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Recurrent Natalizumab-Related Aseptic Meningitis in a Patient with Multiple Sclerosis

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SUMMARY

Natalizumab is a recombinant humanized monoclonal antibody that decreases T-cell migration into the CNS through $\alpha 4$ integrin:adhesion-molecule inhibition, thereby increasing the risk for opportunistic CNS infection. Herein we report a case of infusion-associated aseptic meningitis in a patient receiving natalizumab.

Search Terms

Multiple sclerosis; Natalizumab; Disease-modifying therapies; MRI

OBSERVATIONS

A 26-year-old right handed Caucasian female diagnosed with multiple sclerosis (MS) in 2008 began disease-modifying therapy with natalizumab following incomplete clinical (several relapses, including one 5 months prior to starting natalizumab) and radiographic (several typical lesions throughout the brain and spinal cord, including an enhancing lesion at C7 3 months prior to starting natalizumab) disease control on interferon β -1b and subsequently glatiramer acetate. She concomitantly enrolled in a longitudinal natural history of MS study at the National Institutes of Health.

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Foley RW: Manuscript writing

Tagg NT, Schindler M, Reich DS, Cortese I: Image selection & acquisition, Manuscript editing, Critical revision for important intellectual content

Fenton KM: Manuscript editing, Critical revision for important intellectual content

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A few days after the third natalizumab infusion, the patient noticed, but did not report, post-infusion headaches that recurred after the two subsequent infusions, lasting a few days each time. She had no previous headache history. JC virus antibody status was documented as low-positive (titer 0.53) at the time of the second infusion but was repeated and was negative at the time of the fourth infusion. The day after her sixth natalizumab infusion, she underwent a routine brain MRI at the NIH, which showed new leptomeningeal contrast-enhancement, which was best seen on the post-gadolinium FLAIR sequence. The enhancement was extensive and incompletely affected sulci overlying the left posterior frontal, parietal, and temporal lobes (Figure, a–d). There were no new or enhancing parenchymal lesions, and she was asymptomatic at this time. Three days later, she developed severe headache, neck pain, photophobia, and fever of 38.9° C (102° F). The pain was exacerbated with movement, albeit not specifically worse with neck flexion, and it was not responsive to aspirin. Kernig's and Brudzinski's signs were absent.

She underwent lumbar puncture nine days after the infusion, by which time the symptoms had already begun to improve; cerebrospinal fluid (CSF) analysis demonstrated 3 white blood cells, protein level of 22 mg/dL, and glucose level of 56 mg/dL. CSF Gram stain was negative, and bacterial and fungal cultures were negative. CSF VZV, HSV1, JCV, and EBV PCRs and Lyme antibody were all negative. Cytopathology was negative for malignancy. Repeat brain MRI 5 days after the headaches began showed that the left hemispheric leptomeningeal enhancement had resolved, but new leptomeningeal enhancement was seen in the left occipital lobe (Figure, e & f). Again, no new or enhancing parenchymal lesions were seen.

The patient's symptoms improved and were completely resolved at a follow-up 15 days after the infusion. A repeat MRI one month following her last infusion demonstrated complete resolution of the leptomeningeal enhancement. Given the negative work-up and that the symptoms and imaging findings resolved over a short time period, an infectious etiology was thought unlikely. Testing for anti-natalizumab antibodies was negative. Considering these data and that her disease activity was previously unresponsive to injectable therapies, the decision was made to attempt natalizumab therapy again, approximately 3 ½ months after the last infusion.

Two weeks post-infusion, the patient again developed a diffuse, throbbing headache, 9/10 in severity, associated with nausea, photophobia and five episodes of vomiting. She complained of neck pain, which was worse with flexion, and reported a home temperature of 38.7° C (101.7° F). Brain MRI (this time in the hospital emergency department) demonstrated no new lesions or abnormal parenchymal enhancement to suggest active demyelination. The patient refused a lumbar puncture despite medical advice and was treated with intravenous fluids, antipyretics, metoclopramide, diphenhydramine, and a low-dose steroid taper. Natalizumab was discontinued, and she then transitioned to dimethyl fumarate. Follow-up brain MRIs have not demonstrated any ongoing leptomeningeal enhancement.

DISCUSSION

We present a case of recurrent, self-limited headache and meningismus following natalizumab infusion. The initial differential diagnosis focused on infectious meningitis, particularly reactivation of HSV or VZV. Fine *et al.* reported a series of 20 CNS herpesvirus infections in patients on natalizumab treatment, including encephalitis, meningitis, and meningomyelitis [1]. The authors also found a predilection of these viral infections in patients receiving natalizumab compared to other MS drug regimens. Valenzuela and colleagues reported a case of natalizumab-associated cryptococcal meningitis [2]. However, our patient's CSF studies did not show evidence of infection, and the symptoms and imaging findings resolved rapidly without further treatment. Another possible explanation we considered was the development of neutralizing antibodies to natalizumab. In clinical studies, 9–12% of patients developed antibodies to natalizumab [3, 4]. Our patient was tested for and did not have evidence of such antibodies. There is a report of recurrent aseptic meningitis as a possible disease manifestation of MS [5], but this was not temporally related to medication administration. Also of note, the appearance of the abnormalities in this case was not similar in appearance to the small foci of enhancement noted on post-gadolinium FLAIR sequences reported in subsets of MS patients [6]. Finally, migraine was excluded because the patient did not have a previous history of headaches and because the fever along with meningeal signs would be highly atypical of that diagnosis; further, in a small series, natalizumab didn't appear to exacerbate migraines.[7] While others have suggested a possible increase in the risk of headache following lumbar puncture in natalizumab-treated patients,[8] the headache syndrome described here is likewise atypical of that syndrome, and our patient's clinical symptoms occurred before, rather than after, the lumbar puncture.

Ultimately, we believe that our patient may have had natalizumab-induced aseptic meningitis. This diagnosis of exclusion was reached based on the temporal relationship of this patient's symptoms to drug infusion, the absence of CSF abnormalities, the relapse of symptoms after each infusion of natalizumab, and the self-limited nature of these episodes. A cause-effect relationship according to the Naranjo adverse drug reactions probability scale defines this as "probable" [9]. Further, natalizumab is a monoclonal antibody, and aseptic meningitis has been associated with intravenous immunoglobulin (IVIg) infusions [10] as well as with the use of other monoclonal antibodies, including infliximab [11], cetuximab [12], efalizumab [13], and ipilimumab [14].

Drug-induced aseptic meningitis is an uncommon occurrence [10] and has not previously been reported with natalizumab. That being said, it may be possible that more mild cases thereof occur with some frequency, and it would be ideal to systematically evaluate cohorts of people receiving natalizumab to assess headache frequency and to characterize the types and timing of headaches experienced by patients. The mechanism by which drug-induced aseptic meningitis associated with natalizumab and other monoclonal antibodies occurs is unclear; others have suggested, in delayed-onset cases such as ours, a serum sickness-like illness may be explanatory [11]. Regardless, natalizumab-related aseptic meningitis should be included in the differential diagnosis of symptoms consistent with meningitis in patients treated with natalizumab and likely other such biological agents likely to be increasingly used by people with MS, although this diagnosis should be made only after a full infectious

workup is negative. Whether medications such as non-steroidal agents, anti-histamines, or corticosteroids could help to prevent such symptoms is unclear, although in the case of our patient, the delayed-onset symptoms after the re-challenge with natalizumab made a trial of preventive medications, particularly with steroids, unfavorable due to the presumed need to continue them for some time after each infusion.

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Figure.

A. T2-FLAIR showing a typical periventricular multiple sclerosis lesion (arrow). B. Post-gadolinium T2-FLAIR showing leptomenigeal enhancement in several left fronto-parietal sulci (enlargement in inset). C. Leptomenigeal enhancement is present, but more subtle, on the post-gadolinium T1-weighted scan. D. Post-gadolinium T2-FLAIR showing leptomenigeal enhancement in the left temporal lobe. E and F. Post-gadolinium T2-FLAIR 8 days after the scan in panels A–D showing new leptomenigeal enhancement in the left occipital lobe.