Case Report

Immune-reconstitution Inflammatory Syndrome in Multiple Sclerosis Patients Treated With Natalizumab: A Series of 4 Cases

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ABSTRACT

Purpose: Natalizumab (NTZ) is an effective treatment for relapsing-remitting multiple sclerosis (RRMS). Progressive multifocal leukoencephalopathy (PML) is a rare complication of NTZ treatment. In patients developing PML, NTZ cessation causes a reconstruction of cellular immunity, a rapid transition of cells through the blood-brain barrier, and significant inflammation in the central nervous system, leading to immune-reconstitution inflammatory syndrome (IRIS), with potentially poor outcomes. The occurrence of this syndrome is accelerated by plasmapheresis, the standard treatment for NTZ-PML, due to enhanced clearance of NTZ and thus rapid reconstitution of cellular immunity. IRIS can also occur after cessation of NTZ in the absence of PML.

Methods: We describe 4 patients who developed IRIS after NTZ cessation.

Findings: For the first patient, treatment was switched to fingolimod to avoid risk of developing PML. Despite plasmapheresis, corticosteroids, and other therapies, the outcome in this patient was fatal. For the 3 other patients, PML was detected early on magnetic resonance imaging, and IRIS after NTZ cessation was managed with a favorable outcome; 1 of these patients was managed without plasmapheresis or corticosteroid treatment.

Implications: These cases demonstrate the need to consider and manage therapeutic strategies relative to the individual patient's risk for PML or IRIS. NTZ cessation to avoid PML risk can lead to severe IRIS without PML. On the other hand, if PML develops and is detected early, plasmapheresis may not be considered necessary and IRIS may be limited, with a favorable outcome. These 2 scenarios should be considered when managing NTZ MS patients. (*Clin Ther*. 2016;38:670–675) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Keywords: immune-reconstitution inflammatory syndrome, JC virus, multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy.

INTRODUCTION

Natalizumab (NTZ), a humanized anti-α4-integrin recombinant monoclonal antibody, is an effective monotherapy in patients with active relapsing-remitting multiple sclerosis (RRMS).[1] Its use is associated with an increased risk of developing the rare disorder, progressive multifocal leukoencephalopathy (PML).[2] PML is caused by reactivation of the JC virus (JCV), and occurs almost exclusively in patients with suppressed cell-mediated immunity. It leads to central nervous system demyelinating lesions and can cause disability or death.[3]

PML diagnosis in NTZ-treated patients leads to NTZ cessation. In almost all such cases, NTZ cessation results in rapid reconstruction of cellular immunity with trafficking of cells through the blood-brain barrier.[2] This can lead to an immune-reconstitution inflammatory syndrome (IRIS) characterized by extended lesions on magnetic resonance imaging (MRI)

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and a significant deterioration of the patient's clinical condition.[2] The clearance of NTZ from the central nervous system can be accelerated by plasmapheresis, which has been reported to increase the occurrence and severity of IRIS.[2] Moreover, symptomatic IRIS is treated with corticosteroids, which have been shown to impair the JCV-specific T-cell response *in vitro*.[4] One approach to avoiding PML risk has been to switch from NTZ to another MS treatment, but this can also lead to severe MS reactivation and non-PML IRIS.[5]

We describe 3 PML-IRIS cases with favorable outcomes due to early detection, 1 of which was not treated with plasmapheresis, and 1 case of a fatal IRIS without PML after NTZ cessation.

CASE REPORTS

Case 1

A 24-year-old man with capricious autoimmunity, as he had developed Guillain-Barré syndrome in 2005, with tetraparesis and need for tracheotomy, was diagnosed with RRMS in 2010 and treated initially with glatiramer acetate.

After several relapses and the appearance of new voluminous brain lesions on MRI, glatiramer acetate was stopped 1 year later and the patient started NTZ treatment. No new relapse occurred and no new lesion was detected on MRI.

However, after 3 previous anti-JCV-negative tests after 35 months of NTZ, the patient became JCV-positive (JCV index 1.682). No polymerase chain reaction (PCR) for JCV was performed at that time, as no clinical or radiologic suspicion of PML was present. Nevertheless, given the risk for PML, the patient decided to stop NTZ. After a short washout period of 1 month, fingolimod 0.5 mg was initiated. No new lesion was detected on MRI on the day of the initiation of fingolimod treatment (**Figure 1A**; series 1).

Three months later, the patient developed left hemiplegia and hemihypesthesia. MRI revealed several new T2/fluid-attenuated inversion recovery (FLAIR) lesions in the left internal capsule, and the right and frontal left middle cerebellar peduncle with gadolinium enhancement (**Figure 1A**; series 2). The diagnosis was MS relapse; a lumbar puncture was performed and JCV DNA testing by PCR was negative. Tests for a number of other potential infections (eg, hepatitis A, B, and C; cytomegalovirus; Epstein-Barr virus; herpes simplex virus 1 and 2; human herpesvirus 6; varicella zoster virus; enterovirus; adenovirus; Coxsackie; human immunodeficiency virus; measles; rubella; mumps; syphilis; *Borellia burgdorferi*; toxoplasma; and cryptococcus) were negative. The patient was treated with corticosteroids and had incomplete motor recovery. Fingolimod was continued.

Two months later, the patient developed tetraparesis and left hemihypesthesia. The MRI revealed new T2/FLAIR lesions in the left periventricular and right frontoparietal region with gadolinium enhancement (**Figure 1A**; series 3). A new PCR test for cerebrospinal fluid (CSF) JCV DNA was negative. All tests to exclude other possible infections were negative. During the next 2 months, the patient's clinical and radiologic condition deteriorated. MRI clearly revealed an inflammatory cascade, suggesting an IRIS due to NTZ cessation (**Figure 1A**; series 4–5). No brain biopsy was performed to confirm the diagnosis. The patient died despite trying several therapies (eg, corticosteroids, plasmapheresis, daily and monthly cyclosphosphamide).

Case 2

A 42-year-old female MS patient, who had been treated with NTZ for 49 months, presented with an asymptomatic cortical T2/FLAIR lesion in the left frontoparietal region on a routine MRI (**Figure 1B**; series 2). She had been treated previously with intramuscular interferon-beta 1a and, at the time of initiating NTZ treatment, was JCV-seropositive (index not available). Upon detection of the new cortical lesion, JCV DNA was detected in the CSF by PCR (1271 copies/mL). NTZ was stopped and plasmapheresis was performed, followed by treatment with corticosteroids (1g per day intravenously, for 5 days).

Two months later, the patient developed left partial epileptic seizures characterized by right arm tonic-clonic movements and motor aphasia. Brain MRI revealed several new hyperintense T2/FLAIR lesions in the bifrontal regions and left parietal–temporal–occipital with gadolinium enhancement compatible with IRIS (**Figure 1B**; series 3). Four months later, IRIS regressed on MRI (**Figure 1B**; series 4). The patient is still treated with antiepileptic drugs and presents slight cognitive impairment characterized by dyslexia and executive difficulties.

Case 3

A 23-year-old MS patient, previously treated with intramuscular interferon-beta 1a and who had been treated with NTZ for 43 months, experienced complete clinical remission. On a routine MRI, a small right