Varicella Zoster Associated Vasculopathy and Retinitis with Natalizumab Use in Multiple Sclerosis

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ABSTRACT

Natalizumab (Tysabri®, NTZ) is a monoclonal autoantibody approved for treatment of relapsing-remitting multiple sclerosis. NTZ inhibits leukocyte migration across the blood-brain barrier, preventing autoreactive cells from inciting an inflammatory immune response. This immunosuppression is highly efficacious in attenuating the risk of relapse of disease, but has been associated with opportunistic central nervous system (CNS) infections, most notably progressive multifocal leukoencephalopathy. Varicella-zoster and herpes simplex viruses have-also been associated with NTZ, inciting a spectrum of disease, including encephalitis, meningitis, and acute retinal necrosis. While rare, these infections can result in devastating outcomes even when promptly identified and treated.

We present a case of combined CNS varicella zoster vasculitis and acute retinal necrosis in a 57-year-old woman maintained on monthly Natalizumab therapy, who presented with headache and visual field deficits.

KEYWORDS: multiple sclerosis, immunotherapy, CNS, retina

HISTORY

A 57-year old female with relapsing-remitting multiple sclerosis (MS) was maintained on monthly infusions of Natalizumab (Tysabri®) since 2009, with good compliance. The last clinical flare of MS occurred over 20 years ago. She presented to the emergency department with a 10-day history of visual changes. She reported symptoms of blurry vision and a light headache 10 days prior, which lasted for one day and resolved without intervention. Symptoms returned five days later with blurry vision, floaters, and retro-orbital headaches. Despite no prior history of migraine headaches, the presentation was believed to be related to migraine with aura, for which the patient was prescribed sumatriptan. Her visual complaints continued to progress to a complete left-sided visual field deficit, prompting her to seek emergent medical care.

On examination there were visual field restrictions involving left superior temporal and superior nasal and right superior and inferior nasal fields, with 2mm pupils that responded sluggishly to light. The remainder of the neurological examination was unremarkable.

The patient had normal ophthalmologic examinations in the past, though she had not been seen by an ophthalmologist in the past few years. At presentation, fundoscopic images of both eyes revealed retinal necrosis with associated hemorrhage, particularly along the inferior arcade (**Figure 1**).

T2-weighted fluid-attenuated inversion recovery (FLAIR) MR imaging obtained 17 months prior to presentation demonstrated characteristic findings of multiple sclerosis, including both juxtacortical and periventricular white matter lesions (**Figure 2A**). T2-FLAIR on admission showed unchanged white matter lesions (**Figure 2B**). Axial diffusion-weighted images (DWI) showed new punctate foci of reduced diffusivity, notably at the grey-white matter interface (**Figure 3A**) and in the bilateral thalami (**Figure 3B**). Gadolinium-enhanced T1-weighted MR images demonstrated punctate foci of enhancement, some of which corresponded to diffusion-restricted lesions (**Figure 3C).**

Diagnosis of vasculitis and acute retinal necrosis caused

Figure 1. Fundoscopic images of the right eye (OD) demonstrates retinal necrosis along the inferior arcade with temporal dot-blot hemorrhages and of the left eye (OS) shows extensive retinal necrosis particularly along the inferior arcade with associated hemorrhage.

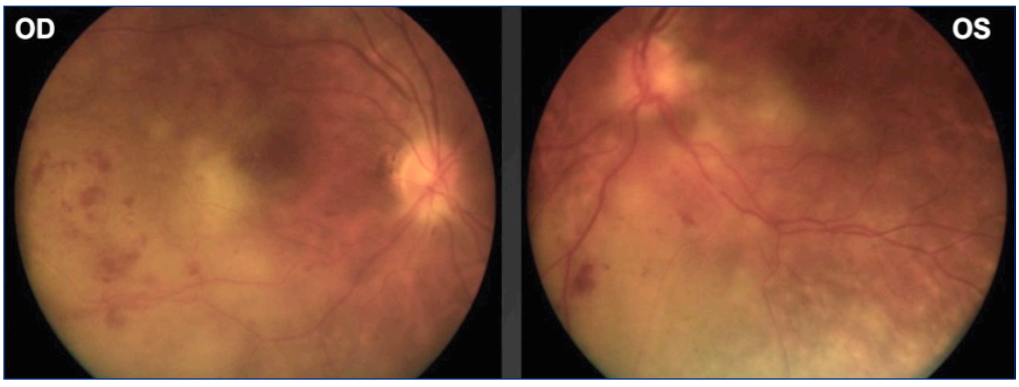


Figure 2. [**A**] Axial T2-FLAIR MR imaging performed 17 months prior to presentation demonstrates typical juxtacortical and periventricular white matter hyperintensities seen in multiple sclerosis. [**B**] Axial T2-FLAIR imaging performed at time of presentation shows near identical appearance of lesions, consistent with chronic multiple sclerosis.

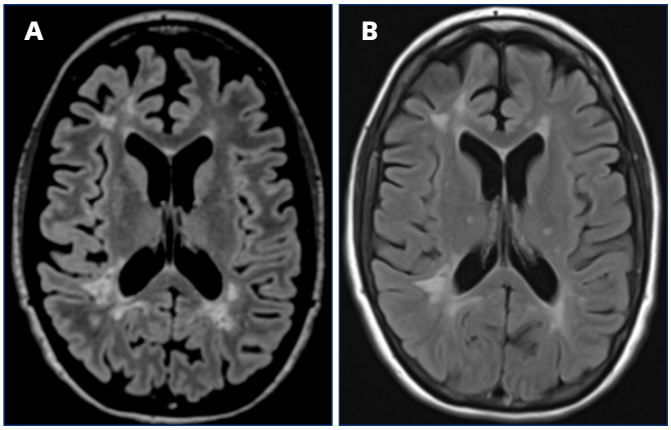
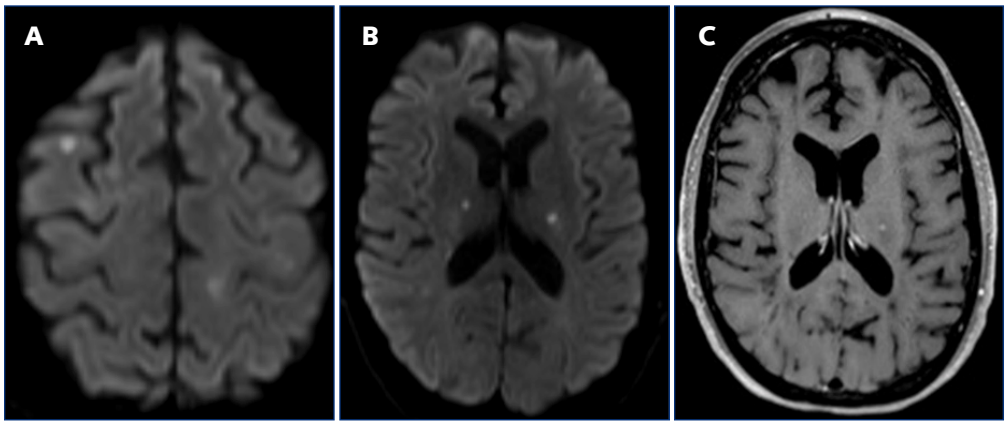


Figure 3. [**A**] Axial DWI MR imaging performed at time of presentation show multiple foci of reduced diffusivity including in the right middle frontal gyrus and [**B**] bilateral thalami. [**C**] Post-contrast Axial T2-weighted MR imaging shows punctate foci of enhancement, including a focus of enhancement which corresponds to diffusion restricting lesion in the left thalamus.



by infection with varicella zoster virus (VZV) was confirmed by the presence of anti-VZV antibodies in the cerebral spinal fluid (CSF) and polymerase chain reaction (PCR) of anterior chamber paracentesis with greater than 8 million copies/mL of VZV. Serum human immunodeficiency virus (HIV) screening was negative. Cytomegalovirus (CMV) and herpes simplex virus 1 and 2 (HSV) PCR testing in the CSF and intraocular fluid were negative. Bilateral acute retinal necrosis was treated with intravitreal ganciclovir and foscarnet but progressed to bilateral retinal detachment. She was systemically treated for VZV vasculopathy with intravenous acyclovir for two weeks, then transitioned to oral valacyclovir to complete therapy as an outpatient.

DISCUSSION

Natalizumab has been implicated in the development of opportunistic infections, including-CNS infections. To date only a few case reports of VZV reactivation with the development of acute retinal necrosis and small-vessel vasculopathy have been reported with use of NTZ.

Natalizumab is a monoclonal antibody approved for treatment of relapsing-remitting MS and Crohn's Disease. NTZ binds to the alpha4-integrin expressed on activated T-cells and other leukocytes by antagonizing the interaction with adhesion molecules on endothelial cells such as VCAM-1. This inhibits transmigration of T-cells and autoreactive leukocytes across the vascular wall into the CNS.[1,2] However, NTZ substantially decreases the CD4(+)/CD8(+) ratio in CSF compared with peripheral blood, resulting in impaired immune surveillance.[3] Consequently, NTZ has been associated with severe CNS infections. For this reason, NTZ was briefly removed from the market following the development of cases of progressive multifocal leukoencephalopathy. The medication was reintroduced, but with mandatory surveillance through the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program.[2] While rare, there is also an increased risk for NTZ associated herpes infection, most commonly encephalitis and meningitis. Even less frequent are cases of vasculitis and retinitis, only described in the setting of varicella zoster virus.[4,5]

Primary infection with VZV produces the viral exanthem chickenpox, following which the virus establishes latency in ganglionic neurons along the neuroaxis. With advancing age or immunosuppression, a decline in VZV-specific cell-mediated immunity results in viral reactivation, causing herpes zoster, which may be complicated by postherpetic neuralgia, neurological disorders, and ocular disease. The most common manifestation of VZV reactivation in the central nervous system is vasculitis. Meningitis, encephalitis, and myelitis are less common. A diagnosis can be confirmed by demonstration of intrathecal synthesis of anti-VZV antibodies, presence of viral DNA in CSF, or temporal association of herpetic rash with disease onset, either alone or in combination.[6]

Natalizumab has also been implicated in the development of acute retinal necrosis (ARN), a rare condition characterized by necrotizing retinitis, retinal detachment, and vitritis. Varicella zoster virus is the leading cause of ARN

accounting for 50% to 80% of cases, followed by herpes simplex virus types 1 and 2. Since the incidence of ARN in the general population is only 0.63–2.0 per million, it is posited that the risk for VZV-associated ARN in patients treated with NTZ may be increased by as much as 16 times.[7] Severe vision loss often occurs despite expeditious medical treatment with intravitreal and systemic antivirals.

In summary, this is a case of small-vessel vasculopathy and acute retinal necrosis caused by varicella zoster virus infection in a patient whose long-standing multiple sclerosis had been well-controlled on Natalizumab. In addition to both fundoscopy and MR imaging, this diagnosis was confirmed by presence of anti-VZV antibodies in CSF and identification of VZV by PCR in anterior chamber aqueous humor. The chronically immunocompromised state from NTZ treatment was believed to be primary etiology for reactivation of VZV. Following confirmation of the diagnosis, acute retinal necrosis was treated with intravitreal ganciclovir and foscarnet, but progressed to bilateral retinal detachments. Treatment with intravenous acyclovir and oral valacyclovir led to stabilization of MR imaging signs of vasculitis with resolution of multiple diffusion restricting and enhancing foci on follow-up imaging obtained one month after presentation.

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