Neuromyelitis Optica: A Case Report

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NMO has recently been recognized as a separate disease entity from MS. Although the two illnesses share common features related to demyelination of the central nervous system, their natural history and treatment are different. We present a patient with an aggressive form of NMO that resulted in severe disability and multiple medical complications. The disease activity was ultimately controlled with rituximab. We provide evidence that the latter should be considered a first-line agent for treatment of this condition.

Key Words: autoimmunity, monoclonal antibody, multiple sclerosis, neuromyelitis optica

Abbreviations Used: CSF, cerebrospinal fluid; IgG, immunoglobulin G; MR, magnetic resonance; MS, multiple sclerosis; NMO, neuromyelitis optica

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Optic neuritis and transverse myelitis are common manifestations of MS. However, some patients present only with recurrent optic neuritis and severe episodes of myelitis. A variant of MS known as opticospinal MS has been recognized, especially in the Japanese population.[5] Several years ago an antibody highly specific for this condition was identified in the serum of those patients, and NMO was recognized as a disease entity separate from MS.[3] Even though the pathogenesis of the condition has not been elucidated fully, NMO appears to be an autoimmune illness in which an IgG auto-antibody targets aquaporin-4 in astrocytic foot processes.[2]

Aquaporins, proteins expressed in the brain and kidney, function as channels for the maintenance of fluid balance. The NMO-IgG auto-antibody initiates a cascade of events that leads to severe inflammatory reactions and tissue destruction. Patients with NMO suffer from recurrent attacks that unpredictably involve the optic nerves and spinal cord and cause irreversible damage and permanent disability.[6] Because NMO is a demyelinating disease of the central nervous system, patients have been treated with chemotherapies after medications approved for MS were proven to be ineffective. We present a patient with NMO who was managed with rituximab, a monoclonal antibody that holds promise for the treatment of this debilitating disease.[1]

Case Report

In April 2006 a 39-year-old man sought treatment for an acute episode of severe transverse myelitis that led to para-

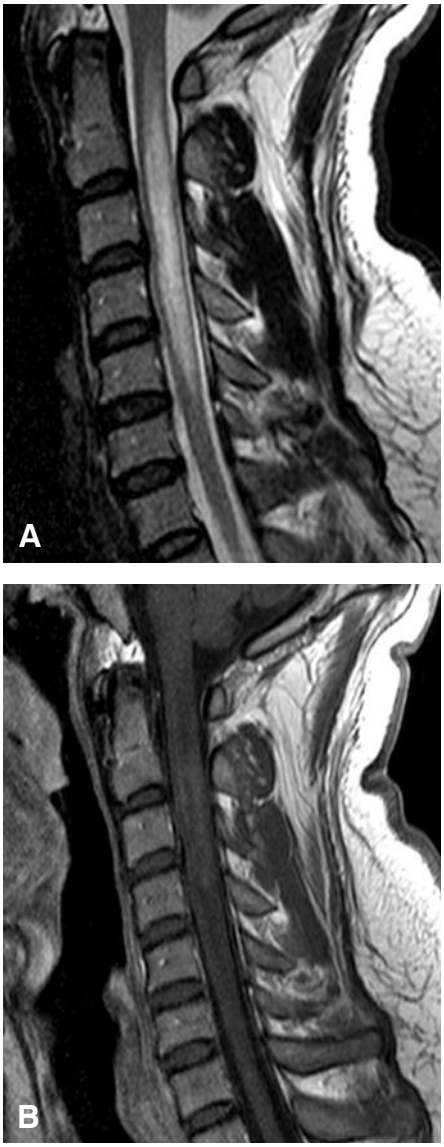

Figure 1. (*A*) Sagittal fluid-attenuated inversion recovery and (*B*) sagittal postcontrast MR images of the cervical spine obtained in November 2006 show the cervical cord expanded by a lesion that extends between C1 and C5.

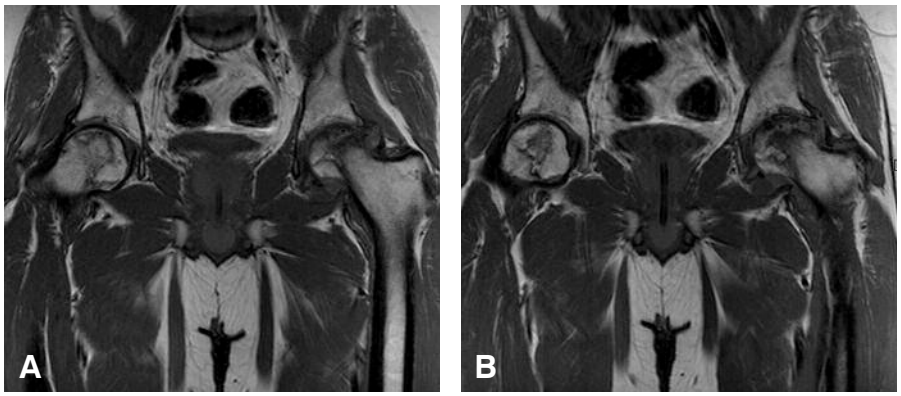

Figure 2. Coronal MR images of the pelvis show the osteonecrosis of the (*A*) left and (*B*) right femoral heads.

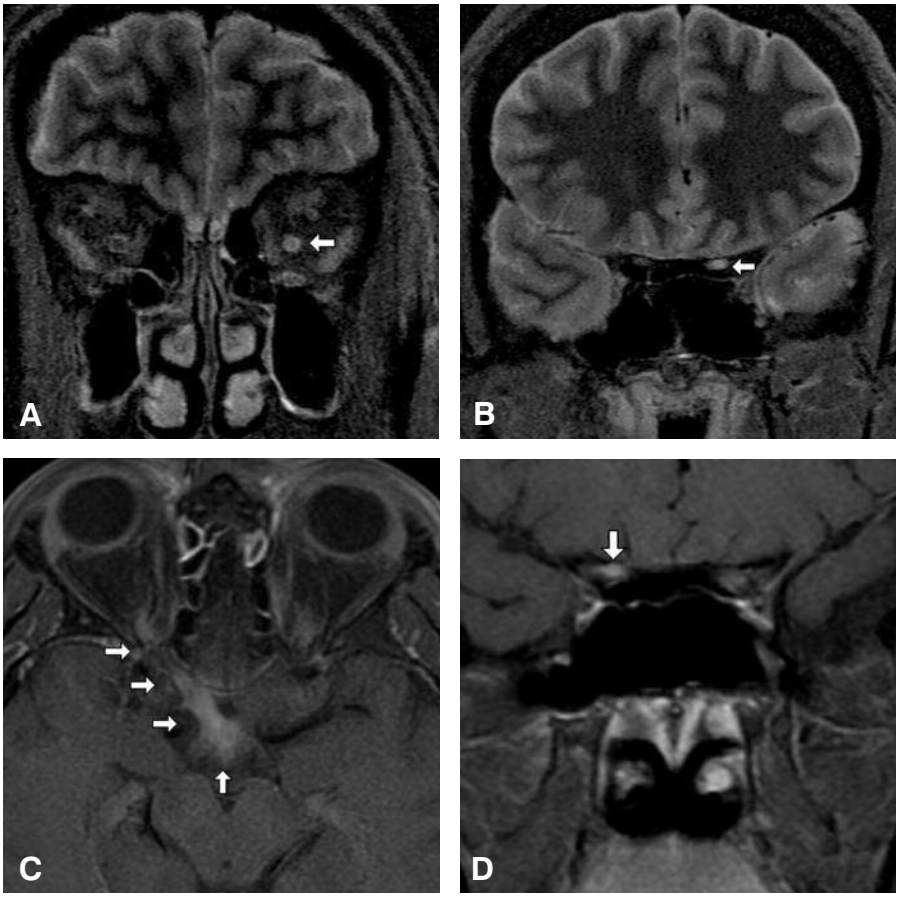

Figure 3. MR images of the brain obtained in February 2007 show acute bilateral optic neuritis involving various segments of the optic nerve. (*A* and *B*) Coronal MR images show inflammation of the left optic nerve at two points (*arrow*) along its course. (*C*) Axial MR image shows inflammation along the length of the right optic nerve extending to the optic chiasm (*arrows*). (*D*) Coronal MR image shows inflammation of the right optic nerve (*arrow*).

plegia. MR imaging of the thoracic spine showed an expanded spinal cord with signal abnormalities from C7 to T8 and heterogeneous postcontrast enhancement between C7 and T4. The patient received 1 gram of intravenous methylprednisolone for 5 days followed by plasmapheresis. Over the next 5 months he recovered ambulation with bilateral support.

Early in November 2006, the patient had a second episode of transverse myelitis and was admitted to the hospital with progressive weakness that also involved the arms. MR imaging showed a large contrast-enhancing demyelinating cervical lesion that extended five vertebral segments (Fig. 1). MR imaging of the brain was normal. Analysis of his cerebrospinal fluid (CSF) was as follows: albumin 56 mg/dL (normal < 35 mg/dL), IgG 7.6 mg/dL (normal < 6.0mg/dL), albumin index 12.9 (normal < 9.0), synthesis rate 29.2 mg/day (normal < 8 mg/day), IgG index 2.43 (normal < 0.66), and IgG/Alb 0.13

(normal = 0.09–0.25). Oligoclonal bands were negative. Serum was positive for NMO-IgG. The patient was again treated with high doses of intravenous steroids and plasmapheresis. He also received 5 days of intravenous immunoglobulins (0.4 gm/kg/day).

When examined about a month later, the patient had weakness graded 2-3/5 in the right upper extremity and legs and about 4/5 in the left upper extremity. Sensory testing demonstrated loss of sensation to all modalities below the neck. Vision and function of the other cranial nerves were intact.

In January 2007 the patient complained of left hip pain and was found to have avascular osteonecrosis of the femoral head bilaterally, which was worse on the left than on the right (Fig. 2). The necrosis was attributed to steroid use. At that point, the patient had recovered little motor function. He was scheduled to receive cyclophosphamide (1000 mg/m^2) monthly for 3 months and received the first dose at the end of January 2007. Two weeks later, he lost vision in his left eye. Given the degeneration of his hip, no steroids or other therapy was offered.

Several weeks later he presented with impaired vision in his right eye that worsened over the course of a few days. MR imaging of the brain showed findings consistent with severe bilateral optic neuritis extending into the optic chiasm (Fig. 3). MR imaging of the spine showed improvement of the demyelinating cervical lesion, which correlated with increased strength in all four extremities. He underwent another cycle of plasmapheresis that was followed by the second dose of cyclophosphamide at the end of February 2007.

One month later his vision had improved to perception of shadows in the left eye and to 20/200 in his right eye. He had also regained the ability to transfer independently and to take a few steps with bilateral support. He began mycophenolate mofetil, which was discontinued in July 2007 when he was readmitted for increasing weakness of the lower extremities, painful paresthesias of the entire body, and bowel and bladder incontinence. This episode was considered a new relapse, and he underwent another course of intravenous steroids and plasmapheresis. He also received two doses of rituximab (500 mg) administered 2 weeks apart. The patient gradually regained strength in his legs, and his vision continued to improve. In October 2007 MR imaging showed resolution of the enhancement of the spinal cord lesion previously noted between T1 and T10 (Fig. 4).

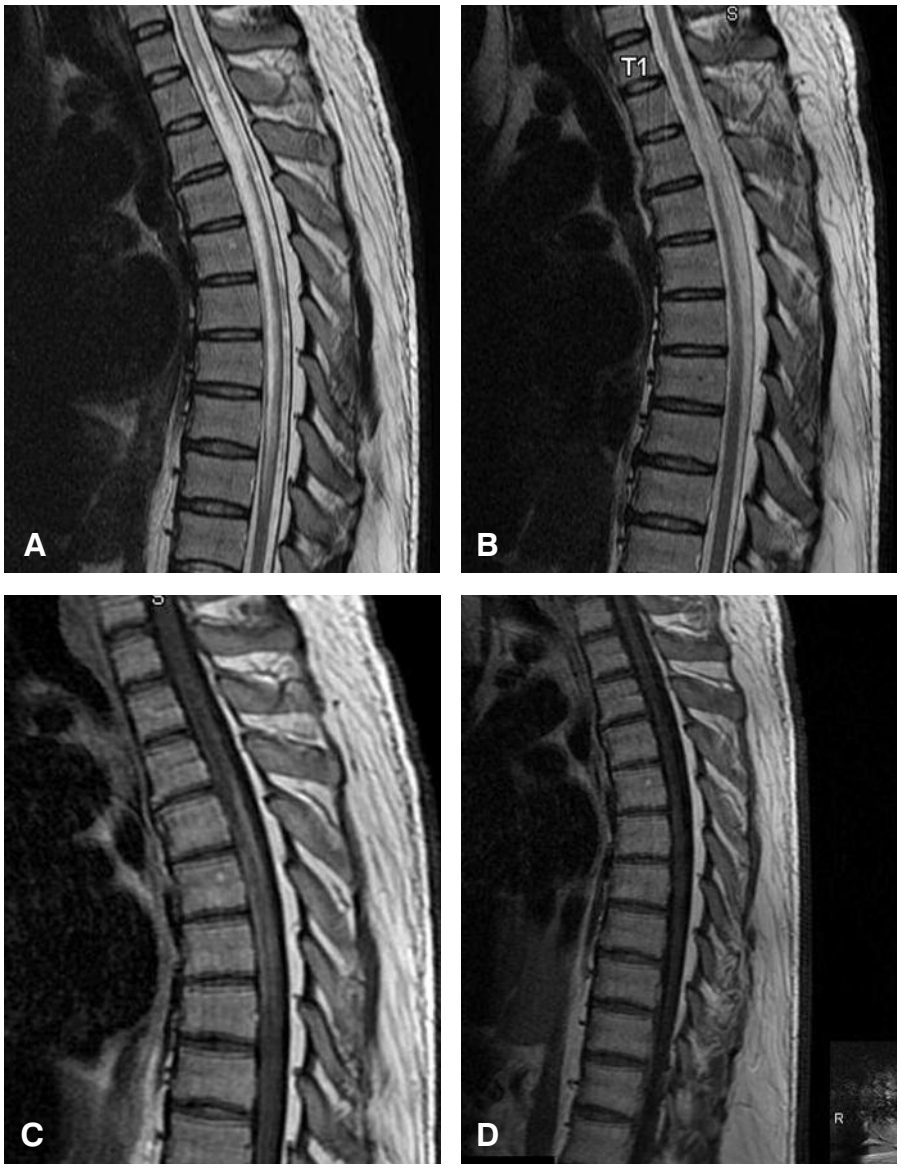

Figure 4. MR images of the thoracic spine show that the acute changes resolved between (*A* and *B*) July 2007 and (*C* and *D*) October 2007.

Over the next 8 months, the patient remained free from relapses. However, he developed a severe urinary tract infection that spread to the scrotum and required hospitalization. He also continued to experience relentless bilateral hip pain related to the osteonecrosis for which the chronic use of high doses of opiates became necessary. In February 2008 the patient's B-cell counts were still below normal (< 2%), indicating that he was responding appropriately to the rituximab.

In March 2008 when his CD19+ cells were reconstituted to the normal range, the patient was again hospitalized for acute exacerbation of optic neuritis involving the right eye. He underwent

plasmapheresis and received another dose of rituximab. As of March 2009, the patient has remained stable with no further relapses. In July 2008 he underwent a left hip replacement. Surgery for the contralateral hip is planned. Meanwhile, he is again ambulatory with bilateral support. He has residual visual impairment with only light perception in the left eye. Rituximab is considered the sole treatment modality for future relapses. Consequently, his B-cell counts are monitored periodically to allow the timing of further dosing to be planned.

Discussion

NMO is a disease that has posed real treatment challenges. The severity of attacks is almost always debilitating and potentially fatal; they occur unpredictably and lead to a progressive accumulation of disability.

Our case illustrates several characteristics of the disease that meet the revised diagnostic criteria for NMO.[4] The patient's spinal cord was involved with an expansive lesion that extended longitudinally beyond three contiguous vertebral bodies, and he had recurrent episodes of severe optic neuritis that alternated with myelitis.

The use of high doses of steroids in combination with cycles of plasmapheresis is recommended for the management of acute attacks of NMO. The potential risk of serious side effects, such as avascular osteonecrosis of the hip as occurred in our patient, is not cause to withhold treatment that increases the chances of recovery. Our patient continued to experience relapses while receiving the other proposed therapies for NMO, but he became stable on rituximab.

The theoretical view of an antibody-mediated disease is supported by our patient's dramatic response to the rituximab, which specifically targets B cells. The patient's one relapse while on this therapy was related to a delay in the administration of the subsequent dose, and the patient's B-cell count was allowed to normalize. This finding suggests that suppression of circulating B-cell counts to less than 2% during active stages of the disease is critical to prevent progression and further relapses. We have also observed this phenomenon in other patients with NMO treated with rituximab (unpublished data).

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