12-15-2020

Treating MS after surviving PML: Discrete strategies for rescue, remission, and recovery patient 2: From the National Multiple Sclerosis Society Case Conference Proceedings

Roberto A. Cruz  
*The University of Texas Rio Grande Valley, roberto.cruzsaldana@utrgv.edu*

Nick Hogan  
Jayne Sconzert  
Megan Sconzert  
Eugene O. Major

*See next page for additional authors*

Follow this and additional works at: [https://scholarworks.utrgv.edu/som_pub](https://scholarworks.utrgv.edu/som_pub)

Part of the Medicine and Health Sciences Commons

**Recommended Citation**

This Conference Proceeding is brought to you for free and open access by the School of Medicine at ScholarWorks @ UTRGV. It has been accepted for inclusion in School of Medicine Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.
Treating MS after surviving PML: Discrete strategies for rescue, remission, and recovery patient 2

From the National Multiple Sclerosis Society Case Conference Proceedings

Roberto Alejandro Cruz, MD, Nick Hogan, MD, PhD, Jayne Sconzert, PT, LLC, Megan Sconzert, BSN, RN, Eugene O. Major, PhD, Robert P. Lisak, MD,* Esther Melamed, MD, PhD, Thomas C. Varkey, BS, MBA,* Ethan Melzer, MD, Andrew Goodman, MD, Oleg Komogortsev, PhD, Matthew S. Parsons, PhD, Kathleen Costello, MS, ANP-BC,* Jennifer S. Graves, MD, PhD,† Scott Newsome, MD,‡ Scott S. Zamvil, MD, PhD,* Elliott M. Frohman, MD, PhD,*† and Teresa C. Frohman, MPAS, MSCS, PA-C*§

Neurol Neuroimmunol Neuroinflam 2021;8:e930. doi:10.1212/NXI.0000000000000930

Case presentation

The patient is a right-handed White woman with relapsing-remitting MS diagnosed subsequent to left acute optic neuritis (AON). She described a previous transient episode of severe, electrical, and paroxysmal facial pain consistent with trigeminal neuralgia. Initial MRI demonstrated supratentorial hyperintensities consistent with plaques of inflammatory demyelination. CSF analysis demonstrated oligoclonal bands that were not present in blood samples.

The patient’s medical history was significant for multiple evanescent white dot syndrome (MEWDS) in her left eye and a left hemianopic defect at baseline. MEWDS, typically affects young women, is commonly unilateral and secondary to viral illness. Transient white dots are observed at the level of the retinal pigmented epithelium and result in painless, sudden monocular visual field loss localized to the central field.

The patient was adherent with azathioprine as an MS disease-modifying therapy (DMT), and she remained neurologically stable for 8 years from her initial episode of AON until she developed a second episode of painful left AON. Believed to represent breakthrough activity in the patient’s MS, she was transitioned to a combination therapy regimen comprising weekly IM interferon β-1a and mycophenolate mofetil (figure 1).

She remained stable for an additional 12 years until she developed a third episode of painful left AON. Further investigations, including cell-based assay assessments for both aquaporin 4 and antemyelin oligodendrocyte glycoprotein antibodies, were unrevealing. The patient’s DMT regimen at this point was changed to fingolimod, with a clinical course complicated by herpes
simplex 1 meningitis 3 months after initiation of this new therapy and recovered after a course of IV acyclovir.

Fingolimod was continued for 12 months until she developed the abrupt onset of profound hearing loss on the left. Investigations confirmed central hearing loss, with an approximately 90 dB threshold on the left (figure 1). MRI failed to exhibit any new or active lesions, and MR angiographies of the carotid and vertebrobasilar circulations were normal.

In the absence of any improvement in her hearing after the administration of both IV and oral corticosteroids, we intensified her therapy with punctuated cycles of plasma exchange (PLEX). These treatments resulted in an improvement of 10–20 dB of hearing threshold after each of 3 cycles of plasma exchange (each consisting of 5 full volume exchanges), rescuing about 50 of the 90 dB threshold derangement that characterized her left-sided hearing loss (figure 1).

Given concern of auditory complications as a drug side effect of fingolimod, it was discontinued. The patient was started on weekly etanercept, an antitumor necrosis factor (TNF) agent with audiologic protective effects. Specifically, TNF modulatory medications are beneficial in treating severe neurosensory hearing loss, autoimmune labyrinthitis, noise-related hearing loss, and in promoting recovery after facial nerve injury. Alternately, TNF blockers have been associated with the CNS and peripheral nervous system demyelinating syndromes.

In lieu of this risk that etanercept might precipitate an MS exacerbation, we further intensified the patient’s MS DMT with natalizumab. Given the patient’s positive John Cunningham (JC) virus immunoglobulin G status, we decided to administer every 8-week extended interval dosing (EID) of natalizumab, given that evidence was emerging to demonstrate that such a longer latency between treatments was not associated with a compromise in clinical or paraclinical measures of MS disease activity while simultaneously mitigating the risk of progressive multifocal leukoencephalopathy (PML), when compared with standard interval dosing of every 4-week treatments. The first infusion was strategically administered 1 week before inception of etanercept treatment.

Ten months after the inception of EID of natalizumab, etanercept, and cycles of PLEX, our patient noticed diminished coordination and volitional control when attempting to use her right arm, and 2 months henceforth, she developed dysarthric speech and intermittent falls.

Urgent examination demonstrated downbeat nystagmus and saccadic dysmetria. Eccentric gaze holding to the right revealed gaze-evoked nystagmus, consistent with a “leaky”
neural integrator (implicating cerebellar flocculus dysfunction). Furthermore, we observed low-gain smooth pursuit eye movements to the right and a reduced vestibulo-ocular reflex suppression (VORS) on attempted head/eye combined motion to the right in conjunction with a course tremor in the right arm.

Brain MRI revealed many “punctate” enhancing lesions spanning all 3 levels of the brainstem, albeit most significantly affected was the right pons and the right cerebellum (figure 2).

Differential diagnosis
The constellation of punctate enhancements was reminiscent of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). We failed to detect the 68kd inner ear antigen antibody (also known as heat shock protein 70); a potential etiology of inner ear autoimmune disease. Given the administration of intensive immune therapies, a diagnosis of PML was most likely and was confirmed when CSF analysis revealed the presence of 2180 JC viirions/mL (figure 1).10–12

Final diagnosis
The patient was diagnosed with PML, and treatment was aimed at first promoting an attenuated immune reconstitution to avoid CNS damage from the immune reconstitution inflammatory syndrome (IRIS), then followed by the initiation of a new MS DMT.

Natalizumab was discontinued and 3 courses of PLEX (at 1 full volume daily for a total of 3 days) were performed to remove natalizumab. To reduce the risk of CNS IRIS, we initiated 12 weeks of IV methylprednisolone dosed 1 g per week, then followed by every other week infusions of methylprednisolone for 6 doses, and then monthly for 3 final doses.13

After PLEX and corticosteroids, the patient demonstrated improvement of her saccadic dysmetria, right arm coarse tremor, VOR cancellation, down beating nystagmus, and dysarthria. Notwithstanding improvements she exhibited substantial neurologic deficits including dependency on a cane and walker for ambulation. Seven months after corticosteroid therapy, JC virus was undetectable in both blood and CSF (figure 1).

In June 2016, it was decided to commence MS DMT with alemtuzumab, an anti-CD52 monoclonal antibody. After cellular depletion, bone marrow mobilization of B lymphocytes in large numbers occurs producing a discordant B cell hyper-repopulation (generally within 3–6 months) with T cells approximating baseline levels at 12–24 months. This period of B cell hyper-repopulation includes the presence of CD20+ T cells—exhibiting a proinflammatory phenotype, which has been hypothesized to promote B cell antigen presentation in the absence of T cell help—a time where B cells cannot differentiate between self and non–self-

Figure 2 Cataclysmic disease activity associated with PML is abolished with intensive immunotherapy

(A) T1-weighted postgadolinium MRI images performed on April 2014. (B) T2-weighted MRI images performed on April 2014. (C) T2-FLAIR MRI images performed on July 2019 and revealing striking resolution of the disease processes previously active from PML, and potentially with some component of IRIS. FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy.
epitopes; and which may be mechanistically germane to the high incidence of secondary autoimmunity associated with alemtuzumab DMT in MS.14

A recently published report theorized that a “Whack-A-Mole” B cell depletion strategy involving the punctuated administration of 100 mg of rituximab, temporally synchronized with the return of B lymphocytes, may be capable of mitigating secondary autoimmunity associated with alemtuzumab DMT for MS by abolishing the discordant and precocious B cell hyper-repopulation while also deleting CD20+ T cells.

Our patient received 1 course of alemtuzumab (5 consecutive days of IV treatment). Furthermore, she was treated with the “Whack-A-Mole” B cell depletion regimen with 100 mg of rituximab when her CD19+ cells approximated 40%–50% of baseline levels.14

One year after alemtuzumab therapy, our patient’s dysarthria resolved, and she recovered her ability to ambulate independently. All of her cerebellar and brainstem signs and symptoms disappeared. Likewise, marked improvements on her brain MRI (figure 2) and near resolution of her left eye hemianopic field defect was documented (figure 3). Fifty-one months since the inception of alemtuzumab treatment, our patient exhibits “no evidence of MS-related disease activity,” and she remains free of any evidence of secondary autoimmunity.

Discussion

Our patient’s disease course was characterized by multiple inflammatory exacerbations despite adherence to different treatment strategies, including long periods of combination therapy. While on fingolimod, she developed herpetic meningitis and, about a year later, left-sided neurosensory hearing loss. A broad diagnostic series of investigations for infectious, vascular, inflammatory/demyelinating, neoplastic, paraneoplastic, and autoimmune disorders failed to elucidate an explanation, other than an adverse manifestation of fingolimod.

The principal objectives for the aggressive interventions characterized in our case report, were first aimed at achieving remission of the disease process responsible for our patient’s neurosensory hearing loss, followed by our attempt to promote recovery in her hearing on the left.

At the time of beginning the every 8-week dosing of natalizumab, there was already report of a cohort of patients with MS treated with EID of natalizumab with no documented cases of PML.8,15 Nevertheless, the previous utilization of immune suppressive therapies in the context of etanercept and steroid therapy—along with the coadministration of natalizumab (even at 8-week dosing)—likely combined to escalate the risk for the development of PML in our patient.

Figure 3 Serial pattern deviation plots from Humphrey automated perimetry reveals recovery following intensive immunotherapy

(A) Pattern deviation for automated Humphrey visual fields (HVFs) using the 30-2 test from July 1996. (B) Pattern deviation for automated HVF 30-2 from January 2000. (C) Pattern deviation for automated HVF 30-2 from July 2016. (D) Pattern deviation for automated HVF 30-2 from February 2020 demonstrating striking resolution of the previously protracted visual field suppression in a left homonymous hemianopic pattern.
mortality. Furthermore, alemtuzumab therapy in conjunction with our "Whack-A-Mole" B-cell depletion strategy was used for purposes of promoting a durable remission and potentially to obviate the development of alemtuzumab-associated secondary autoimmunity.

Acknowledgment
The authors thank medical illustrators Mr. Jason Ooi and Dr. Matthew Parsons for their creation of the chronological heat map (figure 1) and for the organization of both figures 2 and 3.

Study funding
The National Multiple Sclerosis Society Case Conference Proceedings is both a live educational Webinar, in conjunction with a peer review publishing initiative from the monthly "Diagnostic and Treatment Challenges in MS and Neuroimmunology Webinars"; sponsored by the National Multiple Sclerosis Society Fellowship Training Program.

Disclosure
R.A. Cruz has received speaker fees from Genzyme. N. Hogan, J. Sconzert, and M. Sconzert have nothing to disclose. E.O. Major: PML Adjudication Committees for Takeda/Millennium Pharma; Roche/Genentech, GSK, and Shire; consult PolpharmaBiologics, S.A. R.P. Lisak serves as a member of the Editorial Board of Clinical Neuropsychopharmacology; he serves on the Medical Advisory Committee of the Myasthenia Gravis Foundation of America and on its Grants Review Committee, on the Clinical Advisory Committee of the GBS/CIDP Foundation, International and its Research/Grants Committee and its Committee on Centers of Excellence, the Board of Trustees of the Michigan Chapter of the National Multiple Sclerosis Society and is Health Care Advisory Committee and on the Board of Trustees of the DMC Foundation; he has served as a consultant for ArgeneX, Novartis, Janssen, GLG Consulting, Guidepoint Consulting, Third Bridge Consulting, and Globe Life Sciences; he chaired the adjudication committee for a medDay Pharmaceutical clinical trial; he receives research funding (with salary support paid directly to Wayne State University) from NIH, ArgeneX, UCB Ra Pharmaceuticals and Alexion; and he has received royalties from Wiley-Blackwell (International Neurology) and Oxford University Press (Neuroimmunology). Unrelated to the current work, E. Melamed has served as a consultant on advisory boards for EMD Serono and Genentech and has received honoraria for patient educational lectures for MS Society and MS Association of America. T.C. Varkey has nothing to declare. E. Meltzer served as a consultant for Genzyme and received honoraria from Novartis. A. Goodman received personal compensation for consulting from Teva and Adamas; received research support from Biogen, Genentech-Roche, Sanofi-Genzyme, and Teva. O. Komogortsev, M.S. Parsons, and K. Costello have nothing to declare. Unrelated to the current work, J.S. Graves over the past year has grant/contract research support from the National MS Society, Biogen, and Octave Biosciences; she serves on a steering committee for a trial supported by Novartis; she has received honoraria for a non-promotional, educational activity for Sanofi-Genzyme; and she has received speaker fees from Alexion and BMS and served on an advisory board for Genentech. S. Newsome has received consultant fees for scientific advisory boards from Biogen, Genentech, Celgene, EMD Serono, Novartis, Greenwhich Biosciences, is an advisor for Autobahn Therapeutics and BioInCcept, a clinical adjudication committee member for a medDay Pharmaceuticals clinical trial and has received research funding (paid directly to institution) from Biogen, Novartis, Genentech, National MS Society, Department of Defense, and Patient Centered Outcomes Institute. S.S. Zamvil is Deputy Editor of Neurology: Neuroimmunology & Neuroinflammation and is an Associate Editor for Frontiers in Immunology and Frontiers in Neurology; he serves on the Advisory Committee for the American Congress on Treatment and Research in Multiple Sclerosis (ACTRIMS) and is a standing member of the research grant review committee for the National Multiple Sclerosis Society (NMSS); he has served on the Editorial Board of the Journal of Clinical Investigation, The Journal of Immunology and The Journal of Neurological Sciences; and has been a charter member of the grant review committee for the NIH Clinical Neuroimmunology and Brain Tumors (CNBT); he has served, or serves, as a consultant and received honoraria from Alexion, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals Inc., and has served on Data Safety Monitoring Boards for Lilly, BioMS, Teva and Opera Therapeutics; currently, S.S. Zamvil receives research grant support from the NIH, NMSS, Well Institute, Race to Erase MS and the Maisin Foundation. E.M. Frohman has received speaker honoraria from Genzyme, Novartis, Alexion and Acorda. T.C. Frohman has received Advisory Board fees from Alexion. Go to Neurology.org/NN for full disclosures.

Publication history

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberto</td>
<td>Department of Neurology, Dell Medical School at the University of Texas at Austin</td>
<td>Conception and critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Alejandro</td>
<td>Department of Ophthalmology, UT Southwestern School of Medicine, Dallas</td>
<td>Conception and critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Cruz, MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nick Hogan, MD, PhD</td>
<td>Wellness Care Centers and Pediatric Rehabilitation, Denton, TX</td>
<td>Conception and critical revision of the manuscript for accuracy of the clinical course and for intellectual content</td>
</tr>
<tr>
<td>Sconzert, PT, LLC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## References


Treating MS after surviving PML: Discrete strategies for rescue, remission, and recovery patient 2: From the National Multiple Sclerosis Society Case Conference Proceedings
Roberto Alejandro Cruz, Nick Hogan, Jayne Sconzert, et al.
Neurol Neuroimmunol Neuroinflamm 2021;8;
DOI 10.1212/NXI.0000000000000930

This information is current as of December 15, 2020

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/8/1/e930.full.html

References
This article cites 15 articles, 4 of which you can access for free at:
http://nn.neurology.org/content/8/1/e930.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
Multiple sclerosis
http://nn.neurology.org//cgi/collection/multiple_sclerosis

Errata
An erratum has been published regarding this article. Please see next page or:
/content/8/2/e968.full.pdf

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
Treating MS after surviving PML: Discrete strategies for rescue, remission, and recovery patient 2
From the National Multiple Sclerosis Society Case Conference Proceedings

In the Neurology® Neuroimmunology & Neuroinflammation Article “Treating MS after surviving PML: Discrete strategies for rescue, remission, and recovery patient 2: From the National Multiple Sclerosis Society Case Conference Proceedings” by R. Cruz et al.,¹ the 15th author’s name and credentials should be listed as “Scott D. Newsome, DO.” The authors regret the error.

Reference