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PML-IRIS IN A PATIENT TREATED WITH BRENTUXIMAB

A 38-year-old woman was diagnosed with cutaneous anaplastic T-cell lymphoma that proved refractory to methotrexate, bexarotene, denileukin diftitox, interferon γ -1b, interferon α -2b, vorinostat, and pralatrexate. She was therefore started on the newly approved monoclonal anti-CD30 antibody brentuximab vedotin. Treatment with brentuximab 1.8 mg/kg IV every 3 weeks quickly led to disappearance of her cutaneous tumors. The day after her second brentuximab infusion she developed word-finding difficulties and unsteady gait. Due to further neurologic deterioration, she was admitted to an outside hospital. Brain MRI revealed multifocal enhancing white matter lesions throughout bilateral cerebral hemispheres and posterior fossa (figure, A–C). Brain biopsy was performed 15 days after her last brentuximab dose to rule out metastases and she was diagnosed with progressive multifocal leukoencephalopathy (PML) (figure, J). The patient was discharged home with hospice care. Upon discharge, she was started on prednisone 50 mg daily to help treat her eczema. Her family brought her to our clinic for a second opinion.

The patient presented to us with a mixed nonfluent aphasia, mild apraxia, 4/5 strength in all extremities, and gait ataxia that required one person assist. Repeat brain MRI demonstrated worsening white matter lesions and contrast enhancement, concerning for immune reconstitution inflammatory syndrome (IRIS) (figure, D–F). Additional immunostaining of her brain biopsy was performed, which demonstrated a mixed population of T-cell infiltrates with a predominance of CD4⁺ T-cells (figure, K and L). We continued her on high-dose oral corticosteroids for suspected PML-IRIS. Since she had not received brentuximab in more than 8 weeks, we opted not to initiate plasma exchange therapy. Over the ensuing weeks, our patient demonstrated slow but definite improvement. She is currently ambulating without assistance and has increased spontaneous speech and comprehension. Her most recent brain MRI showed decreased lesion load and reduced enhancement (figure, G–I). She continues to be followed closely clinically and with frequent MRIs.

Discussion. Recently, PML has been seen in an increasing number of patients receiving monoclonal antibodies. Most prominently, it has been described in patients with multiple sclerosis receiving natalizumab, an α -4 integrin blocker.¹ However, PML has also occurred in patients receiving other immunomodulatory therapies.²

Several cases have been reported in patients on the B-cell-depleting anti-CD20 antibody, rituximab, and the adhesion molecule inhibitor, efalizumab, which binds the α -1 integrin CD11a.³ The Food and Drug Administration recently added a black box warning to the package insert of brentuximab in response to the report of 2 additional cases of PML that were associated with this medication (included our patient). Brentuximab is an antibody-drug conjugate linking the antimicrotubule agent monomethyl auristatin E to a CD30 monoclonal antibody. CD30 (TNFSF8) is frequently expressed on anaplastic large-cell lymphoma cells as well as in Hodgkin lymphoma.⁴ It is not surprising that alterations in immune cellular function can lead to PML; however, it is not entirely clear why PML occurs with higher frequency in certain patient populations or with particular immunomodulatory agents. Our patient developed PML after 2 courses of brentuximab, which raises concern that this therapy increased her risk for developing PML, although the combination of her underlying lymphoma and exposure to prior immune-altering medications likely added to that risk.

Patients with PML frequently develop IRIS. The exact pathobiology of IRIS is not entirely understood, although rapid infiltrates of cytotoxic T-cells have been implicated.⁵ While reconstitution of the immune system is important for controlling the JC virus infection, CNS inflammation due to IRIS can result in death or permanent neurologic disability; therefore, IRIS needs to be recognized early.⁶ The diagnosis of PML-IRIS can be challenging as there currently are no established diagnostic criteria, though rapid clinical worsening and patchy contrast enhancement on MRI raise the concern for IRIS.⁶ In our patient, the exact timing of onset of IRIS is not entirely clear as she was not followed closely until establishing care with us. However, the presence of

Figure Radiographic and pathologic evidence of progressive multifocal leukoencephalopathy and progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome

(A-I) Axial MRI over time shows worsening of signal abnormality on fluid-attenuated inversion recovery (FLAIR) (top 2 rows) at 2 months (D, E) compared to initial presentation (A, B) with some improvement at 3 months (G, H). There is significant increase in gadolinium enhancement 2 months after initial presentation (F) compared to initial imaging (C), which is essentially unchanged at 3 months (I). (J-L) Left frontal brain biopsy reveals subsets of large gemistocytic astrocytes and oligodendrocytes with prominent nuclear enlargement that were positive after immunostaining with a polyclonal antibody against JC virus (Santa Cruz Immunochemicals, Santa Cruz, CA) (J). Multiple infiltrating T cells are seen on immunohistochemistry staining for CD4 (K) and CD3 (L).

T-cell infiltrates on her brain biopsy and enhancement on her initial MRI suggests early IRIS or simultaneous PML-IRIS. Previous reports have suggested that treating patients with PML-IRIS with corticosteroid therapy may help facilitate better neurologic outcomes.⁵ Additionally, severe cases of CNS-IRIS may require a longer duration of corticosteroid treatment, as highlighted by our case. Studies of the benefits, optimal timing, dosage, and duration of corticosteroids are needed to help guide long-term management in these patients. While management of PML and PML-IRIS can be challenging, early initiation of hospice care may not

be the appropriate decision. As highlighted in this case report, favorable outcomes are possible with patience and close monitoring.

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1. Clifford DB, DeLuca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010;9:438–446.
2. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. *Annu Rev Med* 2010;61:35–47.
3. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol* 2009;10:816–824.
4. Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res* 2012;18:248–255.
5. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. *Neurology* 2011;77:1061–1067.
6. Harrison DM, Newsome SD, Skolasky RL, McArthur JC, Nath A. Immune reconstitution is not a prognostic factor in progressive multifocal leukoencephalopathy. *J Neuroimmunol* 2011;238:81–86.

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A 66-YEAR-OLD PATIENT WITH VANISHING WHITE MATTER DISEASE DUE TO THE p.Ala87Val EIF2B3 MUTATION

Vanishing white matter (VWM; OMIM # 603896) is one of the most prevalent inherited childhood leukoencephalopathies. It has, however, become evident that VWM has a wider clinical spectrum, with age at onset inversely related to clinical severity. Many affected women experience a combination of leukoencephalopathy and primary amenorrhea or premature ovarian failure, a condition named ovarioleukodystrophy. Mutations in any of the genes encoding the 5 subunits of the Eukaryotic Initiation Factor 2B gene (*EIF2B1*, 2, 3, 4, and 5) can independently cause VWM.¹

Case report. A 66-year-old woman presented with a 5-year history of progressive gait impairment and behavioral and cognitive disturbances. Her medical history showed premature ovarian failure (at age 24 years), subclinical hypothyroidism, and late-onset diabetes. Her familial history was unremarkable.

She reported a rapid worsening of her clinical condition in the last 10 days. Neurologic examination showed lower limb hypertonia, spastic paraparesis, brisk reflexes, Babinski sign in the right foot, dysdiadochokinesia, and ideomotor apraxia. Neuropsychological testing performed during a previous hospitalization in 2010 showed planning, praxis, and visuospatial memory deficits associated with less prominent abstraction and lexical retrieval impairment. As the rapid worsening of cognitive disturbances in the presence of the above-mentioned neurologic signs was poorly consistent with the diagnosis of a primary neurodegenerative disease, a brain MRI was performed. T2-weighted images showed symmetric diffuse signal abnormality in the hemispheric white matter, sparing the U fibers (figure, A); diffusion-weighted images showed diffusion restriction (figure, B); cortical and subcortical atrophy was also reported (figure, C). A muscle biopsy, performed to rule out a metabolic disease, showed an aspecific myopathic pattern. A point-resolved spectroscopy sequence showed a reduction of all metabolites in

Figure Brain MRI

(A) T2-weighted scan shows symmetric diffuse signal abnormality in the hemispheric white matter, sparing the U fibers. (B) Diffusion-weighted imaging scan shows diffusion restriction. (C) T1-weighted scan shows cortical and subcortical atrophy.