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Cryptococcal meningitis in a multiple sclerosis patient treated with Fingolimod: a case report and review of imaging findings

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ABSTRACT

Fingolimod is an oral medication approved by the Food and Drug Administration in 2009 for the treatment of relapsing remitting multiple sclerosis (RRMS). Initial clinical trials did not show a significantly increased rate of serious infections with fingolimod therapy. However, a mildly increased risk of less serious infections, such as varicella zoster virus and herpes simplex virus, was reported. Recently, however, several instances of serious opportunistic infections have been reported. In the years following approval of fingolimod for use in multiple sclerosis (MS), seven cases of cryptococcal meningitis in patients undergoing treatment have been described in the literature. We present a 40-year old woman with RRMS on fingolimod therapy presenting with a rare case of cryptococcal meningitis exhibiting alterations of consciousness, which was initially diagnosed as an MS relapse.

1. Introduction

Fingolimod is an oral disease-modifying agent approved by the Food and Drug Administration (FDA) in 2009 for the treatment of relapsing-remitting multiple sclerosis (RRMS) [1]. By binding to the sphingosine phosphate 1 receptors in the secondary lymphoid tissue, fingolimod reduces the egress of lymphocytes, which decreases the number of lymphocytes in the central nervous system and also results in peripheral lymphopenia [1–3]. During clinical trials, fingolimod did not have significantly increased rates of serious infections compared to placebo therapy despite peripheral lymphopenia [2,4,5]. However, a slight increase in the risk of varicella zoster virus and herpes simplex virus infections, in addition to a few isolated serious infections have been documented during the post-marketing surveillance period [2,4,6].

Cryptococcus neoformans is an encapsulated yeast that is the most common cause of fungal meningitis in humans, particularly in immunocompromised individuals, and causes a severe, life-threatening illness. Furthermore, only approximately 20% of cases in the United States are not associated with individuals diagnosed with human immunodeficiency virus (HIV) [7]. While not originally reported to be associated with multiple sclerosis (MS) therapies, one of the first cases of cryptococcal meningitis related to MS therapy was reported in a patient being treated with natalizumab in 2014 [8]. Since then, additional sporadic cases have emerged in association with MS therapies. To date in the literature, there are only seven documented cases of fingolimod-related cryptococcal meningitis [4,6,9–13]. We present a case of an MS patient on fingolimod therapy with imaging findings, including enhancement pattern and lesion location atypical for active demyelination seen in MS, that were ultimately discovered to be manifestations of cryptococcal meningitis.

2. Clinical vignette

A 40-year-old female with a history notable for RRMS on fingolimod therapy for 2 years and 3 months presented to the emergency department with a 1-day history of confusion, anomia, and generalized weakness. Physical exam revealed no focal neurologic deficits aside from the reported anomia. Laboratory evaluation was notable for an elevated white blood cell (WBC) count of 11×10^9 cells/L with a depressed absolute lymphocyte count (ALC) of 0.2×10^9 cells/L. Despite the mildly depressed ALC, the patient was not initially considered immunocompromised as fingolimod has been shown to spare essential lymphocyte functions. A computed tomography (CT) of the brain without contrast was negative. MRI of the brain without and with gadolinium contrast was ordered and revealed numerous T2 FLAIR hyperintense lesions in the supratentorial white matter, consistent with the patient's known history of demyelinating disease (Fig. 1a). Some of these lesions were enhancing and suggestive of active areas of demyelination (Fig. 1b). Subtle enhancement of the trigeminal nerves was also present but not initially described (Fig. 2). The patient was diagnosed with an MS exacerbation, treated with 5 days of intravenous methylprednisolone, and returned to her baseline level of functioning.

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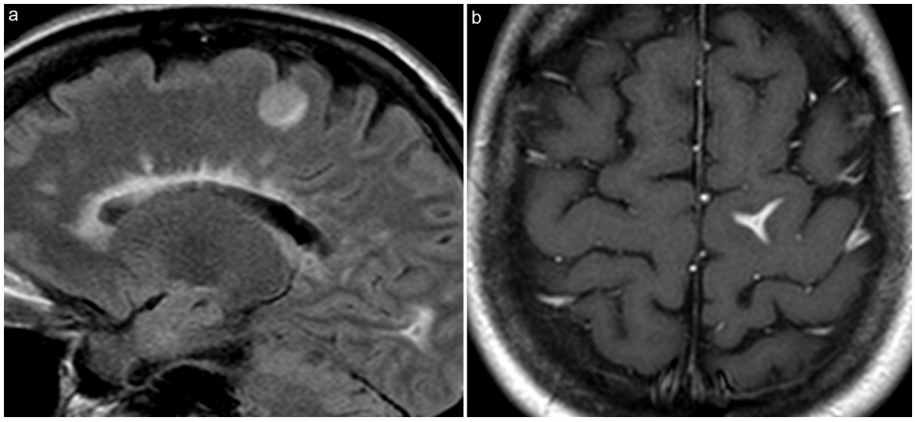

Fig. 1. (a) Sagittal T2-weighted FLAIR and (b) axial T1-weighted post-contrast images demonstrate cortical and juxtacortical T2 hyperintense lesions with enhancement morphology atypical for actively demyelinating lesions.

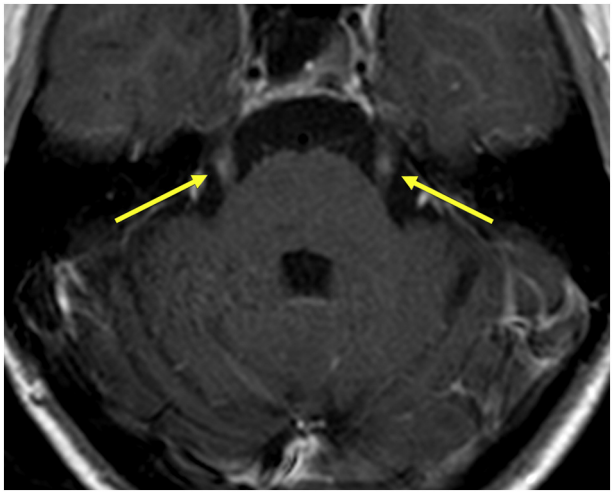

Fig. 2. Axial T1-weighted post-contrast image demonstrates subtle bilateral trigeminal nerve enhancement (arrows).

Fingolimod therapy was also halted with the intent of transitioning to a higher intensity regimen, such as natalizumab, given presumed breakthrough MS exacerbation despite fingolimod therapy.

However, 2 weeks later, the patient presented again to the emergency department with a 4-day history of generalized weakness, anorexia, headaches, and visual and auditory hallucinations. Physical exam was notable for nuchal rigidity, and a lumbar puncture was performed with a normal opening pressure. Analysis of the cerebrospinal fluid (CSF) revealed an elevated leukocyte count of 22×10^{-3} cells/L (7% neutrophils, 35% lymphocytes, 55% monocytes, and 3% eosinophils), an elevated protein of 142×10^{-5} kg/L, and a significantly depressed glucose of 7.0×10^{-5} kg/L. The infectious disease service was consulted, and the patient was started on broad-spectrum meningitis coverage with the exception of fungal coverage. However, the India ink prep of the CSF revealed encapsulated yeast the same that the CSF cryptococcal antigen resulted as positive. Subsequently, this yeast grew to be *Cryptococcus neoformans* on cultures. Additionally, the CSF cryptococcal antigen returned positive, which was confirmed on multiple subsequent CSF samples. A repeat brain MRI with and without contrast demonstrated stable cortical and juxtacortical enhancing lesions. However, it also demonstrated the interval development of bilateral, diffuse leptomeningeal enhancement. This finding was presumed to represent cryptococcal meningoencephalitis given the CSF study results (Fig. 3). Our patient was immediately transitioned to amphotericin B and flucytosine therapy based on CSF results and corroborating meningeal enhancement. No evidence of extra-CNS sites of cryptococcal infection were found on additional imaging.

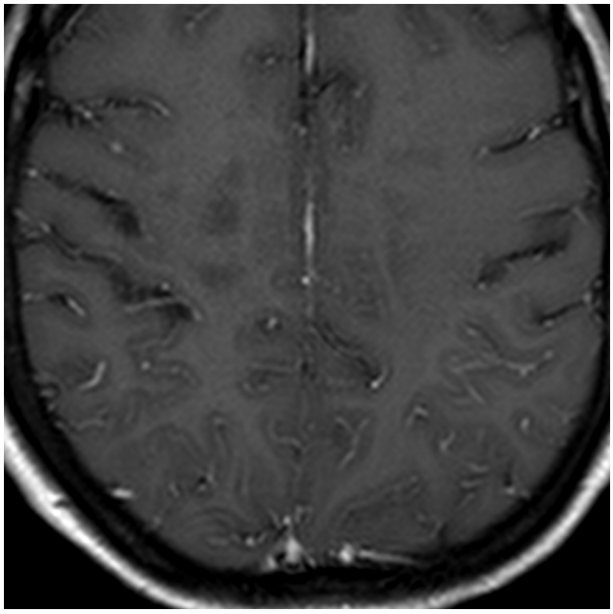

Fig. 3. Axial T1-weighted post-contrast image on a follow-up brain MRI demonstrates diffuse leptomeningeal enhancement, most prominently in the bilateral parietal lobes.

Despite the initial anti-fungal therapy, the patient's mental status continued to decline with increasing agitation and auditory and visual hallucinations, thought to be partially attributable to increasing intracranial pressure noted on subsequent lumbar punctures. However, a second repeat brain MRI with and without contrast demonstrated a further increase in the degree of leptomeningeal enhancement (Fig. 4). A lumbar drain was placed, and the dosages of the patient's antifungal medications were increased. However, several days after the placement of the lumbar drain, the patient was found to be only responsive to painful stimuli. A CT scan of the head revealed findings suggestive of intracranial hypotension. Subsequently, the lumbar drain's rate was reduced with concomitant improvement in the patient's responsiveness. With the aggressive anti-fungal therapy and the presence of the lumbar drain, the patient continued to recover. At the time of drafting this case report, the lumbar drain was removed, and the patient was progressing well with physical therapy. The infectious disease team planned to continue with at least 6 weeks of combination therapy involving both amphotericin B and flucytosine.

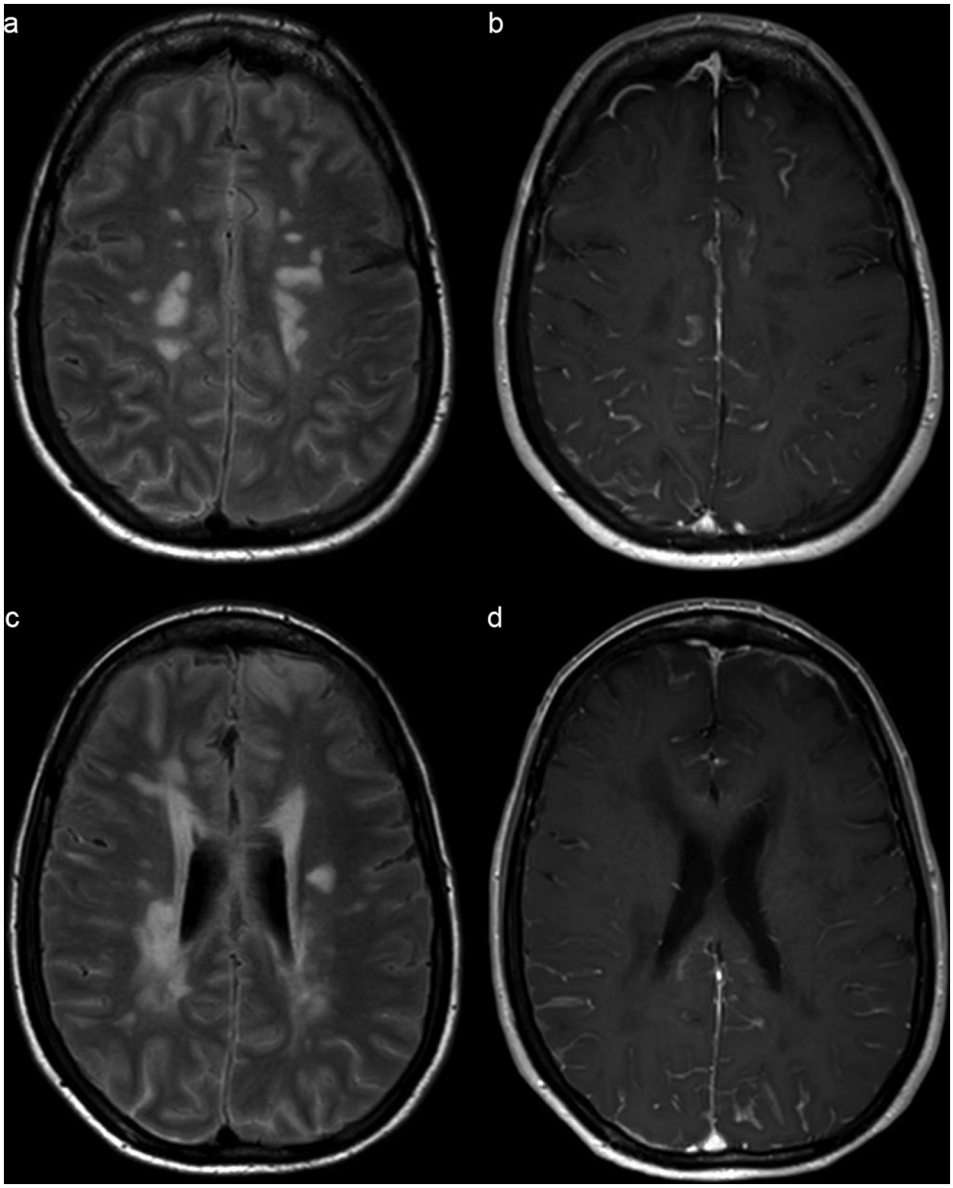

Fig. 4. Axial T2-weighted FLAIR and T1-weighted post-contrast images at the level of the centrum semiovale (a, b) and the corona radiata (c, d) on a second follow up brain MRI performed one month after the prior demonstrate worsening leptomeningeal enhancement and the development of increased T2/FLAIR within the sulci.

3. Discussion

Opportunistic cryptococcus is a common pathogen among immunocompromised patients such as those with HIV and those who have undergone organ transplantation. Fingolimod was the first oral drug approved by the FDA for the treatment of MS and is particularly adept at treating the RRMS variant. Through its mechanism of decreasing the egress of peripheral lymphocytes from lymphoid tissue, fingolimod decreases lymphocyte infiltration into the CNS, thus reducing the likelihood of inflammation and tissue damage normally seen in patients with MS. Despite this fingolimod-induced lymphopenia, initial studies demonstrated that the rates of serious infections were not significantly increased [1,2,4,5]. Additionally, patients on fingolimod are not traditionally considered immunocompromised as many essential lymphocyte functions are preserved [1,2,5]. However, since its introduction to the market in 2009, seven cases of cryptococcal meningitis and several cases of cutaneous cryptococcal infections in patients undergoing fingolimod therapy are accounted for in the literature [12–15]. In response, a warning was appended to the prescribing information in 2015 regarding the risk of cryptococcal infection [10,11].

Based on our literature review of previously reported cases, our patient is the eighth case of cryptococcal meningitis in an MS patient undergoing fingolimod therapy. Several imaging features are shared among previously reported cases as well as our case (Table 1) [4,6,9–13]. For example, our case as well as 3 of 6 prior cases of patients that were on fingolimod treatment for at least 2 years prior to clinical deterioration exhibited leptomeningeal enhancement on MRI [10,11,13]. Our case is the first case to demonstrate the presence of bilateral trigeminal nerve enhancement despite the lack of neurological symptoms to suggest cranial nerve V deficits. By itself, bilateral trigeminal nerve enhancement is not specific to diagnose infection as it can also be seen in active demyelination in approximately 2% of patients with MS [16,17]; however, a meningitic process such as infection may be a more reasonable etiology for bilateral trigeminal nerve enhancement when taking into account our patient's presentation. Another finding on the patient's initial brain MRI was enhancement (Fig. 1b) of lesions involving the cortical and subcortical white matter (Fig. 1a) that did not exhibit the typical morphologic pattern seen in

Table 1
Summary of cases of cryptococcal infections involving the CNS in MS patients on fingolimod therapy.

Authors	Year	Age	Gender	Treatment duration	Findings
Achtnichts et al.	2015	40	Male	2 years	Nodular basal ganglia enhancement
Huang et al.	2015	50	Male	4 years	Leptomeningeal enhancement; ring enhancing lesions
Grebenciucova et al.	2016	62	Male	3 years	No acute findings
Seto et al.	2016	63	Male	2 years	No acute findings
Ward et al.	2016	67	Female	4 years	Leptomeningeal enhancement
Pham et al.	2017	61	Female	3 years	Leptomeningeal enhancement
Anene-Maidoh et al.	2018	61	Female	5 years	No MRI due to AICD

CNS = central nervous system; MS = multiple sclerosis; MRI = magnetic resonance imaging; AICD = automated implantable cardioverter defibrillator.

acute MS lesions such as nodular, ring, or incomplete ring enhancement without sparing of the subcortical U fiber. Other common MRI findings in patients with cryptococcal meningitis are basal ganglia enhancement, peripheral nodular enhancement patterns, and ring-enhancing lesions, all of which were seen in the published case reports of patients diagnosed with cryptococcal meningitis while undergoing fingolimod therapy [18–20]. Other differential diagnoses that could have been considered are tuberculosis, Kaposi's sarcoma, non-Hodgkin's lymphoma, immune reconstitution inflammatory syndrome, and leptomeningeal manifestation of multiple sclerosis. Several studies using high resolution ultra-high field 7 T MRI have demonstrated leptomeningeal inflammation and subpial cortical demyelination in multiple sclerosis [21]. However, it is unlikely that the MRI scanner at our facility would have sufficient sensitivity to detect and demonstrate diffuse leptomeningeal enhancement as a manifestation of underlying multiple sclerosis. Moreover, leptomeningeal enhancement in multiple sclerosis is often nodular in morphology [22]. Definitive diagnosis of cryptococcal meningitis requires cerebrospinal fluid analysis.

Given the recent approval and use of fingolimod, the long-term effects of this therapy on a patient's immunosuppression status have to yet to be well-established [2,4]. As the number of patients undergoing fingolimod therapy and the duration of their therapy increases, more cases of opportunistic infections may become evident over time. As a radiologist, expertise and familiarity with this associative side effect is necessary to allow for prompt management of the patient.

4. Conclusion

The possibility of cryptococcal meningitis is an important diagnosis to consider while a radiologist reviews brain MRIs of MS patients on fingolimod therapy when enhancement atypical for MS is present: leptomeningeal enhancement, atypical location of enhancing lesions, or atypical morphology of enhancing lesions.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2018.11.005.

References

[1] Grebenciucova E, Pruitt A. Infections in patients receiving multiple sclerosis disease-modifying therapies. Curr Neurol Neurosci Rep 2017;17(11):88.
[2] Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010;33(2):91–101.
[3] Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for replasping multiple sclerosis. N Engl J Med 2010;362(5):402–15.
[4] Grebenciucova E, Reder AT, Bernard JT. Immunologic mechanisms of fingolimod and the role of immunosenescence in the risk of cryptococcal infection: a case report and review of literature. Mult Scler Relat Disord 2016;9:158–62.
[5] Levin SN, Kaplan TB. Infectious complications of novel multiple sclerosis therapies. Curr Infect Dis Rep 2017;19(2):7.
[6] Anene-Maidoh TI, Paschall RM, Scott Graham R. Refractory cryptococcal meningoencephalitis in a patient with multiple sclerosis treated with fingolimod: a case report. Interdiscip Neurosurg 2018;12:8–9.
[7] Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the US: 1997–2009. PLoS One 2013;8(2):e56269.
[8] Valenzuela RM, Pula JH, Garwacki D, Cotter J, Kattah JC. Cryptococcal meningitis in a multiple sclerosis patient taking natalizumab. J Neurol Sci 2014;340(1–2):109–11.
[9] Achtnichts L, Obreja O, Conen A, Fux CA, Nedelchev K. Cryptococcal meningoencephalitis in a patient with multiple sclerosis treated with fingolimod. JAMA Neurol 2015;72(10):1203–5.
[10] Ward MD, Jones DE, Goldman MD. Cryptococcal meningitis after fingolimod discontinuation in a patient with multiple sclerosis. Mult Scler Relat Disord 2016;9:47–9.
[11] Pham C, Bennett I, Jithoo R. Cryptococcal meningitis causing obstructive hydrocephalus in a patient on fingolimod. BMJ Case Rep 2017;2017.
[12] Seto H, Nishimura M, Minamiji K, Miyoshi S, Mori H, Kanazawa K, et al. Disseminated cryptococcosis in a 63-year-old patient with multiple sclerosis treated with fingolimod. Intern Med 2016;55(22):3383–6.
[13] Huang D. Disseminated cryptococcosis in a patient with multiple sclerosis treated with fingolimod. Neurology 2015;85(11):1001–3.
[14] Carpenter AF, Goodwin SJ, Bornstein PF, Larson AJ, Markus CK. Cutaneous cryptococcosis in a patient taking fingolimod for multiple sclerosis: here come the opportunistic infections? Mult Scler 2017;23(2):297–9.
[15] Forrestel AK, Modi BG, Longworth S, Wilck MB, Micheletti RG. Primary cutaneous cryptococcus in a patient with multiple sclerosis treated with fingolimod. JAMA Neurol 2016;73(3):355–6.
[16] van der Meijs AH, Tan IL, Barkhof F. Incidence of enhancement of the trigeminal nerve on MRI in patients with multiple sclerosis. Mult Scler 2002;8(1):64–7.
[17] da Silva CJ, da Rocha AJ, Mendes MF, Maia Jr. AC, Braga FT, Tilbery CP. Trigeminal involvement in multiple sclerosis: magnetic resonance imaging findings with clinical correlation in a series of patients. Mult Scler 2005;11(3):282–5.
[18] Saremi F, Helmy M, Farzin S, Zee CS, Go JL. MRI of cranial nerve enhancement. AJR Am J Roentgenol 2005;185(6):1487–97.
[19] Miszkiel KA, Hall-Craggs MA, Miller RF, Kendall BE, Wilkinson ID, Paley MN, et al. The spectrum of MRI findings in CNS cryptococcosis in AIDS. Clin Radiol 1996;51(12):842–50.
[20] Orlowski HLP, McWilliams S, Mellnick VM, Bhalla S, Lubner MG, Pickhardt PJ, et al. Imaging spectrum of invasive fungal and fungal-like infections. Radiographics 2017;37(4):1119–34.
[21] Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med 2018;378(2):169–80.
[22] Harrison DM, Wang KY, Fiol J, Naunton K, Royal III W, Hua J, et al. Leptomeningeal enhancement at 7T in multiple sclerosis: frequency, morphology, and relationship to cortical volume. J Neuroimaging 2017;27(5):461–8.