Simultaneous PML-IRIS and myelitis in a patient with neuromyelitis optica spectrum disorder

Eoin P. Flanagan, MBCh

Allen J. Aksamit, MD

Neeraj Kumar, MD

Neha P. Morparia, MD

B. Mark Keegan, MD

Brian G. Weinshenker, MD

Progressive multifocal leukoencephalopathy (PML) is a destructive and often fatal infection of oligodendrocytes caused by the human polyomavirus JC virus (JCV).¹ Risk factors include prior JCV infection detected serologically and immunosuppression, including HIV infection, hematologic malignancy, systemic autoimmune disease, and immunosuppressant use.¹ Immune-reconstitution inflammatory syndrome (IRIS) may occur after restoration of immunocompetence.¹ PML is associated with natalizumab treatment of multiple sclerosis (MS),¹ but not with neuromyelitis optica (NMO) or NMO spectrum disorders (NMOSDs). We describe a patient with NMOSD who simultaneously developed PML-IRIS and longitudinally extensive transverse myelitis (LETM).

Case report

A 72-year-old woman with a history of NMOSD developed progressively worsening gait unsteadiness and falls over many months. Neurologic examination revealed new nystagmus, left-sided dysmetria, gait ataxia, and preexisting mild right spastic hemiparesis. Her neurologic history included recurrent attacks of LETM beginning 8 years previously and she was found to be seropositive for NMO-immunoglobulin G (IgG) (>160 U/mL; normal range [NR], <1.6). She received azathioprine 100 mg per day for 6 years and was attack-free for the preceding 4 years. Systemic lupus erythematosus manifest by photosensitivity, butterfly rash, and positive antinuclear antibody (>12 units; NR, <1) was diagnosed 21 years previously, although she never received immunosuppression for these symptoms. Her history also included pernicious anemia and herpes zoster ophthalmicus. MRI revealed suggestive cerebellar white matter lesions of PML (figure, A.a and A.b).² CSF PCR detected JCV, confirming PML. White blood cell count was $4.1 \times 10^9/L$ (NR, $3.5\text{--}10.5 \times 10^9/L$) and lymphocyte count was $1.59 \times 10^9/L$ (NR, $0.9\text{--}2.9 \times 10^9/L$). Azathioprine was

Department of Neurology Mayo Clinic, Rochester, MN.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article** at Neurology.org/cp.

Correspondence to: weinb@mayo.edu

Figure MRI head and thoracic spine

Symmetric axial-T2-signal hyperintensities are noted in both cerebellar hemispheres (A.a) and do not enhance after gadolinium administration (A.b). One year later, axial-T1-postgadolinium image demonstrates enhancing lesions in the cerebellar peduncles/hemispheres (B.a, white arrows) and spinal cord MRI demonstrates longitudinally extensive T2 signal hyperintensity from T2 to T5 (B.b, white arrow) with enhancement (B.c and B.d, white arrow).

discontinued and she received a 5-day course of cytosine arabinoside,³ although convincing evidence of its efficacy in controlled trials is lacking.¹

She stabilized until 9–10 months later, when her cerebellar dysarthria worsened and she developed subacute right leg weakness. Repeat MRI revealed enhancement of previously nonenhancing cerebellar lesions and a longitudinally extensive thoracic cord lesion (figure B). Repeat CSF PCR was negative for JCV and NMO-IgG titer remained high (>160 U/mL). Simultaneous acute NMOSD relapse and immune reconstitution inflammatory syndrome (IRIS) were diagnosed. Treatment with 5 days of high-dose IV methylprednisolone was followed by improved strength and speech. Maintenance intermittent plasma exchange was commenced, but recurrent LETM developed 10 days later. IV steroids were given and intermittent plasmapheresis was maintained.

DISCUSSION

This case of PML in a patient with NMO/NMOSD raises a number of clinical questions. Did NMO itself or its treatment predispose to PML? Was IRIS or NMO responsible for the late progression of cerebellar disease? What is the optimum treatment for an autoimmune disorder in the face of recent PML?

Whether NMO/NMOSD itself is a risk factor for PML is uncertain. Systemic autoimmune diseases coexist with NMO/NMOSDs in one-third of cases⁴ and are established risk factors for PML (especially lupus) either in their own right or because of their treatment.⁵ Azathioprine treatment itself predisposes to PML. The recent recognition of NMO as a disease distinct from MS requiring long-term immunosuppression⁴ and high frequency of coexisting autoimmune diseases suggest PML will continue to be recognized in patients with NMO/NMOSDs. PML should be considered in patients with NMO with progressive symptoms or suspicious white matter lesions.

The cerebellar lesions of PML typically involve middle cerebellar peduncles.² Crescent-shaped lesions on MRI, as seen in our case, are suggestive.² We concluded that the enhancement in cerebellar lesions represented IRIS rather than worsening PML or NMO for several reasons. Gadolinium enhancement is associated with immune reconstitution, and occurred within PML lesions and the cerebellar hemisphere; this location is atypical for NMO-associated brain lesions. Slowly evolving dysarthria is more consistent with IRIS than NMO attack.

The LETM probably represented an NMOSD attack as the lesion was typical for NMO, the NMO-IgG titer was high, and PML (and hence presumably PML-IRIS) very rarely affects the spinal cord.⁶ Co-occurrence of an NMO attack and IRIS in this patient likely resulted from reconstitution of immunocompetence after azathioprine withdrawal.

We chose intermittent plasmapheresis for long-term treatment to avoid cell-mediated immunosuppression predominantly associated with PML. PML has been reported with immunoglobulin deficiency in X-linked agammaglobulinemia,⁷ suggesting the risk of PML reactivation with intermittent plasmapheresis is not completely eliminated, although its use in natalizumab-associated IRIS has not been implicated in worsening PML.¹ We avoided rituximab, which has been associated with PML in patients with lupus.¹ The most recent relapse suggests future additional treatments may be necessary. Despite being limited by a lack of long-term follow-up, our case highlights the dilemma of managing simultaneous PML-IRIS and NMO disease activity.

REFERENCES

1. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. *Lancet Neurol* 2010;9:425–437.
2. Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis. *Eur J Neurol* 2012;19:1060–1069.
3. Aksamit AJ. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. *J Neurovirol* 2001;7:386–390.
4. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007;6:805–815.
5. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy: a national estimate of frequency in systemic lupus erythematosus and other rheumatic diseases. *Arthritis Rheum* 2009;60:3761–3765.
6. Takeda S, Yamazaki K, Miyakawa T, Takahashi H, Ikuta F, Arai H. Progressive multifocal leukoencephalopathy showing extensive spinal cord involvement in a patient with lymphocytopenia. *Neuropathology* 2009;29:485–493.
7. Teramoto T, Kaneko H, Funato M, et al. Progressive multifocal leukoencephalopathy in a patient with X-linked agammaglobulinemia. *Scand J Infect Dis* 2003;35:909–910.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

E. Flanagan, A.J. Aksamit, N. Kumar, and N.P. Morparia report no disclosures. B.M. Keegan serves as Chief Editor for eMedicine; has served as a consultant to Bristol Myers Squibb, Novartis, and Bionest; and has received research support from Terumo BCT and Caridian BCT. B.G. Weinshenker serves on DSMB for Novartis, Biogen Idec, and Mitsubishi Pharmaceuticals; serves on the editorial boards of *Canadian Journal of Neurological Sciences*, *Turkish Journal of Neurology*, and *Multiple Sclerosis*; is author on a patent re: NMO-IgG for diagnosis of neuromyelitis optica; application 20050112116; patent issued and technology licensed to R.S.R. Ltd.; serves as a consultant to Elan Pharmaceuticals, GlaxoSmithKline, Ono Pharmaceuticals, and Asahi Kasei Medical Company; and receives research support from Guthy Jackson Charitable Foundation. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Share Your Knowledge

Neurology® Clinical Practice encourages readers to share their insights, expertise, and experiences.

- How are you employing drugs and devices in your field?
- What ethical challenges do you face?
- Do you have a case report that is illustrative of a clinical challenge?
- What challenges have you faced or successes have you enjoyed in bringing greater efficiency to your practice?

If you are interested in delivering a high-quality, peer-reviewed message to your colleagues in practice, submit your paper **online**.