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Case Report

Cutaneous cryptococcosis in a patient taking fingolimod for multiple sclerosis: Here come the opportunistic infections?

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Abstract

Background: Fingolimod is an oral disease-modifying therapy for relapsing forms of multiple sclerosis, which acts by sequestering lymphocytes within lymph nodes.
Objective: To describe a case of extrapulmonary cryptococcosis in a patient taking fingolimod.
Methods: Case report.
Results: A 47-year-old man developed a non-healing skin lesion approximately 16 months after starting treatment with fingolimod. Biopsy revealed cryptococcosis. Fingolimod was discontinued and the lesion resolved with antifungal therapy.
Conclusion: Despite few reported opportunistic infections in the pivotal clinical trials and first few years post-marketing, there has been a recent increase in reported AIDS-defining illnesses in patients taking fingolimod. Neurologists should be alert for opportunistic infections in their patients using this medication.

Keywords: Cryptococcosis, fingolimod, cutaneous, multiple sclerosis, AIDS, skin

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We report a 47-year-old male patient with relapsing-remitting multiple sclerosis (MS) who developed cutaneous cryptococcosis and cryptococcemia while undergoing treatment with fingolimod. He first developed MS in 1998 and was previously treated with interferon β-1b and dimethyl fumarate, both of which were discontinued due to inadequate disease control. Fingolimod was started in August 2013, and in December 2014, the dose was reduced to 0.5 mg every other day because of persistent lymphocytopenia (ranging from 0.2 to $0.4 \times 10^3/mm^3$). In early 2015, he developed a skin lesion on his left shoulder (Figure 1(a)). When this lesion did not heal after several months he sought medical attention, and staining of punch biopsy revealed a fungal infection consistent with cryptococcosis (Figure 1(b)). Serum cryptococcal antigen was positive at 1:10. Absolute lymphocyte count was $0.3 \times 10^3/mm^3$ and CD4 and CD8 counts were both reduced to $73/mm^3$ and $19/mm^3$ (normal range, 473–1492 and 193–$781 \times 10^3/mm^3$, respectively). CD4/CD8 ratio was 3.84 (normal range, 0.96–3.28). Antibody tests for HIV, histoplasma, toxoplasma, and blastomyces were negative. He was started on fluconazole 400 mg/day. The patient exhibited no signs or symptoms of meningitis. Fingolimod was discontinued, and he was started on glatiramer acetate 40 mg SC 3 days per week, plus methylprednisolone 992 mg PO 1 day per month. The cutaneous lesion healed within 2 months of antifungal therapy. Serum cryptococcal antigen remained positive for 4 months and has been negative since. The fluconazole dose was reduced to 200 mg/day after 6 months and discontinued after 12 months.

Fingolimod was approved in the United States in 2010 and in Europe in 2011 for use in patients with relapsing-remitting MS, making it the first approved oral medication for MS. Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator that inhibits lymphocyte egress from secondary lymphoid tissues, thus reducing circulating lymphocyte counts. Its mechanism of action is thought to be that sequestering lymphocytes prevent their ability to enter the central nervous system (CNS) and participate in inflammatory demyelination. Fingolimod does not affect all lymphocytes equally, as circulating counts

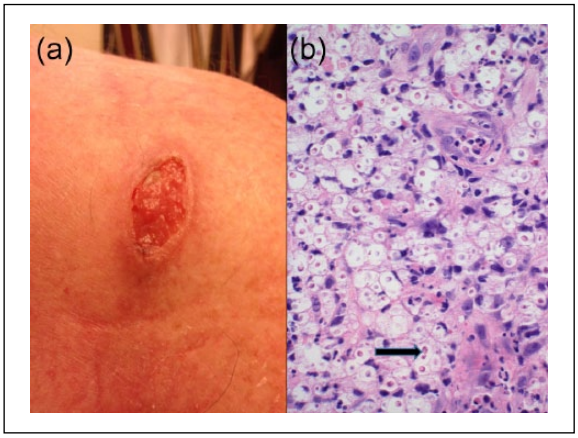

Figure 1. (a) Cutaneous cryptococcal lesion on the left shoulder of the patient. (b) Numerous cryptococci within the dermis. They are surrounded by a clear halo due to their capsule. A rare narrow-based bud is present (arrow). H&E, 40×.

of B cells and $CD4^+$ T cells are dramatically reduced while circulating $CD8^+$ T cells decline more modestly.[1] Among T cells, fingolimod preferentially sequesters naive and central memory T cells that express the lymph node homing receptor CCR7, leading to a relative increase in circulating T effector memory cells which do not express CCR7.[2]

Three phase 3 clinical trials demonstrated fingolimod to be effective and well-tolerated in relapsing-remitting MS. Despite reducing circulating lymphocyte counts by approximately 70%, the clinical trials and the first few years of post-marketing experience showed scant evidence for increased risk of infection in patients taking fingolimod. There were two deaths from herpesvirus infections in one trial, both in patients taking a higher dose (1.25 mg/day) of fingolimod than the Food and Drug Administration (FDA)-approved dose of 0.5 mg/day.[3] There was also a slight increase in herpesvirus infections and one case of pulmonary cryptococcosis.[4] An analysis of multiple trials (phase II and phase III) found no overall increase in infections in the fingolimod-treated groups compared to placebo and no clear trend of increasing infections in subjects with lower circulating lymphocyte counts.[5] This low incidence of infections led to the hypothesis that fingolimod is not (or is minimally) immunosuppressive, despite the lymphocytopenia it induces. Proposed mechanisms of this preserved immunocompetency include that the effector memory T cells remaining in circulation provide sufficient immune surveillance and/or that lymphocytes sequestered in lymph nodes are still functional.[2,5]

Within the last year, however, an increasing number of opportunistic infections in patients taking fingolimod have been reported. The prescribing information for fingolimod was updated in 2015 to include warning and precautions for cryptococcal infections and progressive multifocal leukoencephalopathy. Two other cases of cutaneous cryptococcal infection in fingolimod-treated patients have recently been published,[6,7] as have cases of Kaposi sarcoma[8] and visceral leishmaniasis.[9] All of these conditions are, or have been proposed as, AIDS-defining illnesses according to Center for Disease Control guidelines. The acquired immunodeficiency syndrome (AIDS) is defined as HIV infection plus either a $CD4^+$ T cell count below 200 cells/mm^3 or the presence of one of the AIDS-defining illnesses. Given that fingolimod frequently reduces circulating $CD4^+$ cells to within this range,[1,2] as it did in our patient, these opportunistic illnesses raise concern that the medication may be more immunosuppressive than previously appreciated.

Individual case reports are insufficient to prove a causative link between fingolimod use and cryptococcal infection, which could have been a chance occurrence or related to other factors such as the subject's previous use of dimethyl fumarate (although he took that medication for only 2 months and showed no evidence of lymphopenia during that period). The absolute incidence of cryptococcal infections in patients taking fingolimod cannot be assessed from published data. However, even considering only cutaneous cryptococcus and ignoring meningitis and other sites of infection, the three (including this report) published cases of cutaneous cryptococcus among roughly 240,000 patient-years of exposure as of October 2015[10] imply an annual incidence rate of 1.25/100,000. In comparison, a population-based study in two large US cities from 1992 to 2000 found annual incidence of cryptococcal infection (anywhere in the body) ranging from 0.04 to 0.5/100,000 in HIV-unaffected individuals.[11] Among individuals with HIV/AIDS in the same study, the incidence decreased from 5/100,000 in 1992 (before the introduction of highly active antiretroviral therapy) to approximately 1/100,000 in 2000.[11] This suggests that the risk of cryptococcal infection in patients taking fingolimod is likely higher than the general population and may be similar to all-cause cryptococcal infection in HIV/AIDS patients in the modern treatment era.

Once again, post-marketing case reports do not provide proof of association between a drug and a particular adverse event (AE). Their main value is in bringing to light potential drug-related AEs that are either too rare, or occur at too great a latency, to be

apparent in controlled clinical trials. Fingolimod is an effective and generally well-tolerated medication that has benefitted many people with MS. Nevertheless, given the accumulating reports of AIDS-defining illnesses in patients using fingolimod, it is imperative that neurologists using it in the management of their patients be vigilant for opportunistic infections.

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Declaration of Conflicting Interests

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