Lana Zhovtis Ryerson,
MD

Ilya Kister, MD

Matija Snuderl, MD

Cynthia Magro, MD

Bibiana Bielekova, MD

*Neurol Neuroimmunol
Neuroinflamm*

2015;2:e151; doi: 10.1212/
NXI.0000000000000151

INCOMPLETE SUSAC SYNDROME EXACERBATED AFTER NATALIZUMAB

OPEN

A 66-year-old man with hypertension presented with right-sided numbness and slurred speech. MRI revealed a large left frontoparietal area of T2-weighted hyperintensity with focus of central enhancement (figure, A and B). The patient's symptoms self-resolved within weeks. Over the next 2 years, he experienced multiple relapses including encephalopathy characterized by headache with motor aphasia and sudden incomplete hearing loss. All symptoms except hearing loss were transient, improved with IV methylprednisolone, and were accompanied by new T2 lesions involving the periventricular white matter, corpus callosum, and subcortical white matter, with some demonstrating partial enhancement (figure, C and D).

Extensive workup revealed only anti-endothelial cell antibodies (AECA) (1:50, indirect immunofluorescence, Cornell Dermatopathology Laboratory, New York). CSF analysis performed during remission was unrevealing; oligoclonal bands were absent. Fluorescein angiogram and optical coherence tomography did not show any abnormalities.

The patient was presumed to have multiple sclerosis (MS) and started on natalizumab. Within days of the first infusion, he developed motor aphasia, with MRI revealing extensive T2-hyperintense lesions with corresponding leptomeningeal enhancement (figure, G and H). Repeat CSF analysis revealed elevated protein of 116 mg/dL. Natalizumab antibodies were negative. The patient underwent brain biopsy, which revealed predominantly perivenular demyelination (figure, I) with relative preservation of axons, although axons were focally distended and showed evidence of axonal injury (figure, M) suggestive of demyelinating etiology. In addition, there was evidence of focal microangiopathy. Scattered vessels contained perivascular CD3⁺ CD8⁺ T lymphocytes whereas other vessels showed endothelial cell detachment and early fibrin deposition suggestive of an acute endothelial injury. CD68⁺ and CD163⁺ macrophages were present in the perivascular space (figure, J). Vascular deposits of C3d (figure, K) with lesser but still discernible deposits of C4d and C5b-9 were noted. There was focal red cell extravasation and hemosiderin deposition along with focal

basement membrane zone reduplication compatible with antecedent episodes of vascular injury (figure, L). Glial fibrillary acidic protein stain showed massive reactive gliosis. There was no histopathologic evidence of infection or lymphoma. Overall morphologic features were those of perivenular demyelination and complement-induced endothelial injury.

Discussion. Atypical age at onset, episodes of encephalopathy and hearing loss, unusual elevated protein in CSF, extensive leptomeningeal involvement, and remarkable disease exacerbation after natalizumab suggest a diagnosis of Susac syndrome rather than MS. Susac syndrome is presumed to be an autoimmune disorder with microvascular occlusions in the brain, retina, and cochlea.¹ The triad of encephalopathy, branch retinal artery occlusions, and hearing deficits is seen at some point in the disease in 85% of cases, but only 13% of patients manifest all these symptoms on presentation.² Our patient exhibited 2 core features of Susac syndrome. Further findings supporting the diagnosis on MRI include preferential involvement of the central portion of the corpus callosum (known as “snowball” lesions; figure, E), central callosal holes (figure, F), and extensive leptomeningeal enhancement (figure, G and H), reported in 30% of patients with Susac syndrome. The low titers of AECA seen in our patient are suggestive of Susac syndrome, but this finding is not specific.³ Treatments for Susac syndrome are based solely on clinical experience; steroids in conjunction with IV immunoglobulin (IVIg) and/or cyclophosphamide are the most common agents used.¹ Our patient has been treated with IVIg for the last 14 months and has had no evidence of clinical or radiologic relapses thus far.

Reports of brain biopsy are rare. Pathologic findings include “focal microangiopathic and/or gliotic changes” and T cell perivascular inflammation with CD8 cell predominance, seen in our case as well.^{1,4} Some investigators reported evidence of antibody-mediated endothelial cell injury syndrome/endothelial cell necrosis in concert with C3d and C5b-9 deposition within the capillaries and venules of the brain, although this may not be specific because it was also found in some controls.^{2,4} Our patient's biopsy also showed findings suggestive of microvascular injury (figure, L) and complement deposition (figure, K),

Fluid-attenuated inversion recovery (FLAIR) sequence with a single large T2-hyperintense signal involving the left frontoparietal lobe (A) with gadolinium-enhanced (Gd+) T1-weighted imaging (T1WI) demonstrating a small central area of contrast enhancement (B). FLAIR sequence demonstrating ongoing new T2 lesions involving bilateral hemispheres (C) with evidence of blood-brain barrier opening, with Gd+ T1WI again corresponding to the left parietal lobe lesion (D). Preferential involvement of the central portion of the corpus callosum (known as "snowball" lesions) (E) as well as a central callosal hole (F). FLAIR sequence demonstrating extensive T2-hyperintense lesions (G) with corresponding postcontrast T1WI confirming leptomeningeal enhancement along the left parietal hemisphere (H) days after the patient's first natalizumab infusion. (I) Low-power Luxol fast blue (LFB) hematoxylin & eosin (H&E) stain demonstrates white matter with patchy myelin loss. Myelin loss was most prominent in the perivascular white matter, with greater perivenular than periaxonal involvement. (J) High-power view of perivascular macrophages also contained small particles of LFB- and periodic acid-Schiff-positive material consistent with the myelin accumulation, which can be seen in demyelinating disorders. (K) Vascular deposits of C3d. (L) A venule infiltrated by macrophages and lymphocytes. There is evidence of vascular compromise characterized by marked red cell extravasation. (M) Neurofilament stain, an axonal marker, showed relative preservation of axons; however, axons were focally distended and showed evidence of axonal injury (yellow arrowheads).

consistent with the endothelial cell injury hypothesis. However, we also observed prominent myelin loss (figure, I), which has not been previously reported in Susac syndrome. It is possible that demyelination in our patient was consequent to microvascular injury, or it may be an unrelated process.

Increased relapse frequency after the start of immunomodulatory drugs effective in MS, such as alemtuzumab, interferon β , and natalizumab, in patients with “atypical” inflammatory diseases of the CNS has been described.^{5–7} In our case, there was a dramatic temporal relationship between the initiation of natalizumab and disease exacerbation. It is possible that natalizumab altered the balance of the immune system by decreasing circulating T regulatory cells with a subsequent increase in the number of proinflammatory cytokine-producing T cells or blocked egress of regulatory natural killer cells from the periphery into the brain, hence precipitating the relapse.⁵ Another hypothesis is that natalizumab, being a monoclonal antibody, may be causing activation of the complement and thus inducing the relapse, although no supporting evidence was found in the literature.

Our case highlights the difficulty in diagnosing atypical relapsing idiopathic inflammatory disease of the CNS, even with the help of a brain biopsy, and demonstrates the risk of treating these conditions with MS-specific immune-modulating drugs.

From the Departments of Neurology (L.Z.R., I.K.) and Pathology (M.S.), NYU Langone Medical Center, New York, NY; Department of Dermatopathology (C.M.), Weill Cornell Medical College, New York, NY; and National Institute of Neurological Disorders and Stroke (B.B.), Bethesda, MD.

Author contributions: L. Zhovtis Ryerson: drafting and revising the manuscript for intellectual content. I. Kister: drafting and revising the manuscript for intellectual content. M. Snuderl: drafting and revising the manuscript for intellectual content. C. Magro: drafting and revising the manuscript for intellectual content. B. Bielekova: drafting and revising the manuscript for intellectual content.

Study funding: The study was partially funded by the intramural research program of the National Institute of Neurological Disorders and Stroke, NIH (B.B.).

Disclosure: L.Z. Ryerson is on the scientific advisory board for Biogen, received travel funding and speaker honoraria from Biogen and Teva, has consulted for Biogen, is on the speakers' bureau for Biogen and

Teva, and received research support from Biogen. I. Kister is on the scientific advisory board for Biogen and MS Franchise Data Generation, has consulted for Biogen, and received research support from Biogen, Serono, Novartis, Guthy-Jackson Charitable Foundation, and National Multiple Sclerosis Society. M. Snuderl received research support from the Friedberg Foundation and holds stock/stock options in Arca Biopharma, Bluebird Bio, Catalyst Pharmaceutical, Cellceutix, Epizyme, Geron, Isis Pharmaceutical, Nanostring, Sevion Therapeutics, and Acceleron Pharma. C. Magro reports no disclosures. B. Bielekova is co-inventor on several NIH patents related to daclizumab, has received patent royalty payments from the NIH, and received research support from National Institute of Neurological Disorders and Stroke, Biogen/Abbvie, and Santhera Pharmaceuticals. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received May 26, 2015. Accepted in final form July 23, 2015.

Correspondence to Dr. Zhovtis Ryerson: lane.zhovtisryerson@nyumc.org

1. Susac JO, Egan RA, Rennebohm RM, Lubow M. Susac's syndrome: 1975–2005 microangiopathy/autoimmune endotheliopathy. *J Neurol Sci* 2007;257:270–272.
2. Dörr J, Krautwald S, Wildemann B, et al. Characteristics of Susac syndrome: a review of all reported cases. *Nat Rev Neurol* 2013;9:307–316.
3. Magro CM, Poe JC, Lubow M, Susac JO. Susac syndrome: an organ-specific autoimmune endotheliopathy syndrome associated with anti-endothelial cell antibodies. *Am J Clin Pathol* 2011;136:903–912.
4. Hardy TA, O'Brien B, Gerbis N, et al. Brain histopathology in three cases of Susac's syndrome: implications for lesion pathogenesis and treatment. *J Neurol Neurosurg Psychiatry* 2015;86:582–584.
5. Kitley J, Evangelou N, Küker W, Jacob A, Leite MI, Palace J. Catastrophic brain relapse in seronegative NMO after a single dose of natalizumab. *J Neurol Sci* 2014;339:223–225.
6. Chen S, Wu A, Zhang B, et al. A case of exacerbated multiphasic disseminated encephalomyelitis after interferon β treatment. *J Neurol Sci* 2013;325:176–179.
7. Gelfand JM, Cotter J, Klingman J, Huang EJ, Cree BA. Massive CNS monocytic infiltration at autopsy in an alemtuzumab-treated patient with NMO. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e34. doi: 10.1212/NXI.000000000000034.

Neurology® Neuroimmunology & Neuroinflammation

Incomplete Susac syndrome exacerbated after natalizumab

Lana Zhovtis Ryerson, Ilya Kister, Matija Snuderl, et al.

Neurol Neuroimmunol Neuroinflamm 2015;2;

DOI 10.1212/NXI.0000000000000151

This information is current as of September 24, 2015

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/2/5/e151.full.html
References	This article cites 7 articles, 1 of which you can access for free at: http://nn.neurology.org/content/2/5/e151.full.html##ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Demyelinating disease (CNS) http://nn.neurology.org/cgi/collection/all_demyelinating_disease_cns Autoimmune diseases http://nn.neurology.org/cgi/collection/autoimmune_diseases Multiple sclerosis http://nn.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright © 2015 American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.