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FINGOLIMOD-ASSOCIATED PML IN A PATIENT WITH PRIOR IMMUNOSUPPRESSION

Fingolimod, a sphingosine-1-phosphate receptor modulator, was the first oral disease-modifying drug approved for relapsing-remitting multiple sclerosis (RRMS).¹ Fingolimod decreases multiple sclerosis disease activity through a presumed mechanism of sequestration of lymphocytes in lymph nodes, thereby reducing circulating lymphocytes available for entry into the CNS. Its lymphopenic effect has raised concern for predisposition to opportunistic infections.² Recently, the US Food and Drug Administration (FDA) issued a new warning on labeling for fingolimod following reports of 2 cases of progressive multifocal leukoencephalopathy (PML) associated with fingolimod therapy.³

Herein, we report a patient with RRMS and prior exposure to immunosuppression who developed PML while on treatment with fingolimod for 3 years (figure).

Case report. A 51-year-old woman with RRMS since 1997 was previously treated for 15 years with glatiramer acetate and then interferon beta-1b. During this time, she was also treated for inflammatory bowel disease and later for colon cancer. For inflammatory bowel disease, she received intermittent steroids for 10 years and azathioprine in 2005 for 2 months. In 2009, she was diagnosed with colon cancer and received chemotherapy with 6 cycles of capecitabine and a course of oxaliplatin over a period of 4 months. She also had radiation therapy and went into remission after surgical resection.

In 2012, she was switched to fingolimod for RRMS because of clinical and radiologic disease progression. At that time, her absolute lymphocyte count (ALC) was 2,100 cells/mm³ and she was positive for JC virus (JCV) antibody, hence natalizumab was avoided. ALC ranged between 500 and 700 cells/mm³ during the course of fingolimod therapy from 2012 to 2015.

In August 2015, she was referred to our institution with progressive cognitive dysfunction and dysarthria for 1 month. Neurologic examination revealed moderate dysarthria and impaired delayed recall and attention. Fingolimod had been discontinued by

her community neurologist because of suspected PML. Her brain MRI showed several lesions that were suspicious for PML,⁴ including fluid-attenuated inversion recovery/T2 hyperintense areas in the right temporoparietal subcortical area, involving the U-fibers and callosal splenium with punctate contrast enhancement. CSF revealed 0 nucleated cells, 0 red blood cells, protein 34 mg/dL and glucose 66 mg/dL. JCV DNA PCR by the NIH assay was positive with 336 copies/mL. Serum JCV antibody testing was positive with an index of 2.41. She tested negative for HIV, ALC was 500 cells/mm³, and white blood cell count was 7,300 cells/mm³.

Discussion. This case raises important questions about predisposing factors for PML and the need for PML surveillance in patients treated with fingolimod. Of note, this JCV-seropositive patient had exposure to immunosuppressive therapy more than 5 years before fingolimod treatment.

The association between PML and natalizumab has been clearly established and this has led to caution in its use for RRMS.⁵ Factors increasing the risk of PML with natalizumab include JCV seropositivity, duration of treatment more than 2 years, and prior use of immunosuppressive agents, all of which are now routinely considered before and during natalizumab therapy.⁵ Recently, a case of PML was reported in a patient with multiple sclerosis who was treated with dimethyl fumarate. That patient had no prior immunosuppressive therapy but had grade 3 lymphopenia while on dimethyl fumarate.⁶

In pivotal studies, fingolimod reduced ALC to a mean of 500 cells/mm³ and was discontinued only when ALC fell below 200 cells/mm³.⁷ This patient had grade 2 lymphopenia (500–700 cells/mm³) during fingolimod therapy. It is unclear what effects the duration of fingolimod therapy and level of lymphopenia had in the development of PML in our patient. It is plausible to hypothesize that both of these factors, in combination with known JCV seropositivity and prior exposure to immunosuppression, were contributory.

The first 2 FDA-reported cases of fingolimod-associated PML occurred on therapy with fingolimod for 4 and 2.5 years, respectively. Both patients

(A) This timeline illustrates chronologically the patient's course of MS and treatment decisions up until the diagnosis of PML, in conjunction with other immunosuppressive treatment for cancer and inflammatory bowel disease. ALCs are reported in cells/mm³. (B) MRI October 2014. T2-weighted FLAIR images demonstrating multiple T2 hyperintensities periventricular and juxtacortical consistent with MS. (C) MRI August 2015 with new confluent T2 hyperintensities on FLAIR sequences in the right parietal lobe consistent with PML. The splenium of the corpus callosum is involved, which is a change compared to 2014, where the corpus callosum was spared. (D) Within those regions, there is subtle patchy diffuse contrast enhancement on T1 post-contrast studies (white arrows). ALC = absolute lymphocyte count; FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; WBC = white blood cell.

received interferon beta for 10 months and 11 years, respectively, before fingolimod. The second case was also treated with mesalazine for ulcerative colitis.³ A prior case in 2013 could not be exclusively linked to fingolimod because the patient had been treated with

azathioprine shortly before starting fingolimod and also received multiple courses of steroids before and during fingolimod therapy.³

We suggest that fingolimod should be used with caution in JCV-seropositive patients who have had

prior exposure to immunosuppressive agents. Patients who develop new neurologic symptoms concerning for PML should be urgently evaluated and have expeditious imaging and CSF JCV PCR analysis if clinically warranted. There is clearly a need to establish guidelines regarding PML risk and PML surveillance with use of more potent immunotherapy in RRMS.

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