Emilio Gómez-Cibeira, MD
Yerko Ivanovic-Barbeito, MD
Eduardo Gutiérrez-Martínez, MD
Enrique Morales, MD
Manuel Abradelo, MD
Amaya Hilario, MD
Ana Ramos, MD
Juan Ruiz-Morales, MD
Alberto Villarejo-Galende, MD

ECULIZUMAB-RELATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the CNS caused by reactivation of the polyomavirus JC (JCV). In the context of immunosuppression, JCV can reactivate and spread to brain infecting oligodendrocytes.¹

Eculizumab is a first-in-class humanized monoclonal antibody developed to target the cleavage of C5, preventing the release of C5a and activation of the terminal complement pathway. It has been shown to be effective in the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS).² Eculizumab can impair neutrophil and monocyte functions and predispose to encapsulated bacteria infections.

We report the novel finding of PML in a patient receiving eculizumab.

Case report. A 26-year-old woman with a double intestinal-kidney transplant for aHUS and intestinal lymphangiectasia complained of unsteady gait and diplopia for 2 weeks. Bilateral facial and palatal palsy, moderate left leg weakness, and ataxia appeared gradually and progressed quickly a few days prior to admission. Four months before the transplant, and 1 year before neurologic presentation, she had been treated with eculizumab 1,200 mg every 14 days to prevent an aHUS relapse. After the transplant 8 months before, her treatment also included tacrolimus 5 mg bid and prednisone 10 mg every day. She had been treated with thymoglobulin 1.5 mg/kg per day the first 5 days after her transplant. Four years before presentation, the aHUS had been treated with plasmapheresis and prednisone 1 mg/kg per day for 3 months. She had not received other immunosuppressive or immunoregulatory drugs.

Brain MRI showed several white matter lesions on T2- and fluid-attenuated inversion recovery-weighted sequences involving brainstem, cerebellum, and cerebral hemispheres (figure). Patchy and punctuate gadolinium enhancement was identified over cerebellum and both cerebral hemispheres.

The patient had mild normocytic anemia (Hb 9.9 g/dL) and the leukocyte and lymphocyte subpopulations and routine CSF analysis were normal. Tacrolimus plasma level was 8.4 ng/mL. The

most important finding in the diagnostic workup was the presence of JCV DNA in the CSF. The microbiology laboratory performed a semiquantitative PCR with an estimated 4,000 JCV DNA copies/mL (detection limit at 100 copies/mL).

The clinical presentation, imaging findings, and detection of the DNA virus in the CSF were consistent with the diagnosis of definite PML.³ Upon admission, the scheduled administration of eculizumab was suspended. Two weeks later, the dose of tacrolimus was reduced to 2.5 mg bid (blood levels from 3 to 7 ng/mL in the following months), and everolimus was started at 1.5 mg bid, without relevant changes in neutrophil and lymphocyte counts. The patient began to improve slowly in the first 2 weeks, making a good functional recovery.

At 1 year follow-up, the patient has moderate left leg spasticity and mild ataxia. MRI obtained 4 and 10 months after clinical presentation revealed residual brainstem and cerebral lesions. She has not developed new abnormalities and the areas of contrast enhancement resolved. One year after PML onset, a new JCV DNA determination in the CSF was negative.

Discussion. PML is commonly observed in immunocompromised hosts and has been described in patients treated with monoclonal antibodies like natalizumab, rituximab, efalizumab, and alemtuzumab.⁴ Natalizumab-related PML is well known to neurologists and has been widely studied. Known risk factors for the development of PML in this situation are prior exposure to JCV, length of treatment duration, and previous or concomitant use of immunosuppressive medications. In cases of natalizumab-induced PML, up to 40% can show enhancing lesions, termed inflammatory PML.⁵ In our case, contrast enhancement suggests an ongoing immune reconstitution inflammatory syndrome and immune response, which may explain why the PML did not progress.

We report the unique finding of PML associated with eculizumab. Other factors like the concomitant use of tacrolimus and low-dose prednisone and the remote use of thymoglobulin are probably involved, but a direct implication of eculizumab is suggested by the fact that the clinical improvement began when this drug was discontinued. Eculizumab is the first

MRI at presentation (A–C): fluid-attenuated inversion recovery images show hyperintense lesions in the dorsal pons, right middle cerebellar peduncle, and left cerebellum (A), and bihemispheric frontal white matter (B). Enhanced T1-weighted image shows multiples areas of punctate enhancement, especially in the right anterior frontal lobe and left frontal white matter. A previous surgery for right traumatic epidural hematoma can also be seen. The same sequences performed 4 months later (D–F) show residual pons lesions (D), reduction in size and number of the bihemispheric white matter hyperintensities (E), and resolution of contrast enhancement (F).

inhibitor of the complement system used in clinical practice. The complement system is a network of proteins that work in concert as part of the innate immune system that rapidly responds to infections. Although patients with complement deficiencies and those treated with eculizumab have a great risk of encapsulated bacteria infections, the complement system also plays an important role in the prevention and surveillance of viral infections.⁶

This case has similarities with natalizumab-induced PML. If more cases were reported, some of the precautionary measures and risk stratification that have been recommended for natalizumab treatment candidates could be applied before starting eculizumab.⁷

From Hospital Universitario Doce de Octubre, Madrid, Spain.

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Correspondence to Dr. Villarejo-Galende: avgalende@yahoo.es

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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. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. *Lancet* 2009;373:759–767.
3. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* 2013;80:1430–1438.
4. Berger JR, Houff SA, Major EO. Monoclonal antibodies and progressive multifocal leukoencephalopathy. *MAbs* 2009;1:583–589.
5. Yousry TA, Pelletier D, Cadavid D, et al. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2012;72:779–787.
6. Stoerner KA, Morrison TE. Complement and viral pathogenesis. *Virology* 2011;411:362–373.
7. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012;366:1870–1880.