Tumefactive Demyelination with White Matter Necrosis Following Cessation of Natalizumab Treatment

Timothy B Steinhoff, BS* 1,2 and Thomas F Scott, MD 2,3

Abstract—Natalizumab has been shown to reduce clinical and radiological evidence of active disease in patients with relapsing remitting multiple sclerosis. Whether or not disease progression accelerates beyond pretreatment levels following drug cessation has become a matter of contention. Here is presented a case of severe and unusual emergence of a large necrotizing inflammatory lesion in a multiple sclerosis patient following cessation of natalizumab. The findings from this patient, and previously reported cases, raise additional concerns related to withdrawal of natalizumab in patients with multiple sclerosis.

Keywords — Multiple Sclerosis, Natalizumab, Relapsing remitting, Rebound, Tumefactive.

I. INTRODUCTION

Natalizumab is known, to decrease rates of relapse in multiple sclerosis (MS) by 68%.1 There is still controversy surrounding whether stopping natalizumab can cause disease rebound activity.2-4 We report a case of abrupt disease reactivation with the emergence of a 3 cm tumefactive lesion following withdrawal of natalizumab after 13 years of treatment and clinical stabilization. Treatment with natalizumab was stopped due to positive JC virus antibody titers, and dimethyl fumarate was started. Clinical, radiological, and pathological evidence from this patient suggest rare and unusual rebound of disease.

II. CASE HISTORY

A 51-year-old male with a 29 year history of epilepsy, initially felt to be idiopathic, presented in March of 1998 with gait ataxia that progressed over a few days. This was followed by left lower extremity weakness, diplopia, and bowel and bladder dysfunction. He was diagnosed with MS supported by MRI and initially started on interferon beta-1-b. He then began to have increased generalized tonic-clonic seizures, occurring approximately one per month, and was switched to glatiramer acetate in September 1998. Approximately 18 months later, he presented with decreased strength, cane dependence for mobility, and minor bladder dysfunction, and was changed to azathioprine. During the next eight years, the patient experienced frequent seizure events despite aggressive medical management (approximately two seizure events per month). His MS remained relatively stable, with one additional relapse of his MS, seen as increased gait ataxia of five days duration, and he remained cane dependent. He was started on natalizumab, in August 2007. At this time, the patient was on phenytoin, divalproex sodium, and topiramate for seizure prevention, and he became seizure free after initiation of natalizumab.

In July 2013, he was found to be newly positive for JC virus antibody (index 0.65) and at that time was changed to dimethyl fumarate. While not clinically necessary to withdraw natalizumab for a titer of this level, the decision was made following in-depth discussion with the patient and his family. With this change, the patient had an increase in seizure frequency, and the dose was decreased, but with questionable reduction in frequency of seizures.

On 25 January 2014 the patient presented to the hospital following a seizure where he remained in a post-ictal state of...
confusion for two days. A CT scan of the head on admission showed no evidence for acute intracranial abnormality. On 9 February 2014 the patient’s mother felt he was “slowed,” and brought him back to the hospital. A CT scan at this time now showed a new 3 cm area of hypodensity in the anterior-inferior right frontal lobe. After two days of a worsening picture, an MRI was obtained and showed a large area of increased FLAIR signal in the right frontal lobe near the convex, with a 1 cm area of post-contrast enhancement (Figure 1).

A craniotomy was performed for biopsy of the right frontal mass (see section “Pathological Examination” below). Follow up of the patient over the next several months, revealed gradual improvement to his baseline of mild cognitive impairment and cane dependence.

III. PATHOLOGICAL EXAMINATION

The pathological specimen of brain tissue shows extensive areas where the white matter is replaced by a microphage-rich infiltrate, lymphocytic inflammation, and reactive vessels with perivascular lymphocytic infiltrate. Collections of hemosiderin-rich microphages are also seen. There is prominent reactive astrogliaosis surrounding this area, and occasional foci of necrosis are also identified. CD68 immunostain highlights marked microphagic infiltrate, and neurofilament highlights areas of relative preservation of axons admixed with areas of almost complete loss myelin; confirmed by AFB/PAS stain. A GFAP stain highlights reactive astrocytes. The findings are consistent with a diagnosis of severe active inflammatory demyelinating disease associated with foci of tissue necrosis (Figure 2).

IV. DISCUSSION

The clinical investigation in our patient included biopsy. This was performed primarily to rule out opportunistic infection, progressive multifocal leukoencephalopathy, and a primary B-cell lymphoma. The MRI findings of a large lesion with increased signal intensity on T2 weighted scanning involving both subcortical white matter and cortex, was consistent with a severe demyelinating process. Pathological findings were remarkable for unusually prominent necrosis (Figure 2).

The decrease in seizure frequency seen after the patient started therapy with natalizumab could possibly be explained by its modulation of underlying inflammatory processes. We are unaware of any proposed antiepileptic property of natalizumab that might otherwise explain this.

It is yet to be determined to what extent cessation of natalizumab treatment in patients with multiple sclerosis results in rebound of disease activity. In the largest studies, it seems clear that disease activity returns only to pretreatment levels in the vast majority of patients. A few case series of impressive disease “rebound” after discontinuation of natalizumab are reported, and a few cases of tumoral demyelination more similar to ours have been reported as well. Although there are rare reports of tumefactive demyelinating disease with other disease modifying therapies, these cases are now sufficiently rare to preclude our ability to make any strong statements concerning risk.

Physicians should discuss with their patients the risk of severe disease recrudescence or rebound following withdrawal of natalizumab. Patients discontinuing natalizumab should be monitored clinically and radiographically for evidence of disease progression. This is only the fourth described case of tumefactive rebound following cessation of natalizumab, and while it is the farthest out, the histology is quite unusual. The extensive necrosis in this lesion is atypical for demyelinating lesions. Therefore, we are not only aware this is somewhat a delayed tumefactive rebound of disease, but feel this is another reason for the importance of this case.

ACKNOWLEDGEMENTS

The authors thank Arie Perry, MD, for assistance as a consulting neuropathologist.

References


Questions (please choose a single answer):

1. What is the proposed mechanism for natalizumab’s anti-epileptic effect in patients with multiple sclerosis?
   - A. Modulation of underlying inflammatory process
   - B. Natalizumab is known to have innate anti-epileptic properties
   - C. A metabolite of natalizumab is known to have innate anti-epileptic properties

2. What is recommended in monitoring patients coming off natalizumab?
   - A. Clinical monitoring
   - B. Radiographic monitoring
   - C. Frequent spinal taps for CSF analysis
   - D. A & B
   - E. B & C
   - F. All the above

3. Natalizumab is known to decrease what aspect of disease in multiple sclerosis?
   - A. Morbidity
   - B. Mortality
   - C. Rates of relapse
   - D. All the above
   - E. None of the above

Answers:

1. A – it is believed that modulation of underlying inflammatory processes affects epileptic events
2. D – It is recommended to monitor both clinically and radiographically for disease rebound. There has not been evidence to suggest that frequent spinal taps have any benefit to monitoring disease progression following natalizumab withdrawal.
3. C – Natalizumab has been shown to decrease rates of relapse in multiple sclerosis by 68%.