (8.4–10.5)
Alkaline phosphatase (U/l)	69 (30–120)
Aspartate aminotransferase (U/l)	23 (0–31)
Alanine aminotransferase (U/l)	30 (0–31)
Urine	
Specific gravity (g/ml)	1.005 (1.003–1.030)
Protein	Negative (negative)
Red blood cells (per high power field)	1 (0–5)
White blood cells (per high power field)	0 (0–5)
Serology and autoantibodies associated with SLE	
ANA titer, pattern	1:1,280, speckled (<1:40)
Anti-dsDNA (U/ml)	168 (0–79)
Anticardiolipin IgM (MPL units)	9 (<10)
Anticardiolipin IgG (GPL units)	8 (<10)
Russell's viper venom time (s)	34.7 (27.0–45.0)
C3 (mg/dl)	101 (79–152)
C4 (mg/dl)	21 (12–42)
Perinuclear ANCA	Negative (negative)
Cytoplasmic ANCA	Negative (negative)
Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; dsDNA, double-stranded DNA; SLE, systemic lupus erythematosus.	

these features—the severity and intractability of ON to treatment, the nonspecificity of white-matter lesions in patients with SLE, and

the absence of oligoclonal bands in cerebrospinal fluid—suggests an alternative diagnosis to that of MS.

Neuropsychiatric systemic lupus erythematosus

The patient initially complained of headache and bilateral hearing loss. Bilateral hearing loss is never a manifestation of a primary demyelinating syndrome, but can be seen in small-vessel vasculitis (i.e. Wegener's granulomatosis). Pial enhancement is part of the varied spectrum of MRI findings that can be seen in vasculitis;⁸ similarly, the initial finding of cystic encephalomalacia represents cavitation of ischemic injury. These early clinical and radiographic findings suggest small-vessel ischemia caused by active neuropsychiatric SLE (NPSLE). Histopathologic findings of postmortem NPSLE brains include ischemia resulting from a hyalinizing microangiopathy, as well as vasculitis.⁹

The early clinical (headache and sensorineural hearing loss) and radiographic (pial enhancement and cystic encephalomalacia) features typical of small-vessel disease resolved after treatment with cyclophosphamide in this patient, who then developed an optico-spinal syndrome with no further evidence of disseminated neurological disease. The rarity of optico-spinal syndromes in patients with SLE justifies a ruthless pursuit of alternative diagnostic explanations.¹⁰ Although ON and myelitis in patients with SLE are usually considered manifestations of active NPSLE, a clinical history and neurological examination offers insight into whether there is a second autoimmune disease present.

The patient's loss of visual acuity indicates dysfunction of the optic nerve. In patients with SLE, mechanisms that cause clinical and radiographic patterns of white-matter disease—owing to a small-vessel microangiopathy—likely contribute to a similar “ischemic” optic neuropathy. Several clinical features can discriminate between ischemic optic neuropathy and the ON seen in demyelinating syndromes. In contrast to ON, ischemic optic neuropathy causes acute (less than 1 day), rather than subacute, loss of vision, and is associated with retro-orbital pain in less than 10% of cases and significant fundoscopic findings of peripapillary hemorrhages.¹¹ The patient's subacute loss of visual acuity, significant retro-orbital pain and normal fundoscopic findings are more consistent with ON than with the ischemic optic neuropathy seen in SLE. Alternative demyelinating syndromes, therefore, need to be considered.

Neuromyelitis optica (also known as Devic's syndrome)

Although NMO was initially considered a diagnostic variant of MS, NMO and MS are now recognized as distinct diagnostic entities. In addition to the mandatory clinical features of ON and myelitis, the 2006 diagnostic criteria of NMO require at least two of the following three features: serological presence of the NMO-IgG antibody, absence of brain lesions diagnostic of MS, and myelitis extending more than three vertebral segments on MRI.¹² The patient's history of ON and recurrent myelitis, as well as the presence of two of the three core diagnostic features (history of NMO-IgG positivity and MRI brain lesions which were not diagnostic of MS), is strongly indicative of NMO. This helps illustrate the following crucial and underappreciated point: in rheumatic patients, NMO-IgG antibody positivity points towards the diagnosis of NMO, a separate and coincidental autoimmune disease; neurological disease occurs as a result of the diathesis of NMO, rather than the underlying rheumatic disease.

In contrast to MS, NMO is associated with severe visual impairment at clinical nadir.¹³ Recognition that the patient's pattern of ON was inconsistent with MS, but also inconsistent with ischemic optic neuropathy seen in NPSLE, prompted us to check for the NMO-IgG auto-antibody. The target of the NMO-IgG antibody is aquaporin-4, which is the main water channel responsible for fluid homeostasis in the central nervous system.¹⁴ The NMO-IgG antibody is 76% sensitive and 94% specific for a clinical diagnosis of NMO, and helps distinguish whether optico-spinal syndromes are occurring in NMO versus MS.¹²

The myelitis seen in NMO typically demonstrates a “longitudinally” extensive (i.e. more than three vertebral segments) pattern of inflammation on MRI. We acknowledge that the patient's “transverse” pattern of spinal cord inflammation—with multifocal lesions extending less than three vertebral segments—is not classical for NMO spinal-cord lesions. This pattern of longitudinally extensive myelitis has been predominantly described in cohorts with “idiopathic” NMO; it is unknown whether a transverse pattern of inflammation might be seen more frequently in NMO associated with rheumatic disease.

The NMO-IgG antibody is only 94% specific, and is present in 6% of patients with MS. In a

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Competing interests

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serological survey that included patients with SLE, however, Pittock *et al.* did not detect NMO-IgG antibodies in any patient with SLE who did not have an opticospinal syndrome indicative of NMO.¹⁵ This suggests that NMO-IgG positivity in patients with SLE is not due to nonspecific B-cell stimulation and is highly specific for NMO, even in patients with coexisting SLE. In contrast to NMO-IgG antibodies, antinuclear antibodies are nonspecific: these occur in up to 27% of patients with MS¹⁶ and in nearly 50% of patients with NMO.¹⁵

The aquaporin-4 antigen is normally sequestered behind the blood–brain barrier, including on abluminal surfaces of pial microvessels.¹⁷ In this patient, previous episodes of inflammation resulting from active NPSLE (as evidenced by regions of pial enhancement) might have potentiated NMO disease by permitting entry of the NMO-IgG antibody across a compromised blood–brain barrier.

TREATMENT AND MANAGEMENT

NMO is relentlessly polyphasic in more than 85% of cases.¹³ Identification of the NMO-IgG antibody represents a narrow therapeutic window to employ appropriate immunosuppressant treatment. Without such treatment, more than 50% of patients with NMO will be functionally blind, or will progress to wheelchair-dependence, within 5 years.¹⁷ Plasmapheresis is recommended for patients with severe opticospinal complications arising from NMO,¹⁸ and might have helped avert functional blindness in this patient. Spinal cords and brains from patients with NMO demonstrate vasculocentric IgG and C9 neoantigen deposition, suggestive of a humorally mediated microangiopathy.¹⁹ The B-cell arm of the immune system, therefore, constitutes an important therapeutic target. An open-label study of eight patients with severe and relapsing NMO treated with rituximab demonstrated improvements in the frequency and severity of relapses.²⁰ Recognition of NMO as a unique diagnostic entity might prompt earlier use of B-cell-depleting agents, especially during the therapeutic window of earlier attacks.

CONCLUSION

In summary, we present a patient with SLE and a coincidental but distinct syndrome of NMO. Early use of plasmapheresis and B-cell-depleting agents can potentially mitigate the ominous

prognostic features of functional blindness and wheelchair-dependence that occur in untreated NMO patients. In patients with SLE and ON or myelitis, identification of clinical or prognostic features consistent with NMO should lead to testing for the presence of the NMO-IgG autoantibody.

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