CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Tumefactive demyelination in a patient with relapsing-remitting MS on ocrelizumab

Vanessa F. Moreira Ferreira, MD, David Meredith, MD, and James M. Stankiewicz, MD

Neurol Neuroimmunol Neuroinflamm 2019;6:e589. doi:10.1212/NXI.0000000000000589

Correspondence
Dr. Stankiewicz
jstankiewicz@bwh.harvard.edu

Ocrelizumab is an intravenously infused humanized monoclonal antibody that induces antibody-dependent cellular cytolysis and complement-mediated lysis of CD20-expressing B cells. Ocrelizumab reduced gadolinium-enhancing activity 94% and 95% compared with subcutaneous interferon beta-1a in relapsing-remitting MS (RRMS).[1] We report a case of tumefactive demyelination (TD) in an ocrelizumab-treated patient with RRMS.

Case report

The patient initially presented in April 2009, at age 27 years, with an episode of numbness in the right arm and torso. In the following months, he developed intermittent lower extremity weakness, requiring bilateral assistance to ambulate. In June 2010, he was diagnosed with RRMS after a brain MRI showed 20 nonenhancing lesions periventricularly and in the white matter on fluid-attenuated inversion recovery (FLAIR) sequence. Cervical and thoracic MRI revealed diffuse cord T2 hyperintensity, and a lumbar puncture (LP) showed 17 oligoclonal bands. The patient began interferon beta-1a subcutaneously but transitioned to cyclophosphamide 3 months later after requiring wheelchair assistance and developing bladder and bowel incontinence. While on cyclophosphamide, brain MRIs in 2011 and 2012 revealed 8 new enhancing lesions and a small enhancing left corona radiata lesion, respectively. He transitioned to dimethyl fumarate in October 2013. A brain MRI in September 2015 demonstrated new nonenhancing FLAIR hyperintensities. He transitioned to ocrelizumab in October 2017 receiving two 300 mg doses 2 weeks apart and then received a 600 mg maintenance dose in May 2018 (preinfusion serum CD19 = 0.6% lymphocytes).

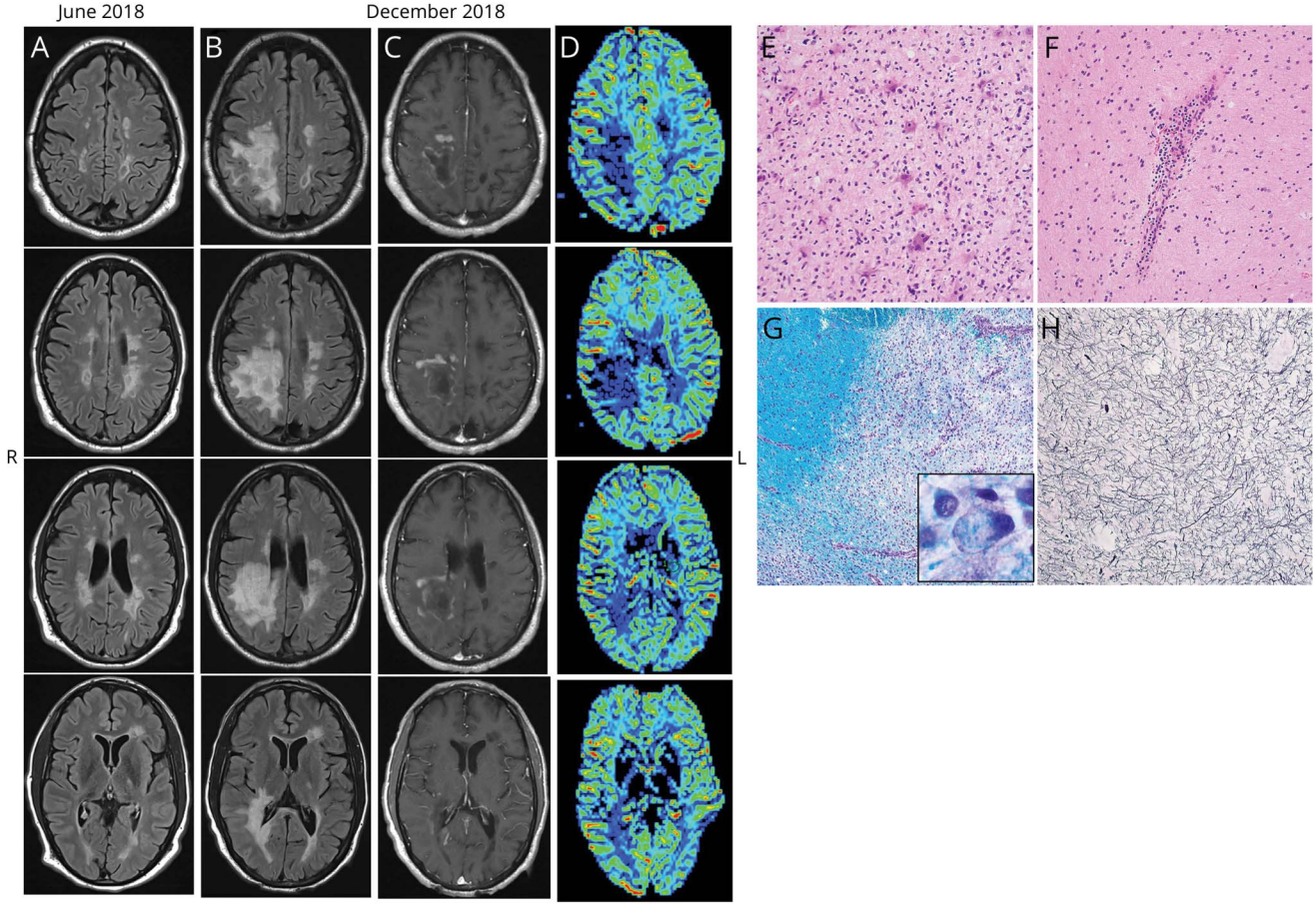
One day before next scheduled infusion in November 2018, the patient reported exacerbated weakness, incoordination, and difficulty concentrating. Ocrelizumab was infused (preinfusion serum CD19 = 0.7% lymphocytes). In the following weeks, the patient developed intermittent weakness in his left upper extremity. He presented to the emergency department. While there, he experienced generalized tonic-clonic seizures and was sedated and intubated. After cessation of seizure activity and extubation, he was transferred to our institution. His neurologic examination was as previously observed except for increased weakness in the left upper extremity and ataxia with finger-nose-finger testing. An MRI demonstrated a 4.5 × 6.7 × 6.7 cm heterogeneous right parietal lobe hyperintensity, which exhibited peripheral enhancement on T1 sequences after gadolinium administration. Magnetic resonance (MR) perfusion imaging found decreased cerebral blood volume (CBV) in the area of interest (figure, B–D). An LP found the following: 16 white cells, 0 red cells, glucose = 63 mg/dL, and protein = 81 mg/dL. High-sensitivity JC virus (JCV) PCR assay was negative. No malignant cells were identified. A stereotactic-guided brain biopsy of the lesion was performed. Pathology was consistent with active demyelinating lesion (figure, E–H). Immunohistochemistry for polyoma virus was negative, excluding progressive multifocal leukoencephalopathy (PML). The patient received 3 days of 1 g IV methylprednisolone and then began oral methotrexate 20 mg weekly.

From the Department of Neurology (V.F.M.F., J.M.S.); and Department of Pathology (D.M.), Brigham and Women's Hospital, Partners MS Center, Harvard Medical School, Boston, MA.

Go to Neurology.org/NN for full disclosure. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Figure MRI appearance of TD compared with the patient's baseline MRI, histopathology showing active demyelination



(A) Axial FLAIR brain MRI (June 2018) shows scattered bilateral foci of T2 prolongation periventricularly and juxtacortically. Follow-up brain MRI (December 2018) reveals (B; FLAIR) a hyperintense lesion in the right parietal lobe that abuts the right lateral ventricular atrium (C; T1 with contrast) presenting heterogeneous peripheral gadolinium-enhancement; (D; perfusion) shows decreased rCBV corresponding to this mass. Representative histopathologic images from the enhancing lesion. (E) Sections of white matter show marked reactive astrocytosis along with dense macrophage infiltrate and perivascular collections of lymphocytes (F). (G) Luxol fast blue stain demonstrates well-demarcated region of pallor, indicating myelin loss. High magnification highlights granular myelin debris accumulation within macrophages (inset). (H) Bodian stain within the region of myelin loss shows preservation of underlying axons. Magnification: 200× for panels E, F, and H; 100× for G; and 600× for the inset. FLAIR = fluid-attenuated inversion recovery.

Discussion

TD has not been reported with ocrelizumab or rituximab, a less humanized anti-CD20 monoclonal antibody. It has occurred with other MS drugs including fingolimod,[2] natalizumab,[2] and alemtuzumab.[3] Our patient has particularly severe MS, as evinced by his rapidly worsening clinical course, high MRI disease burden, and continued accrual of new MRI lesions. It is possible that ocrelizumab was unable to control this patient's fulminant disease. Alternately, it may be that a limited reconstitution of B cells (preinfusion serum CD19 = 0.7%) was sufficient for this patient to mount a potent autoimmune response. We believe that human antichimeric (HACA) antibodies or a direct effect from ocrelizumab can be excluded. One would expect little suppression of CD19 count if HACA antibodies were present. A more proximate relationship between infusion and TD development would be expected if ocrelizumab was causative, and mechanistically, this does not seem likely.

Questions emerge regarding treatment. Because inadequate serum suppression of B cells might have been a contributor, one wonders whether altering dosing to target continuous full CD20 B-cell suppression (preinfusion serum CD19 = 0) is appropriate for patients with particularly inflammatory disease. Methotrexate was combined with ocrelizumab based on a report by Tak et al.[4] that methotrexate offered additional clinical benefit in rheumatoid arthritis without additional side effects. Further work would be beneficial to elucidate whether this is a viable strategy in ocrelizumab patients experiencing breakthrough disease.

Several factors contributed to the decision to perform a brain biopsy. MRI appearance was consistent with PML, tumefactive MS, or glioma. In these conditions, MR perfusion CBV is typically increased rather than decreased,[5,6] as seen in our patient. PML was entertained, given the patient's previous immunosuppressive medication exposure and a false-negative rate

with JCV CSF PCR testing.[7] In addition, it seemed implausible that such florid demyelination could occur with ocrelizumab. It is our hope that this report will alert readers to this possibility.

Study funding

No targeted funding reported.

Disclosure

J.M. Stankiewicz has received consulting fees from Roche-Genentech, Biogen, Genzyme, Novartis, Bayer, EMD Serono, and Celgene in the past two years. V.F. Moreira Ferreira and D. Meredith report no disclosures. Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* February 13, 2019. Accepted in final form May 21, 2019.

Appendix Authors

Name	Location	Role	Contribution
Vanessa F. Moreira Ferreira, MD	Brigham and Women's Hospital, Partners MS Center, Harvard Medical School; Boston, MA, USA	Author	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
David Meredith, MD	Brigham and Women's Hospital, Partners MS Center, Harvard Medical School; Boston, MA, USA	Author	Major role in the acquisition of histopathologic data
James Stankiewicz, MD	Brigham and Women's Hospital, Partners MS Center, Harvard Medical School; Boston, MA, USA	Author	Designed and conceptualized the study; analyzed the data; and interpreted the data and revised the manuscript for intellectual content

References

1. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221–234.
2. Hardy TA, Chataway J. Tumefactive demyelination: an approach to diagnosis and management. J Neurol Neurosurg Psychiatry 2013;84:1047–1053.
3. Barton J, Hardy TA, Riminton S, et al. Tumefactive demyelination following treatment for relapsing multiple sclerosis with alemtuzumab. Neurology 2017;88:1004–1006.
4. Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis 2011;70:39–46.
5. Khoury MN, Gheuens S, Ngo L, Wang X, Alsop DC, Koralnik IJ. Hyperperfusion in progressive multifocal leukoencephalopathy is associated with disease progression and absence of immune reconstitution inflammatory syndrome. Brain 2013;136(pt 11):3441–3450.
6. Essig M, Nguyen TB, Shiroishi MS, et al. Perfusion MRI: the five most frequently asked clinical questions. AJR Am J Roentgenol 2013;201:W495–W510.
7. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology 2013;80:1430–1438.

Tumefactive demyelination in a patient with relapsing-remitting MS on ocrelizumab

Vanessa F. Moreira Ferreira, David Meredith and James M. Stankiewicz

Neurol Neuroimmunol Neuroinflamm 2019;6;
DOI 10.1212/NXI.0000000000000589