MYELODYSPLASTIC SYNDROME WITH PROGRESSIVE MULTIFOCAL PREDOMINANTLY PONTINE DEMYELINATION

We report a patient with fulminant brainstem demyelinating disease in the context of previously treated myelodysplastic syndrome (MDS). We hypothesize that autoimmunity associated with MDS can underlie demyelinating syndromes.

Clinical case. A 64-year-old man with relapsing polychondritis in remission and stable MDS (diagnosed 1.5 years ago, maintained on 5 mg of oral prednisone with anemia, lymphopenia [140 lymphocytes/µL], and mild thrombocytopenia [140,000 platelets/µL]) without history of opportunistic infections was hospitalized after 1 day of difficulty walking. On the first day of hospitalization, he developed dysarthria, bilateral sixth cranial nerve deficits, and bilateral dysmetria. MRI of the brain showed T2 hyperintensities involving the pons and midbrain along with discrete right temporal, right frontal, and left parietal lesions (figure, A–C). All lesions enhanced with IV gadolinium contrast. CSF contained 10 white blood cells per µL (40% lymphocytes), no red blood cells, glucose 45 mg/dL, and total protein 77 mg/dL. Five days after symptom onset, he progressed to no voluntary extraocular movements and decreased arousal. He was treated with broad-spectrum antimicrobials including acyclovir and ampicillin as well as 3-day pulse of methylprednisolone.

Despite these therapies, he became increasingly somnolent and was found to have further expansion of the brainstem and right temporal lesions on imaging. CSF studies were negative for infectious organisms (including serology for West Nile virus, eastern equine encephalitis virus, and varicella-zoster virus; and PCR for herpes simplex virus [HSV], JC virus, and enterovirus). Oligoclonal bands were absent, as were anti-Ri, anti-Hu, and anti-amphiphysin antibodies. Serum neuropeptide-related opti (NMO) IgG and IgM titers showed no evidence of NMO. Histology showed a sharply circumscribed demyelinating lesion with foamy macrophages (myelin stain, figure, D; broken arrow, figure, E) and relative preservation of axons (Bodian stains; not shown). No perivascular lymphocytes—which would be expected in acute disseminated encephalomyelitis (ADEM)—were seen. Lymphocytes were predominantly T cells with virtually no B cells (CD3 and CD20 immunostains; data not shown). There was acute hemorrhage throughout the lesion (solid arrow, figure, E). No viropathic changes or neuronal inclusions were seen. Immunohistochemistry for simian virus 40, HSV, cytomegalovirus, and Epstein-Barr virus antigens was negative. Immediately after the biopsy, the patient became comatose with extensor posturing in bilateral upper extremities. Repeat MRI of the brain showed marked extension of the T2 hyperintensity into superior midbrain and thalami (figure, F). He sequentially received high-dose methylprednisolone, IV immunoglobulin, and induction cyclophosphamide. His mental status, however, did not significantly improve. He died 8 weeks after onset of illness after the family withdrew positive pressure ventilation.

Discussion. This patient had a fulminant demyelinating disease of unclear etiology. Histologically, the circumscribed region of confluent demyelination is most consistent with a multiple sclerosis (MS) plaque, although the patient’s relentlessly progressive course is atypical of relapsing-remitting MS and more suggestive clinically of the Marburg subtype. Histologically, the demyelinating lesion is not characteristic of ADEM, which is marked by perivenular inflammation and demyelination. NMO is unlikely in this patient due to the lack of myelopathy, optic nerve involvement, suggestive pathology, and NMO antibody. The recently described CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) syndrome is associated with prominent brainstem involvement but also with perivascular lymphocytic infiltrate not seen in this patient. Central pontine myelinolysis can cause a similar syndrome with brainstem dysfunction; however, the patient did not have the fluctuations in sodium levels that usually precede pontine myelinolysis.

MDS, on the other hand, has associated autoimmunity in about 10% of patients. A variety of autoimmune diseases can occur with MDS, including both acute syndromes such as vasculitic glomerulonephritis and chronic diseases such as pulmonary fibrosis or Sjögren syndrome. Autoimmunity can precede, present concurrently with, or follow the diagnosis of MDS. Cytokine dysregulation in the

---

Shamik Bhattacharyya, MD
Janice C. Wong, MD
Malak Abedalthagafi, MD
Sarah Wahlster, MD
Henrikas Vaitkevicius, MD
bone marrow secondary to transformed hematopoietic progenitor cell proliferation is hypothesized to lead to chronic immune activation resulting in autoimmunity. While the causality of MDS in our patient’s disease is uncertain, the development of 2 autoimmune disorders (relapsing polychondritis and demyelinating syndrome) following diagnosis of MDS is suggestive of the etiologic role of MDS for these autoimmune disorders. There is one prior report of steroid-responsive recurrent tumefactive frontal and parietal demyelinating lesions in a 70-year-old man preceding diagnoses of MDS and renal cell carcinoma. We present a case of rapidly progressive refractory CNS demyelinating disease associated with MDS. In our patient, the CNS demyelinating disease worsened dramatically after the biopsy. While the biopsy and worsening course of disease may have been coincident, we hypothesize that the demyelinating disorder was antibody-mediated and that the breakdown of the blood-brain barrier from the biopsy exacerbated the disease.

In summary, we propose that MDS may lead to demyelinating disease, which can be fulminant. Recognition of this association clinically may prompt consideration of early aggressive immune modulation therapy. Further epidemiologic research to investigate the association between MDS and demyelinating syndromes is needed.

From the Department of Neurology (S.B., J.C.W., S.W.), Massachusetts General Hospital, Boston, MA; Department of Neurology (S.B., J.C.W., S.W., H.V.) and Department of Pathology (M.A.), Brigham and Women’s Hospital, Boston, MA; and Harvard Medical School (S.B., J.C.W., M.A., S.W., H.V.), Boston, MA.

Author contributions: Drs. Bhattacharyya, Wong, Abedalthagafi, Wahlster, and Vaitkevicius all participated in the conception and writing of the article.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures. 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 No Derivative 3.0 License, which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received November 7, 2014. Accepted in final form January 29, 2015.

Correspondence to Dr. Bhattacharyya: sbhattacharyya3@partners.org


Myelodysplastic syndrome with progressive multifocal predominantly pontine demyelination
Shamik Bhattacharyya, Janice C. Wong, Malak Abedalthagafi, et al.
Neurol Neuroimmunol Neuroinflamm 2015;2;
DOI 10.1212/NXI.0000000000000090

This information is current as of March 12, 2015

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/2/3/e90.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://nn.neurology.org/content/2/3/e90.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
Hematologic
http://nn.neurology.org/cgi/collection/hematologic
MRI
http://nn.neurology.org/cgi/collection/mri

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.