



Case report

Increased risk of disseminated cryptococcal infection in a patient with multiple sclerosis on fingolimod



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ABSTRACT

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS), with an estimated 2.3 million people being affected globally, and is a major cause of permanent disability. About 90 % of the affected patients with MS have relapsing-remitting type. Fingolimod became the first FDA approved oral drug in 2010 with an immunomodulating mechanism to control the relapse rates. However, since its introduction, increased cases of cryptococcal infections have been reported including meningoencephalitis and disseminated infections. Herein, we present the case of a 34-year-old-male with disseminated Cryptococcal and localized varicella zoster virus (VZV) coinfection to highlight the risk of opportunistic infections associated with the long-term use of fingolimod. The objective of this literature review is for clinicians to have a high index of suspicion for cryptococcal infections when dealing with MS patients on Fingolimod, especially those who present with neurological symptoms, as this mimics MS relapse.

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Introduction

Multiple sclerosis is an immune-mediated disease of CNS, causing focal destruction of myelin sheaths. The evidence shows complex interaction between genetics and unknown environmental factors causing autoreactive T cell-mediated inflammation of the brain tissue [1]. Fingolimod was the first FDA-approved oral treatment for relapsing-remitting MS (RRMS) to decrease relapse rates. It interacts with lymphocytes, which results in impaired mobilization to the peripheral blood. This mechanism significantly reduces the access of autoreactive lymphocytes to the CNS, thus modulating the inflammatory process in patients with MS [2]. Initial trial, which led to its approval, showed increased incidence of HSV and VZV infections, but these patients were receiving higher dose of Fingolimod than approved (1.25 mg once daily v/s 0.5 mg once daily). Although the trial did not show any increased infection rates at the approved dose, i.e. 0.5 mg once daily, the first asymptomatic pulmonary cryptococcal infection did appear during this trial [3]. Therefore, since its approval, multiple cryptococcal infections have been reported.

Cryptococcus spp. is an encapsulated fungus, and two species are of prime importance: *Cryptococcus neoformans* and *Cryptococcus gatti*; *C. neoformans* is more prevalent and is an opportunistic fungus in immunocompromised hosts; and *C. gatti* is a pathogen of immunocompetent hosts [4]. Capsule of the fungus plays an important role in immune invasion and pathogenesis [5].

The objective of presenting this case report as well as reviewing the previously reported cases is to highlight that the incidence of Cryptococcal infections are increasing in patients with Fingolimod use, and the risk of incidence proportionally increases with prolonged use. The other diagnostic challenge is the early identification of the infection, as the initial imaging of the brain can remain unchanged from the prior images and the non-enhancing lesions do not completely rule out the infection. Furthermore, the prompt identification and high suspicion of the disseminated infection are critical, as it can lead to permanent neurological, cognitive impairment and even death.

Case report/case presentation

We report the case of a 34-year-old- male with relapsing-remitting multiple sclerosis treated with fingolimod for 5 years. He was presented to the emergency department after fall and brief loss of consciousness. On presentation, the patient was diaphoretic with rigors. Prior to this presentation, patient complained of gait instability, generalized weakness, decreased appetite, and weight

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loss for the last 2–3 weeks, associated with nausea and vomiting for the preceding 2–3 days. On examination, he had an oral temperature of 36.7°C, heart rate of 86 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 122/76 mmHg, and oxygen saturation 99 % on room air. He was alert and oriented with unremarkable neurological findings except for unsteady gait with generalized weakness when standing. Initial laboratory findings revealed leukocytosis of 14.1 k/mL with left shift, lactate of 3.2 mmol/L, and procalcitonin of 0.04 ng/mL. Computed tomography (CT) of the head revealed periventricular hypodensities unchanged from previous imaging studies. Magnetic resonance imaging (MRI) of the brain revealed multiple non-enhancing lesions in cerebral white matter consistent with MS and unchanged from previous MRI obtained 3 months before this presentation (Figs. 1 and 2).

On day 5, initial blood cultures collected in the emergency department resulted positive for yeast-like cells; and the patient was started on intravenous fluconazole. On day 7, yeast was identified as *Cryptococcus neoformans* var *grubii* with serum cryptococcal antigen >1:2560. Patient was initiated on liposomal amphotericin and flucytosine. Absolute cluster of differentiation 4 (CD4) count was noted to be 61/uL, and human immunodeficiency virus (HIV) test was non-reactive. Transthoracic echocardiogram (TTE) was negative for valvular vegetations. Ultrasound (US) of ocular orbits was indicative of increased intracranial pressure (ICP); however, no evidence of endophthalmitis was noted.

On day 13, the patient developed erythematous maculopapular rash in unilateral dermatomal distribution and was started on ten days of intravenous (IV) Acyclovir for localized VZV infection with complete resolution of the lesions.

While in the hospital, the patient required serial therapeutic and diagnostic lumbar punctures for increased ICP. Initial lumbar puncture revealed an opening pressure of 48 cm water (normal 7–18 cmH₂O), glucose 27 mg/dL, protein 58.4 mg/dL, white blood cell 8/mcL, lymphocytes 3, mono 5, RBC 110, and fungal stain showed the presence of yeast. Cerebrospinal fluid (CSF) cultures confirmed *Cryptococcus neoformans* var *grubii*. The diagnosis of disseminated cryptococcal disease was made.

Treatment with amphotericin B lipid complex and flucytosine was continued. During the hospital stay, he completed 4 weeks of amphotericin B and flucytosine therapy. The patient was later discharged on 8 weeks of oral fluconazole 800 mg, with a plan of slow taper down to 200 mg to be continued for 2 years.

Discussion/conclusion

Fingolimod was the first oral drug, approved in 2010 after two large Phase III trials (FREEDOMS and TRANSFORMS), to control relapse rates in relapsing-remitting type of MS. Fingolimod has a sphingosine-like structure, which interacts with sphingosine-1-phosphate (S1P) receptors found on lymphocytes, resulting in the downgradation of these receptors and impairing intracellular signaling. This process leads to the sequestration of lymphocytes



Fig. 1. MRI-Brain Sagittal T2 Flair showing hyperintensity in deep white matter.

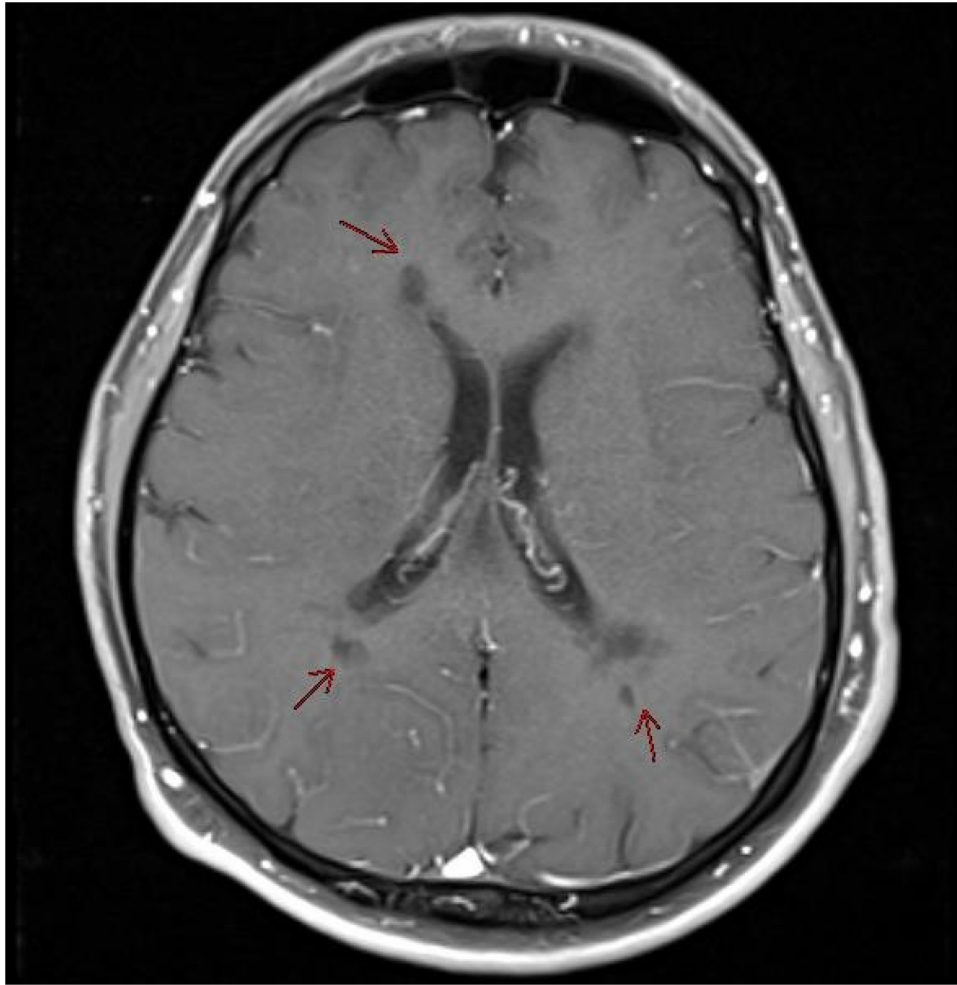


Fig. 2. MRI-Brain with contrast T1 showing multiple MS lesions, no contrast enhancement.

into secondary lymphoid organs and impaired mobilization into peripheral blood [2] and significantly reduces the access of autoreactive lymphocytes to the CNS and reduces the relapsing frequency. Since the introduction of Fingolimod, Cryptococcal infections have been emerging among the patients with the long-term use of Fingolimod. Spectrum of the disease include isolated pulmonary infections [3,6], isolated cutaneous infections [7,8], life-threatening meningoencephalitis, and disseminated infections. Even though the incidence of invasive fungal infections by *Cryptococcus neoformans* remains high in immunocompromised hosts with a mortality rate of 20–50 % in disseminated disease, early diagnosis and effective treatment are critical.

Polysaccharide capsule of the fungus plays an important role in immune evasion, dissemination, and virulence. *C. neoformans* has a special affinity to cross blood brain barrier (BBB), and many mechanisms have been proposed in this regard [4]. So far, eight cases of meningoencephalitis [9–16] have been reported, with 2 reported deaths [11,14] and significant long-term cognitive impairment in one case [9]. To the best of our knowledge, two cases of disseminated disease have been reported [17,18], with significant permanent neurological and cognitive impairment as sequelae in one patient [18]. This case is unique as the patient had disseminated cryptococcal and localized VZV coinfection.

On the analysis of these reported meningoencephalitis and disseminated cases, the patients developed infection after an average use of 3.5 years (range 2–7 years). Interestingly in all the reported cases, initial imaging including CT and MRI of brain

remain unchanged from the baseline imaging showing no new nonenhancing lesions, with concurrent clinically worsening neurological symptoms. MRI findings of the brain in *Cryptococcus*-related meningoencephalitis vary, mostly showing leptomeningeal and parenchymal enhancement [19], which was not present in our case. Additionally, the reported disseminated and meningoencephalitis cases [9–18] showed baseline lesions of MS, with no new lesions and making the early diagnosis difficult. Hence, initial imaging including CT and MRI do not completely rule out the possibility of infection. Therefore, definitive diagnosis of cryptococcosis is made when cultures are positive from either blood, CSF, or urine. Cryptococcal antigen detection in blood is 100 % sensitive with 96–99 % specificity. In CSF, sensitivity is 96–100 % with a specificity of 93–98 % and urine sensitivity of 85 % [20]. Similarly, MS patients treated with Fingolimod who present with symptoms similar to MS relapse, such as headaches, blurry vision, weakness, or unsteady gait, especially if decreased lymphocytes and CD4 cell counts are noted, should have high suspicion of cryptococcal infection.

Opening pressure of the lumbar puncture is an important diagnostic and therapeutic measure and remains high in these cases and is a strong indicator of the fungal infection. Elevated opening pressure on lumbar puncture was consistently present in all the above described cases. India ink analysis is also a sensitive testing in this regard and should be performed.

There are no treatment guidelines in immunocompetent hosts with *Cryptococcus* related disseminated or meningoencephalitis

disease. Yet, previously reported cases and in our case, treatment consists of induction (IV liposomal amphotericin B and Flucytosine), consolidation (oral fluconazole) and maintenance (extended oral fluconazole) phases as similar to Cryptococcal infection management in HIV or immunocompromised hosts.

Complications of cryptococcal infection can lead to permanent neurological, cognitive disabilities, and even death. Consequently, early recognition and appropriate management remain critical in such patients.

CRedit authorship contribution statement

Pushpinder Kaur: Writing - original draft, Writing - review & editing, Resources. **Alana Lewis:** Writing - original draft, Writing - review & editing, Resources. **Abdul Basit:** Writing - original draft, Writing - review & editing, Resources. **Nikolas St Cyr:** Writing - original draft, Writing - review & editing, Resources. **Zaman Muhammad:** Supervision, Writing - review & editing.

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