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Case Report

# Cryptococcal Cerebellitis in the Setting of Fingolimod Use for Multiple Sclerosis: Atypical Presentation of Dystonia and Imaging Finding Misinterpreted as Subacute Ischemic Stroke

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## Abstract

**Objective:** Describe a case of cryptococcal cerebellitis in a patient on Fingolimod with atypical findings of generalized dystonia and imaging findings mistaken for bilateral subacute cerebellar strokes.

**Background:** Fingolimod is used for multiple sclerosis (MS) and is often associated with lymphopenia with prolonged use. Cryptococcal opportunistic infections in patients on Fingolimod, have been rarely described.

**Design/Methods:** Case report and review of literature.

**Results:** 44-year-old man with MS in remission treated with Fingolimod for the last 8 years, and poorly controlled type-II diabetes mellitus (A1c 10.4), transferred to our facility for stroke work-up with brain MRI findings reportedly showing subacute bicerebellar ischemic strokes. On exam, he was somnolent and intermittently followed commands. He had nuchal rigidity and positive Kernig and Brudzinski signs. Meningitis was suspected and empiric treatment was initiated. MRI findings on DWI/ADC/FLAIR sequences were inconsistent with any vascular territory. Leptomeningeal enhancement was noted in the cerebellar folia, basal cisterns, suprasellar cistern, and brainstem surface. Labs were remarkable for lymphopenia (250), cerebrospinal fluid (CSF) and blood culture grew cryptococcus neoformans, so treatment with liposomal amphotericin B and flucytosine was started. On day 4, patient developed generalized dystonia that resolved with diphenhydramine. Unfortunately, patient did not respond to therapy as evident on repeat LP on day 6. His physical exam worsened, and he was intubated 2 days after. Repeat MRI showed with tonsillar herniation and patient expired.

**Conclusion:** Cryptococcal cerebellitis is a rare opportunistic infection occurring in MS patients on Fingolimod. Early recognition is crucial to avoid rapidly worsening neurological outcomes.

***Keywords:** Multiple Sclerosis; Cryptococcal Cerebellitis; Fingolimod; Subacute Ischemic Stroke*

## Introduction

Fingolimod is used for multiple sclerosis and is often associated with lymphopenia with prolonged use. Opportunistic infections, particularly cryptococcus neoformans in patients on Fingolimod, have been rarely described. We discuss here a case of a patient with multiple sclerosis on Fingolimod who developed fatal cryptococcal meningoencephalitis that was initially misdiagnosed as bilateral cerebellar ischemic stroke. [1-10]

## Case Presentation

A 44-year-old man with multiple sclerosis in remission treated with Fingolimod for the last 8 years, and poorly controlled type-II diabetes mellitus (A1c 10.4), was transferred to our facility for stroke work-up with brain MRI findings reportedly consistent with subacute bilateral cerebellar ischemic strokes (Figures 1 and 2). 10 days prior to presentation, patient has been increasingly confused. He works as a truck driver and his coworkers have reported that he has been acting "weird", his speech was incomprehensible. In addition, he was having trouble walking and has been falling frequently without veering to any specific side. He was complaining of constant dull headache and has been extremely sensitive to light. This all prompted the wife to take the patient to the emergency department where MRI brain revealed bilateral scattered.

DWI hyperintensities with variable ADC correlate. Hence, a diagnosis of acute ischemic stroke was made and patient was transferred to us. Further review of imaging showed that the DWI/ADC/FLAIR findings were inconsistent with any vascular territory (figures 1 and 2) and an extensive leptomeningeal enhancement was noted in the cerebellar folia, basal cisterns, suprasellar cistern, and the surface of the brainstem (figures 3 and 4).

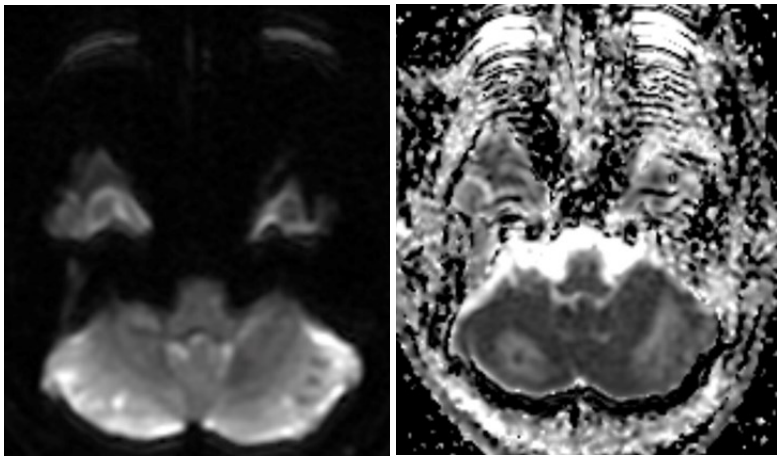

***Fig 1 and 2:*** *Diffusion restriction lesions in bilateral cerebellum as seen on DWI with ADC correlate.*

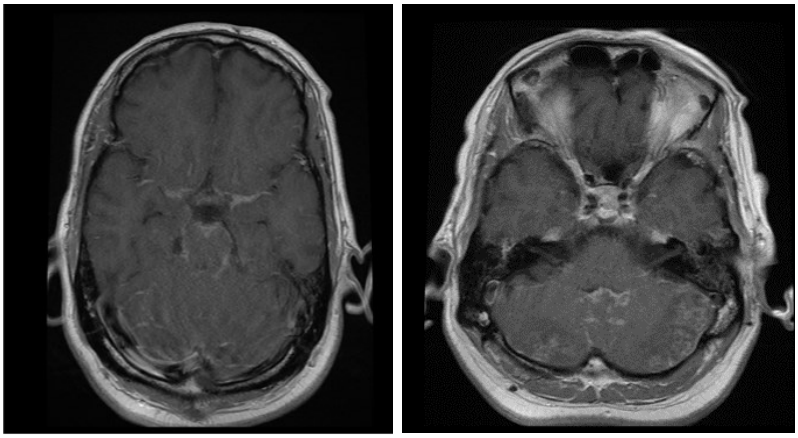

***Fig 3 and 4:*** *T1 post contrast revealed extensive leptomeningeal enhancement the cerebellar folia, basal cisterns, and the surface of the brainstem.*

On physical exam, he was somnolent and intermittently followed simple commands. He also had nuchal rigidity and positive Kernig and Brudzinski signs. Meningitis was suspected and empiric treatment with Vancomycin, Ceftriaxone and Acyclovir was initiated. Labs were remarkable for lymphopenia (Lymphocyte count 250), and both cerebral spinal fluid (CSF) and blood culture grew cryptococcus neoformans so treatment with liposomal amphotericin B and flucytosine was started. On day 4 of admission, patient developed generalized dystonia that resolved with IV diphenhydramine. Unfortunately, patient did not respond to therapy as evident on repeat LP on day 6 of admission (see table 1). His physical exam continued to worsen, and he was intubated on day 8 of admission. Repeat MRI was consistent with tonsillar herniation (figure 5) and patient expired.

**Table 1:** CSF study results on days 3 and 6.

| CSF Lab | Day 3 | Day 6 |
|---|---|---|
| RBC | 40 | 61 |
| WBC | 780 | 163 |
| Neutrophils % | 72% | 40% |
| Glucose | 3 | 2 |
| Total protein | 367 | 285 |
| CSF Culture | C. Neoformans | |

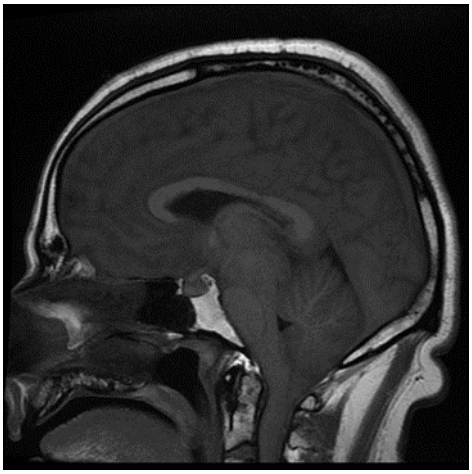

***Fig 5:*** *Tonsillar herniation.*

## Discussion

Fingolimod is a sphingosine-1-phosphate–receptor antagonist which desensitizes T and B ymphocytes, thereby reduces recirculation of auto-aggressive lymphocytes to the central nervous system. It was also found to have a neuroprotective effect. FREEDOMS (I and II) were randomized controlled trials that demonstrated significant benefit of Fingolimod over placebo in terms of relapse rate and the risk of disability progression.[1,2] TRANSFORMS trial demonstrated that Fingolimod significantly reduced annual relapse rate compared to interferon beta-1a.[3]

In a meta-analysis by Francis et al investigating the effect of Fingolimod on lymphocyte count and its relation to opportunistic infections, Fingolimod decreases serum lymphocyte count by 24-30% in the first 2 weeks of therapy and this effect was reversible on discontinuation, without an increase in infection rates compared to placebo (1 to 1.4 respectively).[4] However, the effect of lymphopenia on the occurrence of opportunistic infections might still be underestimated. Fingolimod tends to decrease CSF leukocyte count significantly.[5] The TRANSFORMS study was divided into three arms including: intramuscular interferon beta-1a 30µg, Fingolimod 0.5 mg and Fingolimod 1.25 mg. Fatal infections including disseminated primary varicella zoster and herpes simplex encephalitis in 2/426 patients who received the 1.25 mg dose.[3]

In addition, there are individual case reports describing opportunistic infections with Fingolimod use. In a case report by Carpenter et al, a 47-year-old man with relapsing-remitting MS (RRMS) on Fingolimod, developed a forehead lesion whose biopsy was consistent with cryptococcus neoformans 16 months after starting therapy. The lesion resolved on Fingolimod discontinuation and fungal therapy.[6] Another case report described a 50-year-old man on

Fingolimod for RRMS who developed pulmonary cryptococcosis that resolved with Fingolimod discontinuation and oral Fluconazole therapy.[7] Kaposi sarcoma developed in a 38-year-old man with RRMS 19 months into starting treatment with Fingolimod. He was previously on interferon and was switched to Fingolimod since he had 2 relapses while being on interferon therapy.[8]

Only one case of cryptococcal meningitis to our knowledge has been described recently in the literature in 2022 which was a 39-year-old woman with relapsing-remitting multiple sclerosis diagnosed within 2 days of symptom onset, recovered with IV amphotericin B therapy within few days.[9]

It is important to know that our patient also had uncontrolled diabetes mellitus (A1c 10.4%). Diabetes predisposes to infections through alterations in innate and acquired immune defenses. This makes no surprise that infections are worse in patients with uncontrolled diabetes and cryptococcosis is no exception. In fact, Archuleta et al reported in 2021 in a single US cohort study that uncontrolled diabetes is associated with worse outcomes in pulmonary cryptococcosis, including a 4-fold and 6-fold increased odds of death at 10 weeks and 1 year, respectively.[10] This can possibly explain why our patient's infection was not controlled despite receiving appropriate treatment.

## Conclusion

Opportunistic infections with Fingolimod, particularly cryptococcal cerebellitis have not been commonly reported. It is important that patients on such therapy seek immediate medical attention at the earliest possible after the onset of symptoms to institute aggressive systemic therapy to prevent rapid clinical deterioration as what unfortunately happened with our patient.

It is also very essential to have a thorough understanding of the neuroimaging and look at all the MRI sequences before making a definitive diagnosis.

## Conflict of Interest

The authors declare there is no conflict of interest.

## Funding

None.

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