

Immunoablative Cyclophosphamide for Refractory Lupus-Related Neuromyelitis Optica

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ABSTRACT. Neuromyelitis optica (NMO), or Devic's disease, is an aggressive inflammatory disease of the central nervous system that predominantly affects the optic nerves and the spinal cord. The association with other systemic autoimmune diseases and the discovery of the specific biomarker, NMO-immunoglobulin G (IgG), suggests that NMO is autoimmune in origin. The prognosis of NMO is grave, especially in those patients with early and recurrent relapses. We describe successful use of immunoablative cyclophosphamide in halting relapses in a patient with systemic lupus erythematosus-associated NMO who was unresponsive to high-dose oral and intravenous corticosteroids, intravenous immunoglobulin, mycophenolate mofetil, tacrolimus, low-dose daily oral cyclophosphamide and rituximab. (*J Rheumatol* 2008;35:172–4)

Key Indexing Terms:

NEUROMYELITIS OPTICA
IMMUNOABLATIVE

LUPUS

TREATMENT

TRANSPLANT
CYCLOPHOSPHAMIDE

Neuromyelitis optica (NMO), or Devic's syndrome, is an aggressive, inflammatory disorder of the central nervous system (CNS) that preferentially affects the optic nerves and spinal cord. NMO is often idiopathic but may also be associated with systemic autoimmune diseases including systemic lupus erythematosus (SLE)^{1,2}. The discovery of a novel specific biomarker, NMO-IgG, and its target antigen suggests that the disease is immune-mediated³. The prognosis of NMO is grave, especially in those with early and recurrent relapses⁴. Compared to multiple sclerosis, patients with NMO usually experience more severe disease attacks and have more extensive centrally located longitudinal spinal cord lesions³. We describe the successful use of immunoablative cyclophosphamide (CYC) in halting relapses in a patient with SLE-related NMO who was refractory to high-dose oral and intravenous corticosteroids, intravenous immunoglobulin (IVIG), mycophenolate mofetil (MMF), tacrolimus, low-dose daily oral CYC, and rituximab.

CASE REPORT

A 40-year-old Chinese woman presented with progressive blurring of vision of her left eye, which was diagnosed to be optic neuritis by visual evoked potential and magnetic resonance imaging (MRI) study. While visual acuity

worsened, she developed polyarthritis, lower limb weakness, and sphincter disturbance. An MRI showed swelling of the spinal cord, with multiple longitudinal hyperintense signals at the medulla oblongata and cervical and upper thoracic cord (Figure 1A). Cerebrospinal fluid analysis revealed pleocytosis (leukocyte count 37/mm³, 58% lymphocytes), elevated protein, and depressed glucose level. Oligoclonal IgG bands were absent. Bacterial and viral studies were unrevealing. MRI of the brain was unremarkable. Further investigations demonstrated lymphopenia, hypocomplementemia, positive anti-nuclear, anti-dsDNA, anti-Ro, and anti-La antibodies. Anticardiolipin antibodies, lupus anticoagulant, and anti-β₂-glycoprotein I antibody were negative.

Intravenous (IV) pulse methylprednisolone (MP; 15 mg/kg/day for 3 days) was initiated, followed by high-dose oral prednisolone and IVIG (0.4 g/kg/day for 5 days). She responded partially, with improvement of muscle power and tapered use of urinary catheter after 4 weeks. MMF (2 g/day) was added along with low-dose prednisolone for maintenance therapy. Despite this, in the subsequent 8 months, she had 2 relapses of myelitis and development of optic neuritis in her right eye, which did not respond to IV pulse MP, IVIG, and sequential use of tacrolimus, CYC and rituximab (Table 1). She became blind and bed-ridden.

Immunoablative CYC treatment was finally administered by infusion of high-dose IV CYC (2 g/day for 4 days), followed by restoration of leukocyte count by daily subcutaneous granulocyte-colony stimulating factor (G-CSF) in an isolated ward. Transient leukopenia (lowest 0.2 × 10⁹/l) was observed 1 week later but the marrow started to recover after the second week. Apart from alopecia and transient gastrointestinal upset, no other adverse events were reported. With rehabilitation, her limb power gradually improved and she could manage to walk with aids. Her right eye visual acuity also showed mild improvement, although the left eye remained blind. In the subsequent 18 months, there was no further deterioration of her neurological status or clinical relapses. A repeat MRI showed marked reduction in hyperintense spinal cord signals without cord atrophy (Figure 1B) and her anti-NMO-IgG was negative at this time.

DISCUSSION

NMO is an inflammatory disorder of the CNS characterized pathologically by vasocentric inflammation with comple-

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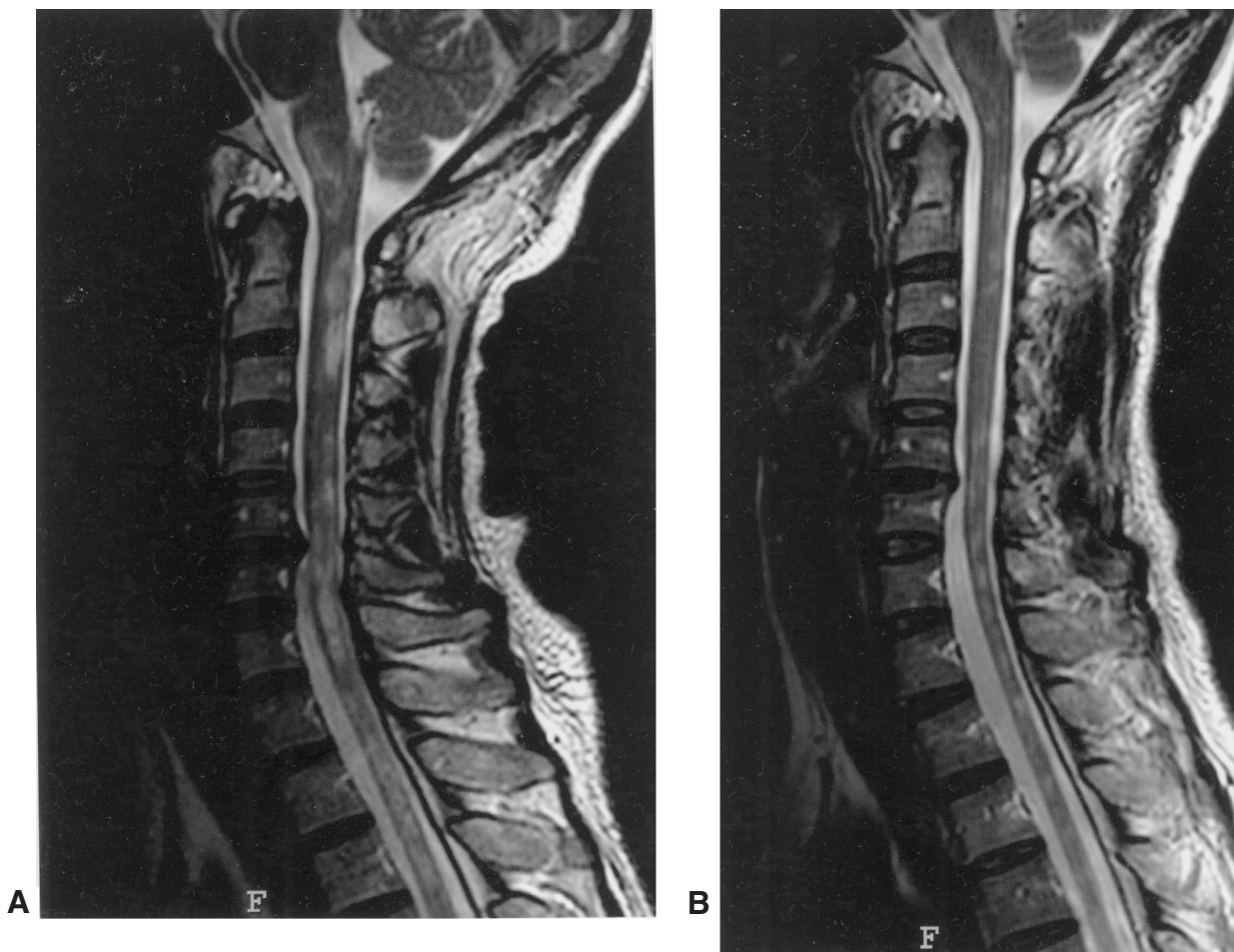


Figure 1. A. T2-weighted sagittal MRI shows mild expansion of the spinal cord and multiple hyperintense lesions at the medulla oblongata and cervical and upper thoracic spinal cord. B. T2-weighted sagittal image 18 months after immunoablative CYC treatment shows marked decrease in size of the lesions without evidence of cord atrophy. The spinal cord is no longer expanded.

Table 1. Clinical course and outcome of each phase of treatment in our patient.

Date	Treatment	Clinical Response and Outcome	MRI Findings
Oct 2004	IVMP, IVIG, Pred, MMF	Partial response with mild residual LL weakness (muscle power 4/5) and urge incontinence. Left eye remained blind. Relapse of myelitis 4 mo later	Multiple T2 hyperintense signal of spinal cord (Figure 1A). Brain MRI normal except optic neuritis of left eye
Feb 2005	IVMP, monthly IV pulse CYC	Partial response with residual LL weakness (power 3/5). Required intermittent bladder catheterization. Relapse of myelitis and right eye optic neuritis 5 mo later	New multiple T2 hyperintense signals of spinal cord (cervical, mid-thoracic to caudal)
July 2005	IVMP, IVIG x 2 courses, tacrolimus, daily oral CYC, rituximab	No response. Patient became chair-bound and catheter-dependent. Right eye could perceive light only	Increasing T2 hyperintense signals of the spinal cord with necrotizing changes (cervical and thoracic level)
Oct 2005	Immunoablative CYC with G-CSF rescue (without stem cell infusion)	Sphincter function and LL power gradually improved. Right eye visual acuity showed mild improvement. No further neurological deterioration or relapses in the subsequent 18 mo despite discontinuation of all immunosuppression	Repeat MRI of the spinal cord 18 mo after immunoablative CYC showed marked reduction in abnormal T2 signals without spinal cord atrophy (Figure 1B)

MP: methylprednisolone; IVIG: intravenous immunoglobulins; Pred: prednisolone; MMF: mycophenolate mofetil; LL: lower limb; CYC: cyclophosphamide; G-CSF: granulocyte-colony stimulating factor.

ment and immune complex deposition, necrosis, and often cavitation in both the spinal cord and the brain, with and without acute demyelinating changes³. Recently, a specific biomarker of the disease, NMO-IgG, that targets the water channel aquaporin-4 located in the foot processes of the astrocytes was discovered⁵. Binding of NMO-IgG to aquaporin-4 through a breach in the blood-brain barrier leads to disruption of the cellular water transport mechanisms and to inflammatory necrosis of the neural tissues induced by activation of the complements. More recently, another anti-aquaporin-4 antibody assay was established that may prove to be more sensitive and specific than NMO-IgG⁶.

A set of revised diagnostic criteria for NMO has recently been proposed to enhance the specificity and differentiating power from other demyelinating diseases such as multiple sclerosis⁷. The proposed criteria require the presence of optic neuritis and acute myelitis together with at least 2 out of 3 supportive criteria: (1) presence of a contiguous spinal cord MRI lesion spanning 3 vertebral levels; (2) absence of brain MRI findings of multiple sclerosis; and (3) a positive NMO-IgG antibody. Although the status of NMO-IgG and anti-aquaporin-4 in our patient was unknown at presentation, she indeed fulfilled the criteria for NMO. At the same time, she also met the American College of Rheumatology criteria for the classification of SLE, which has a specificity of 96%⁸.

The mainstay of treatment of NMO is immunosuppression. IV pulse methylprednisolone is often used for acute attacks of NMO⁹. Plasmapheresis has been employed in patients who do not respond to corticosteroids. The evidence is based on a randomized controlled crossover trial that showed superiority of plasmapheresis to a sham procedure in 36 patients with various inflammatory demyelinating diseases who did not respond to initial corticosteroid therapy¹⁰. Another retrospective series has also reported efficacy of plasma exchange in 6 patients with NMO¹¹. Maintenance immunosuppression is indicated in NMO to prevent disease relapses, especially in those patients seropositive for NMO-IgG³. Small uncontrolled studies have demonstrated benefits of various agents including azathioprine, mitoxantrone, MMF, and rituximab in reducing relapses in patients with NMO^{12,13}. Except for plasmapheresis, our patient was refractory to IVIG and most of the immunosuppressive agents mentioned above. She appeared to respond to immunoablative CYC treatment, which had induced a remission for at least 18 months.

Autologous hematopoietic stem cell transplant (HSCT) has been employed in autoimmune diseases, with the aim to overcome treatment resistance by intensifying the dosage of CYC, eradicating autoreactive cells and dysregulated immune circuits. In patients with refractory SLE, HSCT led to durable clinical remission in two-thirds of cases¹⁴. The most com-

monly used mobilization regimen is a combination of CYC and granulocyte-colony stimulating factor (G-CSF), and the commonest conditioning regimen is high-dose CYC with anti-thymocyte globulin. A less intensive immunoablative CYC regimen (50 mg/kg/day for 4 consecutive days) followed by G-CSF rescue alone has also been used with success in SLE with a lower incidence of adverse events¹⁵. The adoption and success of this regimen in our patient indicates that it may be considered in patients with refractory neuropsychiatric lupus including NMO, but further controlled data are needed to confirm its efficacy.

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