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Posterior reversible encephalopathy syndrome masquerading as progressive multifocal leukoencephalopathy in rituximab treated neuromyelitis optica

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Abstract
Both progressive multifocal leukoencephalopathy (PML) and posterior reversible encephalopathy syndrome (PRES) have been reported as complications of rituximab therapy. These disorders may appear indistinguishable on magnetic resonance imaging (MRI). We report on a 42 year old woman with neuromyelitis optica (NMO) of 10 years duration who developed extensive white matter disease affecting chiefly both parietal lobes 6 months after her first and only dose of rituximab. The MRI findings suggested the diagnosis of PML, but her history was more consistent with PRES. Ultimately, a brain biopsy was performed which was consistent with the diagnosis of PRES. PRES and PML may have overlapping symptomatology and be indistinguishable on MRI. An approach to distinguishing between these two disorders is addressed.

1. Introduction

The experience of progressive multifocal leukoencephalopathy (PML) with natalizumab has heightened awareness of this disorder with other therapeutic agents. At least 5 drugs or monoclonal antibodies, including rituximab, an anti-CD20 monoclonal antibody, carry "black box" warnings for PML. Therefore, when new symptoms accompany white matter lesions on MRI in patients being treated with these agents, concern is rightfully raised about PML. We report a patient who developed new neurological symptoms and MRI abnormalities indistinguishable from PML 6 months after her initial treatment with rituximab for neuromyelitis optica (NMO).

Our patient is illustrative of manifold issues confronting the clinician when a patient develops new neurolo-

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gical symptoms and MRI findings consistent with PML after receiving a therapy that has been linked to the disorder. PML can mimic PRES radiographically. Clinically clues that suggested PRES in our patient were the rather acute onset of symptoms, the associated headache and confusion, and visual complaints that could not be ascribed to a visual field defect. All of these features are observed with PRES (Fugate et al., 2010); however, none excludes PML (Berger, 2014). A negative CSF PCR for JCV does not fully exclude the diagnosis of PML, but is quite unlikely in the face of extensive disease when performed with ultrasensitive PCR techniques as the sensitivity of the test exceeds 95% (Berger, 2014). Similarly, seronegativity for JCV antibody should argue against the diagnosis of PML, as the experience with natalizumab-associated PML indicates that newer generation ELISA studies are rarely, if ever, negative in the months before diagnosis (Lee et al., 2013).

Importantly, the risk of PML developing with therapeutic agents varies greatly. There is a unique association between PML and the administration of natalizumab and efalizumab, a monoclonal antibody used in the treatment of psoriasis that has been removed from the market (Zaheer and Berger, 2012). The risk of PML with rituximab is several orders of magnitude lower than with natalizumab and has almost always occurred in the context of disorders that already increase the likelihood of developing PML (Zaheer and Berger, 2012).

2. Case report

This 42 year old white female with a past medical history of Sjogren's syndrome, chronic liver disease, and Felty's syndrome (rheumatoid arthritis, splenomegaly and neutropenia) developed left optic neuritis in 2004. She was diagnosed with probable multiple sclerosis and started on interferon β1b subcutaneously every other day. The therapy was discontinued the following year due to increasing arthralgias. In 2006, following recurrent episodes of optic neuritis, a diagnosis of NMO was considered. That diagnosis was confirmed in January 2008, when new myelopathic features were associated with hyperintense lesions within the parenchyma of the spinal cord from C4-T1 and T3-T11 on FLAIR and T2 weighted MRIs of cervical and thoracic spine and serological testing showed positive NMO antibodies. CSF examination revealed 206 WBCs/cu mm (88% polymorphonuclear cells), myelin basic protein >8 ng/mL, and no oligoclonal bands (OCBs). She improved with parenteral corticosteroids. Despite mycophenolate mofetil and azathioprine therapy, optic neuritis recurred in the ensuing years. Nonetheless, she remained independent in all activities of daily living and retained useful sight in her right eye.

In August 2013, she received her first dose of rituximab and was scheduled to receive a course of rituximab every 6 months thereafter. On January 14, 2014, she developed left hand and foot tingling and 2 weeks later new onset headache, confusion, worsening vision, and severe imbalance. Her boyfriend and mother reported that she had a difficult time finding food on her plate and could not get a fork to her mouth. Physical examination showed a depressed, anxious female who was crying inconsolably. She had a blood pressure of 124/78 and pulse of 78. She was alert and appropriately oriented, but slow to respond to commands and questions. Pupils were 5 mm with a left Marcus Gunn pupil. There was no light perception in the left eye and at least 20/200 in the right. Both optic disks were chalky white. The cranial nerves were otherwise normal. Profound weakness of the left leg was noted and reflexes were 1+ to 2+ throughout with a right Babinski. There was a questionable sensory loss at T2. Cranial MRI revealed extensive confluent white matter lesions of both parietal lobes, greater on the right side, that were hyperintense on fluid attenuated inversion recovery (FLAIR) and T2 weighted image (T2WI) sequences and hypointense on T1WI. There was no contrast enhancement or mass effect demonstrated. These lesions were not seen on a cranial MRI from August 26, 2013, which showed only a small hyperintense signal abnormality on T2WI and FLAIR adjacent to the left lateral ventricle.

By February 2, 2014, she had developed increased weakness in all four extremities but retained useful movement of

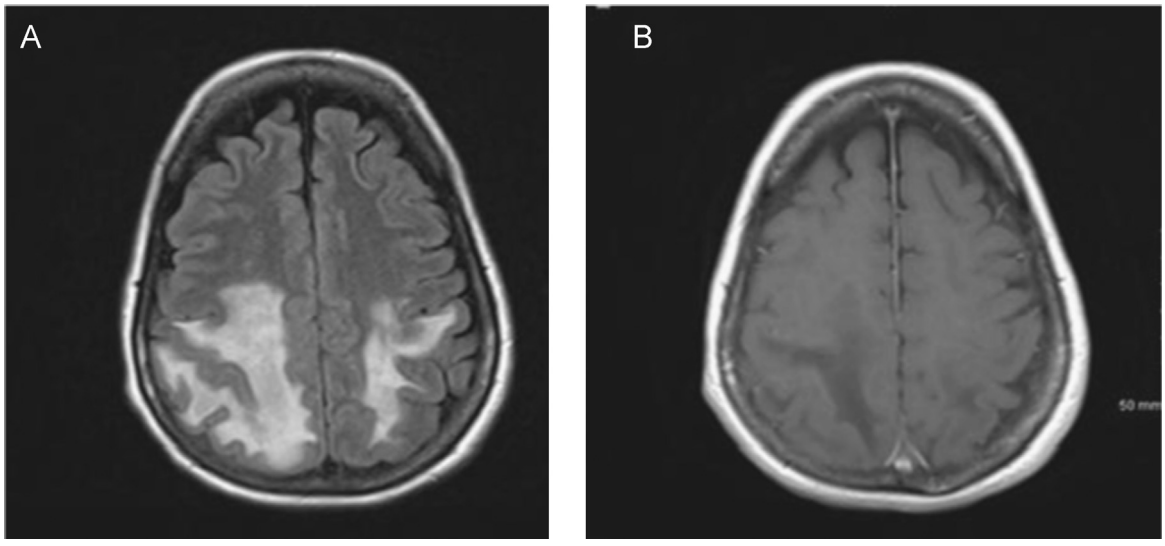

Figure 1 MRI of the brain. (A) FLAIR image shows extensive involvement of the posterior regions of both hemispheres sparing the gray matter and unassociated with mass effect. (B) T1WI with contrast showing bilateral signal hypointensities and no contrast enhancement.