Nineteen Episodes of Recurrent Myelitis in a Woman With Neuromyelitis Optica and Systemic Lupus Erythematosus

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Objectives: To describe the case of a patient with systemic lupus erythematosus (SLE) and neuromyelitis optica (NMO) who experienced 19 recurrent attacks of myelitis.

Design: Case report.

Setting: An outpatient neurorheumatology clinic at the Johns Hopkins Hospital devoted to care of patients with neurological manifestation of rheumatic diseases.

Patient: A woman with NMO and SLE.

Intervention: Rituximab therapy.

Main Outcome Measures: Clinical and neuroimaging features of relapsing disease.

Results: Recurrent and increasingly severe myelitis attacks still occurred after treatment with rituximab.

Conclusions: It may be progressively more difficult to prevent relapses and commensurate disability in patients with later stages of relapsing NMO. Recognition of NMO as a distinct diagnostic entity in patients with SLE and other rheumatic diseases is crucial, in that institution of earlier targeted immunosuppressant treatment may be more effective than later targeted immunosuppression. The cellular arm of the immune system may be recruited by pathogenic B cells and may explain why relapses may occur after treatment with B cell-depleting therapy.

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Neuromyelitis Optica (NMO) is a devastating syndrome characterized by recurrent attacks of myelitis as well as optic neuritis. In recent years, there has been increasing evidence that the NMO-IgG autoantibody may have pathogenic as well as diagnostic relevance. There is also tantalizing, although circumstantial, evidence that NMO is mediated by perturbations in other parts of the humoral immune system.

Approximately 85% of cases of NMO are relapsing. We describe the case of a patient with NMO and systemic lupus erythematosus (SLE) who, remarkably, had 19 attacks of myelitis. To our knowledge, this represents the highest number of myelitis attacks ever reported in a patient with NMO and provides a unique fulcrum for understanding the polyphasic course of NMO. The last 2 attacks occurred after treatment with rituximab, an anti-CD20 monoclonal antibody that leads to functional depletion of B cells. In this study, we propose that ongoing B-cell stimulation may have led to activation of the cellular arm of the immune system during earlier attacks and contributed to treatment intractability to rituximab during later attacks. Potential mechanisms of cell-mediated autoimmunity in relapsing NMO are discussed. Our case suggests that treatments limited to B-cell depletion may not adequately address the potential role played by derangements in the cellular immune system, which, our case suggests, may be especially important during successive episodes of relapsing disease.

Report of a Case

A 48-year-old, right-handed, African American woman had been diagnosed with SLE in 1996 (temporally referenced as year 0) when she presented with high-titer antinuclear antibody positivity, malar rash, photosensitivity, oral ulcers, and polyarthritis. After receiving of 400 mg of hydroxychloroquine per day, she had no further inflammatory symptoms or signs affecting her skin or joints.
In year 3, she developed her first attack of longitudinally extensive transverse myelitis (LETM), and from years 3 through 6 developed 3 further attacks of myelitis. All of the myelitis attacks satisfied the diagnostic criteria proposed by the Transverse Myelitis Consortium Working Group. She developed paraparesis and numbness below a clearly demarcated midthoracic sensory level, with T2-weighted and T1 postgadolinium imaging reportedly revealing LETM that affected the ventral part of the middle to lower thoracic cord. These inaugural attacks were characterized predominantly by sensory symptoms, with intact antigravity strength at nadir (Medical Research Council) 4 to +/5, and minimal urinary urge incontinence. She was treated with 1 g of methylprednisolone. After these attacks, she returned to her complete baseline without any functional impairment. Significantly, all of these inaugural (as well as later) attacks of myelitis occurred in the context of quiescent SLE activity; there was no further malar rash, photosensitivity, oral ulcers, arthralgia/arthritis, shortness of breath, serositis, hematuria, or sicca symptoms.

From year 7 through year 9, she suffered her 5th through 13th attacks of myelitis. Again, each of these attacks satisfied the criteria proposed by the Transverse Myelitis Consortium Working Group. There were clearly demarcated, rostral sensory levels ranging between T1 and T6. Associated with her 5th attack, she developed bilateral optic neuritis with bilateral loss of visual acuity to less than 20/400. She was treated for optic neuritis with 1 g of methylprednisolone for 5 days and recovered to her visual baseline within 3 months. However, she had worsening morbidity with successive myelitis attacks. In contrast to earlier attacks (1st through 4th attacks), these (5th through 13th) featured more significant motor and sphincteric dysfunction. From her 9th attack onward she had loss of antigravity strength at clinical nadir. Although successive attacks were associated with more protracted time to recovery, she still had interictal ability to walk without any ambulatory assist devices.

Each attack was treated with pulse corticosteroids. Because her lupus was quiescent, she was not maintained on immunosuppressant treatment. However, after her 13th attack she started an oral regimen of 75 mg of cyclophosphamide daily. After several months, she developed leiomyosarcoma of the bladder. Despite the abbreviated course of treatment, because of iatrogenic concerns, the cyclophosphamide was discontinued. She underwent cystectomy, and did not have radiation or chemotherapy.

Within a few months of cystectomy, in year 10, she developed her 14th attack of myelitis. In year 11, in the context of a urinary tract infection, she developed her 15th attack. This latter attack was distinguished by its acuity and severity, with rapid progression to complete paraplegia within 12 hours. Magnetic resonance imaging (MRI) revealed a T2-hyperintense, longitudinally extensive lesion extending from T3 through T10 (Figure 1A). Postgadolinium T1 sequences demonstrated a heterogeneous and patchy pattern of enhancement (Figure 1B). Brain MRI findings were normal. She was then referred to the Johns Hopkins Neuro-Rheumatology Clinic for further evaluation.

On neurological examination, visual acuity was 20/40 bilaterally. Bilateral optic disc pallor was noted. On motor examination, she had spasticity in both lower extremities, with sustained clonus at both ankles. She had Medical Research Council power of 4 to +/5 in proximal muscle groups. Reflexes were 3 and symmetric in the upper extremities, 3+ at the patellars with crossed adductors, and plantar stimulation revealed upgoing toes. Sensory examination demonstrated an incomplete pin-prick level to T6. Laboratory tests revealed normal complements, with no evidence of antiphospholipid antibodies.

Because of recurrent LETM and bilateral optic neuritis, we suspected a diagnosis of NMO. The NMO-IgG autoantibody test was positive. Treatment with rituximab was recommended. Before this was approved by her insurance company, over the next 4 months in year 12, she suffered her 16th and 17th attacks of myelitis. She was given 1 g of methylprednisolone intravenously for 3 days and recovered to baseline deficits elicited in the above neurological examination. She ultimately received 2 doses of 1 g of rituximab, given 2 weeks apart, after she had recovered from her 17th attack.

Three months after receiving her second dose of rituximab, she suffered her 18th attack. She was again treated with 1 g of methylprednisolone. One month later, she suffered her 19th attack. Unfortunately, after the 19th attack, she was completely paraplegic and after 3 months has not recovered any motor strength. The MRI after this 19th attack revealed fusiform expansion of the thoracic cord, with LETM hyperintensity seen on sagittal T2-weighted MRI extending from T5 through T8 (Figure 2A) and a heterogenous pattern of enhancement from T7 through T9 (Figure 2).

After 5 months of rituximab therapy, peripheral flow cytometry has documented ongoing CD19 and CD20 cell depletion.

We present a case of a patient with NMO and SLE who had 19 recurrent attacks of myelitis. Our case is unique.
We believe that our patient's unresponsiveness to rituximab, with clinical attacks corroborated by gadolinium-enhancing lesions, suggests that relapsing NMO may have broader immunologic mechanisms than currently appreciated. Hypothesized mechanisms concerning the role of B cells in NMO have mainly centered around the pathogenic role of NMO-IgG autoantibody in the context of the humoral arm of the immune system.9 In comparison, there has been less consideration given to the possibility that ongoing activation of B cells, especially in the context of recurrent myelitis attacks, may lead B cells to become potent antigen-presenting cells and therefore cause propagating damage in NMO due to perturbations in the cellular immune system.

Although B cells are inefficient as antigen-presenting cells,13 with increasing activation—as might be seen with recurrent attacks of LETM in NMO—they may display immunophenotypic features of competent antigen-presenting cells (ie, upregulation of CD40 and B7/B28).14 Antigens presented by B cells may be wholly different from cognate antigens recognized by the T-cell receptor. The endocytic processing of captured antigens may lead to different peptide sequences presented at the B cell–T cell immunologic synapse, leading to epitope spreading. This mechanism of epitope drift may diversify the range of salient epitopes that may lead to propagation of relapsing attacks. Such “kindling” of the immune system may suggest why a subset of patients with NMO may present with such ruthlessly relapsing NMO disease.

Therefore, we propose that, although the humoral arm of the immune system may play a crucial role in the initial attacks of NMO, recurrent attacks may cause the cellular arm of the immune system to mediate ongoing inflammation and damage in NMO. Our patient’s devastating debility from her last 2 attacks, which tragically resulted in complete wheelchair dependence, occurred despite treatment with rituximab. This supports our hypothesis that relapsing NMO may not be exclusively mediated by the humoral arm of the immune system.

Although myelitis may be a manifestation of SLE,15 our patient’s syndrome of NMO occurred in the context of quiescent lupus disease. Especially in patients with SLE and quiescent systemic SLE disease, the presence of clinical or serologic features suggestive of NMO represents the manifestation of a distinct, coincidental autoimmune disease. We have recently suggested that the American College of Rheumatology Classification Criteria for lupus neuropsychiatric syndromes be revised to include mandatory evaluation for NMO-IgG autoantibody in patients with features consistent with NMO.16

In conclusion, we present a patient with SLE and NMO who had 19 distinct episodes of recurrent myelitis, the most ever described in the literature. Our patient’s relapsing course continued even after treatment with rituximab and suggests that pleiotropic mechanisms that cause perturbations in cellular as well as humoral immune responses may be crucial during relapsing attacks.

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