Studies of clinicopathological correlation, such as the UNITE Study,² should help identify clinical features that are sensitive and specific for CTE pathology. Prospective studies that include neuropsychological testing with imaging and fluid biomarkers will be essential to future improvements in diagnosis of CTE during life.

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Primary Cutaneous Cryptococcus in a Patient With Multiple Sclerosis Treated With Fingolimod

A 62-year-old woman with multiple sclerosis treated with fingolimod for 3 years presented to the clinic with a tender nodule on her forehead, which had gradually grown over 3 weeks (Figure). She reported bumping her forehead on an air-conditioning unit several months prior. She denied fever, neck stiffness, and photophobia, and her neurological examination was at her baseline. She lived alone with a pet cat and spent minimal time outdoors. She had no recent exposure to systemic steroids.

A shave biopsy of the skin revealed granulomatous inflammation composed of histiocytes, giant cells, and lymphocytes admixed with numerous narrow-budding yeasts with thick capsules. Tissue culture grew Cryptococcus neoformans. A full workup for systemic disease, including chest radiography, serum and cerebrospinal fluid cryptococcal antigen, and blood and cerebrospinal fluid cultures, was negative. A human immunodeficiency virus test result was negative. She had regular monitoring of her T-cell counts while receiving fingolimod, most recently showing a white blood cell count of 3.9×10⁹/μL (4000-1100/μL to convert to ×10⁹ per liter, multiply by 0.001); lymphocyte count of 0.65/μL (range, 1000-5000/μL to convert to ×10⁹ per liter, multiply by 0.001); absolute CD4 count of 56/μL (range, 560-1840/μL); and CD8 count of 121/μL (range, 260-1230/μL). She had no other lesions on full-body skin examination.

Given the absence of systemic findings, the patient was diagnosed as having primary cutaneous cryptococcosis (PCC) and treated with a loading dose of 800 mg fluconazole, followed by 400 mg daily until complete healing, for a minimum of 6 weeks. Fingolimod was discontinued during workup for disseminated infection and was not restarted because the patient had a change in diagnosis from relapsing-remitting to secondary progressive multiple sclerosis. At 1-month follow up, the forehead lesion was healing with residual scar, and she remained in good health.

Discussion | Fingolimod is a disease-modifying treatment for multiple sclerosis, which acts via downregulation of sphingosine-1-phosphate receptors on lymphocytes, resulting in selective retention of CCR7+ naive T cells and central memory T cells in lymphoid organs. There is less effect on CCR7- CD8+ effector T cells, although there is evidence of...
functional impairment of these cells independent of sphingosine-1-phosphate signaling. It has been suggested that the risk of infection nevertheless remains low with fingolimod because of a smaller effect on CD8 cells. Sequestered lymphocytes have preserved function, and recently activated T cells can “escape” sequestration by downmodulation of CCR7.2,3

Existing evidence largely supports low infection risk with fingolimod; however, there is a reported increase in herpes zoster infections, including 2 cases of disseminated zoster and 11 cases involving more than 2 contiguous dermatomes.4 Influenza and lower respiratory tract infections may also occur more frequently. There is 1 reported case of pulmonary cryptococcal infection in a patient receiving fingolimod.5

Primary cutaneous cryptococcosis is a rare localized cryptococcal infection characterized by skin-only involvement without systemic infection. It is thought to develop after direct inoculation. Cutaneous cryptococcosis strongly suggests disseminated disease, so every effort should be made to rule this out before making the diagnosis of PCC. Primary cutaneous cryptococcosis can also secondarily disseminate, leading to meningoecephalitis and other complications if left unrecognized. The morphology PCC lesions can vary widely, presenting as a papule, nodule, plaque, or ulceration. In contrast, AIDS-related disseminated cutaneous cryptococcosis classically presents with numerous umbilicated papules, resembling molluscum contagiosum.

Risk factors for PCC include exposure to soil and wood, prior injury to the skin site, and immunosuppression, in particular, defects in cellular immunity as seen in human immunodeficiency virus and idiopathic CD4 lymphocytopenia. Our patient’s CD4 count prior to diagnosis was very low at 56/μL. Importantly, however, PCC can occur in immunocompetent patients; therefore, it is not certain whether the patient’s immune status was contributory in this case.6 An association has also been reported between PCC and C neoformans serotype D (var neoformans), but the serotype in this patient is unknown. Further study and monitoring are warranted to define the risk of infection by common and opportunistic pathogens in patients receiving fingolimod.

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25-Hydroxyvitamin D in Patients With Cognitive Decline

To the Editor We read with interest the article by Miller et al.1 In a general population, it was demonstrated for the first time that vitamin D insufficiency, which was more frequently observed in African American and Hispanic individuals, was associated with significantly faster declines in both episodic...