Cerebral Venous Thrombosis due to Cryptococcus in a Multiple Sclerosis Patient on Fingolimod

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Abstract
Fingolimod is a disease-modifying treatment utilized in the treatment of relapsing-remitting multiple sclerosis. Fingolimod has been associated with an increased risk in herpes simplex and varicella infection in clinical trials. We report a case of cerebral venous thrombosis secondary to cryptococcus in a patient receiving fingolimod. A 61-year-old male with multiple sclerosis treated with fingolimod presented with a 2-week history of headache, chills, and night sweats. An MRI of the brain revealed a left transverse and sigmoid sinus thrombosis. Two blood cultures revealed Cryptococcus neoformans; a serum cryptococcal antigen was also positive. HIV testing was negative. A lumbar puncture was deferred as the patient was placed on heparin and, subsequently, warfarin for the cerebral venous thrombosis. The patient received antifungal therapy for 14 days with liposomal amphotericin B and fluycytosine, followed by oral fluconazole for 8 weeks. He was subsequently readmitted 60 days later with bilateral papilledema; his anticoagulation was reversed, and a lumbar puncture revealed a negative cryptococcal antigen and an intracranial pressure of 20. A repeat MRI revealed worsening superior sagittal sinus thrombosis, thought to be the cause of the papilledema; his anticoagulation was reinitiated. He received a brief course of intravenous methylprednisolone, but as his multiple sclerosis was well-controlled, further therapy was deferred. His symptoms had resolved at a 3-month follow-up appointment. This is the first report of a multiple sclerosis patient treated with fingolimod to develop cerebral venous thrombosis secondary to cryptococcal fungemia. The risks of opportunistic infections should be considered in patients managed with fingolimod.
Introduction

Fingolimod is a disease-modifying treatment utilized in the treatment of relapsing-remitting multiple sclerosis. Fingolimod has been associated with an increased risk in herpes simplex [1] and varicella infection [2] in clinical trials. Subsequently, fingolimod administration has been associated with cryptococcal infections of various types, including meningoencephalitis [3], cutaneous cryptococcosis [4], and disseminated cryptococcosis [5]. Cryptococcus has been rarely identified as a cause of cerebral venous thrombosis; one such case has been described in a patient without an apparent immunodeficiency [6]. We report a case of cerebral venous thrombosis secondary to cryptococcus in a patient receiving fingolimod.

Case Presentation

A 61-year-old male with relapsing-remitting multiple sclerosis had previously tolerated fingolimod without difficulty since its initiation 7.5 years earlier; no enhancing lesions had been identified on an MRI of the brain performed 8 months earlier. His multiple sclerosis clinical course had been characterized by persistent fatigue but minimal other symptoms.

He presented to our institution with a 2-week history of headache, chills, and night sweats. Initially, he had been treated as an outpatient empirically for sinusitis with azithromycin and oral methylprednisolone. Subsequently, he developed an acute onset of slurred speech and dizziness 2 days prior to admission. An MRI of the brain (Fig. 1) revealed a left transverse and sigmoid sinus thrombosis, as well as a solitary focus of diffusion restriction within the left parietal periventricular white matter, suggesting actively demyelinating plaque. The initial absolute lymphocyte count upon admission was 0.3 × 10^9/L. Two blood cultures revealed Cryptococcus neoformans; a serum cryptococcal antigen was also positive with a titer >1:256. HIV testing was negative. Fingolimod was withheld. A lumbar puncture was deferred as the patient was placed on heparin and, subsequently, warfarin for the cerebral venous thrombosis.

Fig. 1. MRI T1-weighted images, axial sections – first admission, hospital day 1.
thrombosis. The patient received antifungal therapy for 14 days with liposomal amphotericin B and flucytosine liposomal amphotericin B (4 mg/kg per day) plus flucytosine (100 mg/kg per day), followed by oral fluconazole (800 mg for 8 weeks). His clinical symptoms had improved on discharge. His multiple sclerosis symptoms had stabilized and he was not discharged on therapy for his multiple sclerosis.

He was subsequently readmitted 60 days later with visual disturbance, headache, and bilateral papilledema. His neurological examination revealed loss of visual field in the inferior quadrant of the left eye, and the inferior nasal quadrant of the right eye with impaired color perception and decreased visual acuity. These findings raised the prospect of elevated intracranial pressure due to relapsed cryptococcal meningitis; however, his anticoagulation was reversed, and a lumbar puncture revealed white blood cells of 91/mm³, with 94% lymphocytes and 6% monocytes, a CSF protein of 224 mg/dL and a CSF glucose of 23 mg/dL, a negative cryptococcal antigen, and an intracranial pressure of 20. A serum cryptococcal antigen was not repeated at this time. A repeat MRI of the brain revealed an additional white matter focus of enhancement in the parafalcine posterior right frontal lobe and progression of disease within the lateral aspect of the right thalamic nucleus. However, a magnetic resonance angiogram and magnetic resonance venography revealed interval improvement in the clot burden at the left transverse and sigmoid sinus. An MRI of the orbits revealed mild enhancement of the optic nerve sheath bilaterally. He received a brief course of intravenous methylprednisolone early in his hospitalization; methylprednisolone was initiated because of an initial concern that the patient’s papilledema might represent optic neuritis. However, after careful review of the images with a neuro-ophthalmologist, the enhancement seen on the MRI orbits is not striking and not consistent with optic neuritis. As his multiple sclerosis symptoms were well controlled, further therapy was deferred upon discharge. The papilledema was attributed to the worsening sagittal sinus thrombosis; his anticoagulation was reinitiated. He was placed on maintenance fluconazole prophylaxis with the intent of lifelong therapy. His symptoms had resolved at a 3-month follow-up appointment, and his white matter lesions remained stable over the ensuing 12 months. He therefore required no further disease-modifying therapy for his multiple sclerosis.

Discussion

This is the first report of a multiple sclerosis patient treated with fingolimod to develop cerebral venous thrombosis secondary to cryptococcal fungemia. Cryptococcus is a rare cause of cerebral venous thrombosis in HIV-negative hosts. The incidence of cryptococcus infection as a cause of cerebral venous thrombosis is unknown, and our knowledge of this infrequent complication is limited to case reports [6–8]. Most patients at risk for cryptococcus central nervous system infections are otherwise immunocompromised, such as from leukemia or from posttransplantation immunosuppression. In this case, our patient tested as HIV-negative and had no other immunodeficiency, with the administration of fingolimod as the only identified risk factor for cryptococcal disease.

This case presented multiple diagnostic and therapeutic dilemmas. Management of cerebral venous thrombosis requires the initiation of prompt antithrombotic therapy; in our patient, initiation of anticoagulation was prioritized over an immediate lumbar puncture and measurement of intracranial pressure. This patient responded to induction liposomal amphotericin and subsequent consolidation fluconazole, and a lumbar puncture was deferred on the initial admission.

Corticosteroids had been administered as an outpatient for presumptive sinusitis prior to admission and were offered briefly as the possibility of optic neuritis was considered as an
etiology for his papillitis as an inpatient. In HIV-positive patients, dexamethasone does not reduce mortality in patients with cryptococcal meningitis and is associated with an increase in adverse events [9], although these findings may not be generalizable to HIV-negative patients. Corticosteroids were ultimately deferred given the absence of optic neuritis and the stability of his multiple sclerosis symptoms.

This case adds to an increasing literature on potential infectious complications of fingolimod, including cryptococcal disease. The risks of opportunistic infections should be considered in multiple sclerosis patients managed with fingolimod.

**Statement of Ethics**

Permission was obtained from the subject for use of medical information in the case report per ProMedica Institutional Review Board protocol. The ProMedica Institutional Review Board requires obtaining informed consent from the participant for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the participant for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Joel A. Kammeyer contributed to the conception and design of the case report, drafted and revised the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the work. Nicole M. Lehmann contributed to the conception and design of the case report, assisted with the drafting and revisions of the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the work.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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