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Case report

Musculoskeletal and CNS coccidiomycosis in an individual with multiple sclerosis on fingolimod – A case report

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ABSTRACT

We report the case of a 56-year-old female with a past medical history of multiple sclerosis on disease-modifying therapy of fingolimod who presented with disseminated *Coccidioides* infection, initially of the ankles bilaterally before progressing to the central nervous system. CNS coccidiomycosis has thus far not been associated with any pharmacological therapy for multiple sclerosis. Clinicians should have a high degree of suspicion for *Coccidioides* infection in immunosuppressed patients living in endemic areas.

Introduction

Introduced in 2010, Fingolimod (also known as Gilenya) was the first FDA-approved oral disease-modifying therapy for relapsing-remitting forms of multiple sclerosis (MS) [1]. As a sphingosine-1 phosphate (S1P) receptor modulator, fingolimod inhibits egress of lymphocytes from secondary lymphoid organs, reducing circulating levels of lymphocytes [2]. The resulting reduction of peripheral T cells, necessary for effective treatment of MS, nonetheless can predispose patients to fungal infections [3], including coccidioidomycosis [4].

Coccidioidomycosis, caused by the dimorphic fungi *Coccidioides immitis* and *C. posadasii*, typically presents asymptomatically or as a self-limiting respiratory illness [5]. However, around 5 % of diagnosed cases present with dissemination of the disease outside of confines of the lungs [6]. Patients with the greatest risk for disseminated disease typically are those that are immunocompromised such occurs with AIDS, some forms of chemotherapy, or organ transplantation-related immunosuppression [7]; however, immunocompetent hosts are also at risk [8]. Cases are associated with residence or travel to endemic areas, such as the Southwest United States and parts of Central and South America [9].

While treatment of MS, be it through monoclonal antibodies or immune system modulators, has been associated with fungal infections of the central nervous system (CNS) [10], no case of coccidiomycosis of the CNS and musculoskeletal (MSK) system has thus far been described in the context of patients on medications for the treatment of MS. In this case report, we describe the presentation of a disseminated *Coccidioides* infection with CNS and MSK involvement in a patient with MS taking fingolimod.

Case report

A 56-year-old female from the Southwestern United States presented to the Emergency Room for fever and severe bilateral ankle joint pain. She reported worsening ankle pain over the past 8 months that began in the right ankle but eventually involved both ankles. Upon physical exam, she had left lower extremity ankle edema and erythema over the medial malleolus, with pain upon passive and active movement in the ankles bilaterally. Her past medical history was significant for Type 2 Diabetes Mellitus, treated solely through non-pharmacological methods, and Multiple sclerosis (MS), treated with 0.5 mg of fingolimod once daily for the past sixteen years. She had originally been diagnosed with right foot plantar fasciitis, and a prior 3-Phase Bone Scan (obtained to rule out Diabetic Charcot Foot) had shown a diffuse area of abnormal uptake in the right calcaneal tuberosity in the 2–4 h delayed images; while consistent with a hyperactive lesion such as an infection or tumor, the area was interpreted to be potentially inflammatory in origin, consistent with chronic plantar fasciitis.

On presentation, she was febrile and hypotensive, with a T-max of

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38.6 °C, blood pressure of 91/61 mmHg, respiratory rate of 16 breaths min^{-1} and heart rate of 114 beats min^{-1}. Concern for sepsis was raised due to patient's fever, tachycardia and hypotension. An initial arthrocentesis of the left ankle joint was attempted unsuccessfully in the emergency department, and empiric antibiotic therapy consisting of vancomycin and cefepime were initiated after the procedure was performed. Orthopedic surgery was consulted, and a second arthrocentesis of the left ankle joint was performed, which yielded 5 cc of bloody synovial fluid. Laboratory analysis of the fluid revealed a total Nucleated Cell Count of 1146/mm^2 (68 % Neutrophils) and greater than 1 million/mm^2 RBCs. After 3 days, cultures of the fluid demonstrated growth of a mould with structures similar to *Coccidioides*. Antimicrobials were switched to intravenous amphotericin B (5 mg/kg QD) and oral voriconazole (4 mg/kg BID). A subsequent Magnetic Resonance Image, with and without contrast, of the left tibiotalar joint revealed a 3.5 cm rim-enhancing abscess adjacent to the medial malleolus/distal tibial diametaphysis, with underlying osteomyelitis and surrounding cellulitis.

Irrigation and debridement of the left ankle was performed. Intraoperatively, an abscess measuring 6 cm × 3 cm × 3 cm was found, and fungal bone cultures taken during this procedure grew *Coccidioides*. A fungal blood culture was also obtained and demonstrated growth of *Coccidioides*. Serial blood cultures showed no evidence of bacterial growth. After the debridement, the patient expressed relief of pain in the left ankle joint but stated that her right ankle pain persisted. Further imaging of the right ankle revealed an abscess measuring 3.1 cm × 2.2 cm × 7.3 cm located near the right flexor hallucis longus muscle with involvement of the distal right fibula and right lateral malleolus. Subsequent irrigation and debridement of the right ankle was performed, and subsequent bone fungal cultures collected during this procedure demonstrated growth of *Coccidioides*.

Following the surgeries, the patient was continued on IV liposomal amphotericin B (5 mg/kg QD) for 3 additional days (7 days total) with itraconazole (200 mg BID capsules) added in place of voriconazole due to itraconazole's better bone penetration. The patient was discharged after 18 total days in the hospital and was referred to outpatient Infectious Disease for continued treatment of infection. The patient continued 200 mg BID itraconazole with monthly monitoring for a few months, but eventually discontinued it due to associated alopecia and onycholysis; while fingolimod has also been associated with alopecia [11], the patient's symptoms were attributed to the itraconazole due to the lack of symptoms during the patient's prior sixteen years on fingolimod treatment. Fluconazole 400 mg O.D. was then prescribed at this time, and continued for several months until the patient began complaining of worsening dryness and hair loss, side effects similar to those suffered by the patient when on itraconazole. Due to these symptoms, and the fact that the patient had been on antifungals for six months following their hospitalization, the fluconazole was held while alternative options for the patient were considered.

One month after discontinuing the fluconazole, the patient suffered a syncopal episode at home, resulting in a visit to a nearby community emergency department where her altered mental status was attributed to dehydration. MRI imaging of the brain at this time showed evidence of prior multiple sclerosis lesions, but no active lesions/abnormalities were noted on the scan.

After this incident, the patient was restarted on her prior fluconazole dosage after discharge temporarily until her next Infectious Disease appointment two weeks later. At the time of this visit, the patient reported improvement of most of her previous symptoms (diarrhea, fever, night sweats), but noted that her headache persisted. It should be noted that the patient resumed her fingolimod at this time; the patient had been off her fingolimod for approximately 8 months. A lumbar puncture at this time; CSF studies showed an elevated WBC of 49/mm^3, glucose of 51 mg/dL, elevated protein of 101 mg/dL and a positive *Coccidioides* CSF complement fixation titer of 1:1 undiluted. At this time, she no longer was complaining of adverse reactions to the fluconazole, her current dosage was subpar for treating skeletal *Coccidioides*. The patient was subsequently switched to 300 mg delayed release tablets of posaconazole daily.

One month following her ID appointment, the patient was taken for MR imaging of the brain, with and without contrast. While patient's MR showed evidence of long-standing history of MS, findings also included several new signal abnormalities not on the comparison MR taken 3 years prior; these are shown below in Figs. 1–4. These identified lesions showed either resolution or significant improvement one month later during a follow-up MRI.

The patient had no interval events before her next Infectious Disease office visit eight months later, having tolerated 300 mg Posaconazole without any significant adverse drug reactions; however, she did endorse severe ongoing headaches. Repeat LP was performed shortly before her appointment, and CSF studies from the LP showed elevated WBC of 136/mm^3, glucose of 38 mg/dL, elevated protein of 135 mg/dL, a CSF complement fixation titer of 1:8 showing progression of the patient's CNS coccidioidomycosis. In addition, the CSF *Coccidioides* antigen level of 5.31 ng/mL. Posaconazole levels were obtained 2 months after initiation and were found to be 3.09 mcg/mL. Because of the worsening CSF findings, the patient's fingolimod dosage was reduced to 0.25 mg daily, and subsequently the headaches resolved. A follow-up lumbar puncture is planned. The bilateral osteomyelitis has remained in remission on this treatment.

Discussion

As stated above, fingolimod has been associated with CNS *Cryptococcus* and disseminated *Histoplasmosis* without CNS disease [12], but this is the first case of fingolimod-associated coccidiomycosis of the CNS. Disseminated *Histoplasma* has also been found to be associated with fingolimod treatment, albeit without CNS involvement [13]. Currently in the literature, there are no reported cases of CNS or MSK coccidioidomycosis associated with fingolimod or any other pharmacological therapies for MS. Increasing awareness of such conditions in *Coccidioides* endemic regions, despite their rarity, could potentially improve disease outcomes and lessen the lasting effects, as highlighted in the case presented above.

A unique aspect of the case presented is how the patient's history of multiple sclerosis both contributed to the development of her CNS infection and further complicated the process of diagnosis as evident in the patient's MRI. The signal abnormalities located within the anterolateral cerebellum, left occipital lobe and left frontal lobe potentially were leptomeningeal in nature, which would be consistent with fungal CNS infections. However, these lesions can potentially imitate demyelinating lesions as seen in MS. While MRI can be a highly sensitive diagnostic tool, the limited reported cases of CNS coccidioidomycosis infections and thus scarce radiologic references pose challenges in distinguishing between lesions caused by multiple sclerosis versus *Coccidioides* infection. Nevertheless, the resolution and improvement of the noted lesions one-month post-treatment with an antifungal agent further supports the etiology of these signal abnormalities as being the result of coccidioidomycosal meningitis. *Coccidioides* infection in the ankle can also mimic Charcot arthropathy.

Fingolimod primarily affects lymphocyte trafficking and immune cell distribution, with a specific impact on T-cells. Through its interaction with S1P receptors present on the surface of lymphocytes, fingolimod induces receptor internalization and degradation. This process results in reduced immune cell responsiveness and impaired migration from lymph nodes to peripheral tissues. By modulating the response of T-cells, fingolimod can mitigate the autoimmune-mediated reaction observed in conditions such as multiple sclerosis [14]. While the reduced T-cell response is crucial for the treatment and maintenance of multiple sclerosis, it is also necessary for successful immunity against opportunistic infections such as *Coccidioides*. Understanding the impact that disease-modifying therapies can have on a patient's immune system is paramount for the proper treatment of potential opportunistic

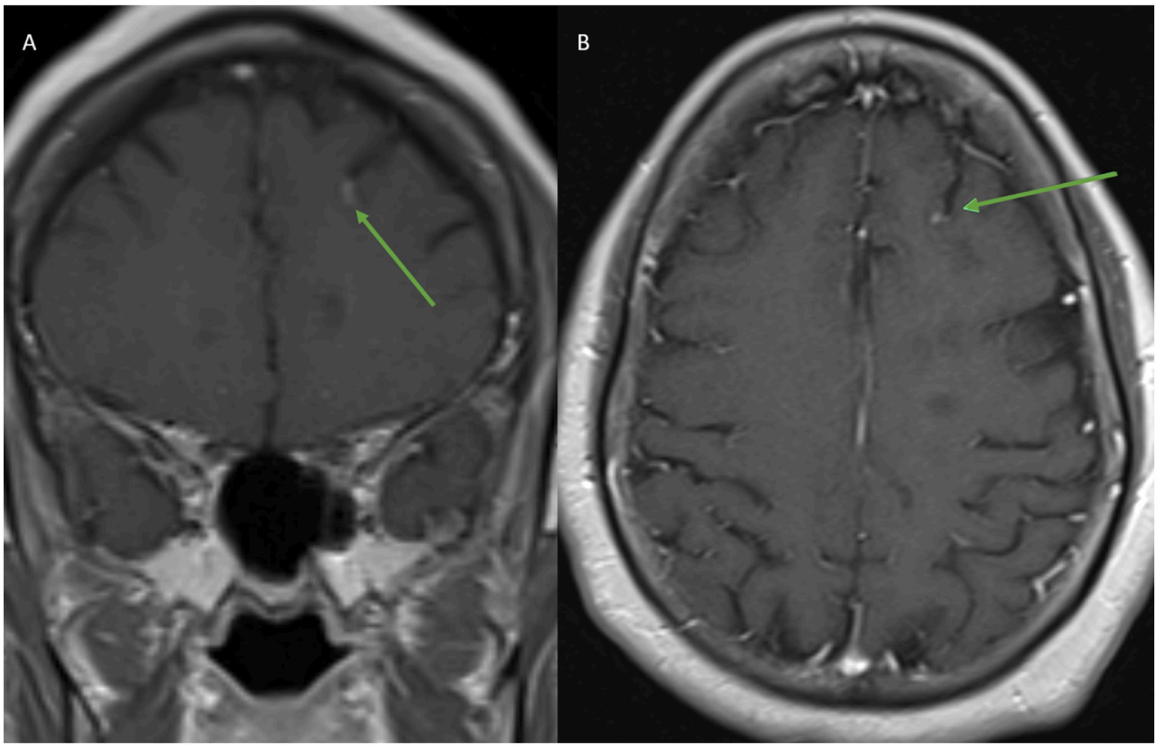

Fig. 1. Coronal (A) and axial (B) views showing leptomeningeal enhancement in the left superior frontal sulcus (T1 post-contrast).

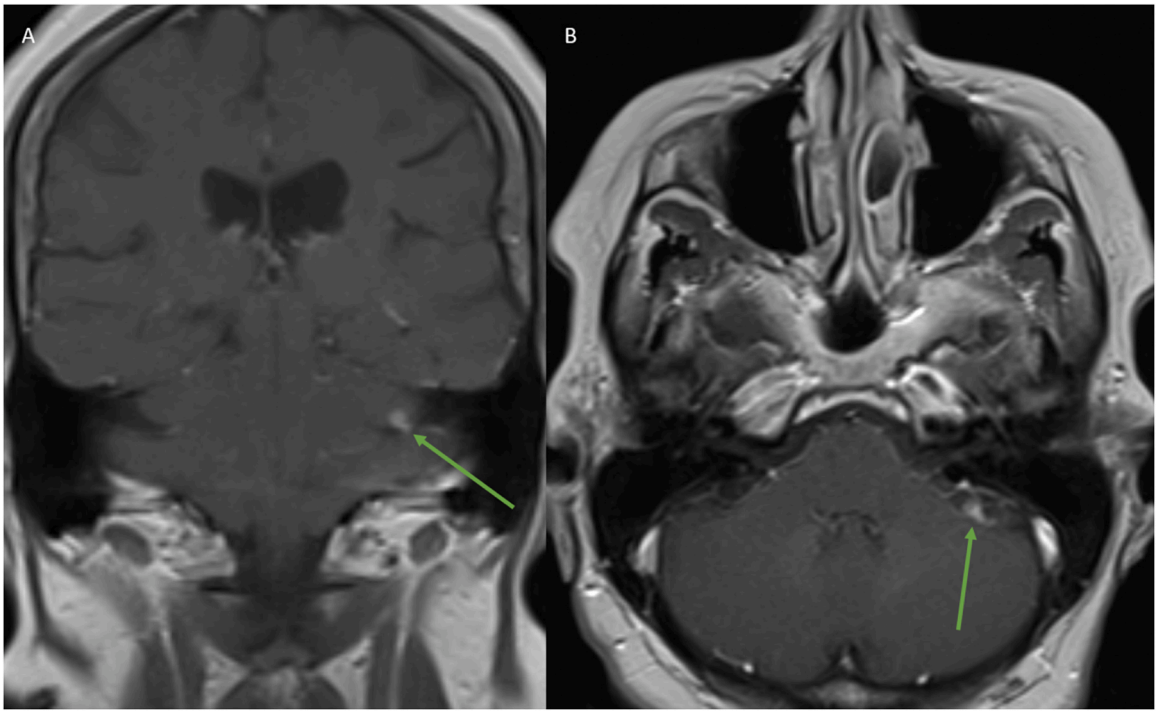

Fig. 2. Coronal (A) and axial (B) views showing enhancing nodule in the left cerebellopontine angle cistern (T1 post-contrast).

infections.

The precise reason behind the lower incidence of coccidioidomycosis-related CNS infections compared to other fungal infections, such as cryptococcosis, is not fully understood. However, the discrepancy in the number of reported cases could be attributed to multiple potential factors including the predominance of coccidiomycosis within endemic and the likelihood that certain cases may have gone undiagnosed due to the unique presentation seen with this pathogen. Additionally, as seen earlier in this patient's disease course, MSK involvement of *Coccidioides* in the foot can resemble Charcot arthropathy clinically and be difficult to distinguish from other inflammatory pathologies on nuclear bone scans. As such, clinical suspicion of *Coccidioides* should be high in endemic regions for patients presenting with such symptoms.

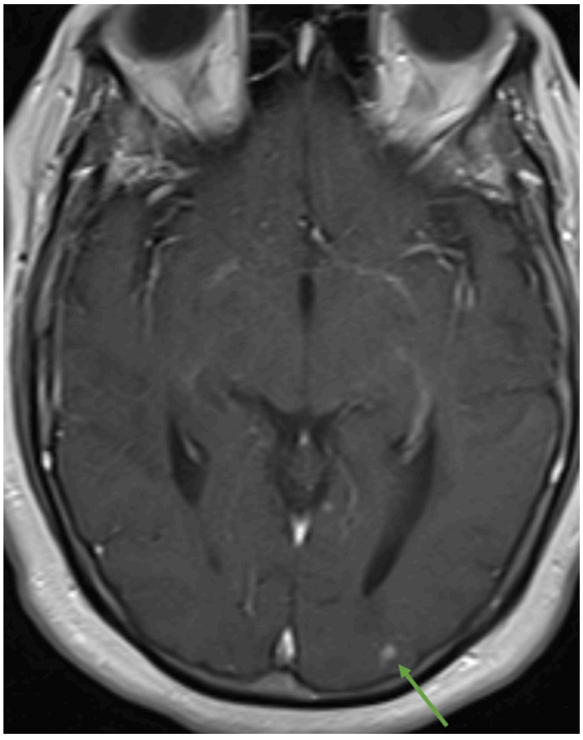

Fig. 3. Axial view showing leptomeningeal nodular enhancement in the left occipital lobe (T1 post-contrast).

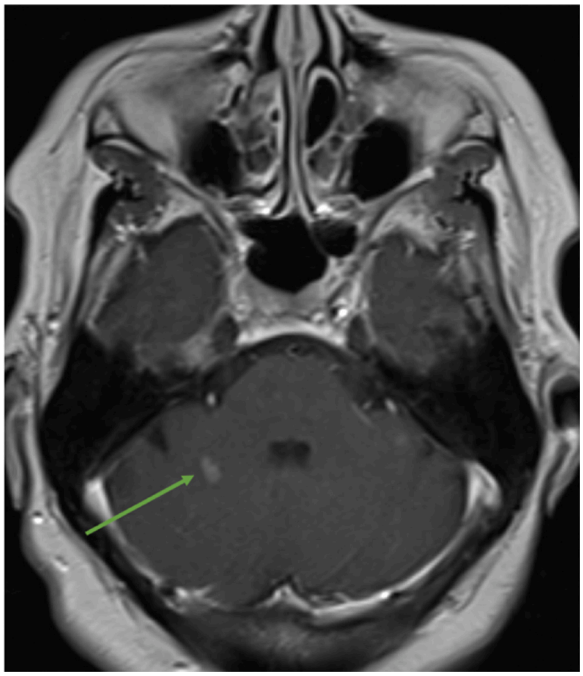

Fig. 4. Axial view showing ovoid enhancing nodule in right cerebellar folia (T1 post-contrast).

Conclusion

Coccidioides imposes a large clinical burden on the regions it is endemic to. Receipt of fingolimod leading to reduction in cell mediated immunity is a well-recognized risk factor, though, disseminated coccidiomycosis has not been previously described. Lesions of multiple sclerosis can mimic CNS *Coccidioides* lesions, making the diagnosis even more challenging. Prompt CSF sampling to rule out CNS coccidioidomycosis is of paramount importance in managing such cases.

Ethical approval

Obtained.

Consent

Obtained from patient.

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CRediT authorship contribution statement

John Galgiani: Writing – review & editing, Supervision. **Talha Riaz:** Writing – original draft, Supervision, Project administration. **Jacob Denton:** Writing – original draft. **Hasan Ozgur:** Validation, Supervision. **Pantea Sazegar:** Writing – original draft.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Conflict of Interest

The authors declare no conflicts of interest.

Authorship Statement

This statement is to verify that the authorship for “Musculoskeletal and CNS Coccidiomycosis in an Individual with Multiple Sclerosis on Fingolimod – A Case Report” has not changed since original submission. All revisions to the original manuscript were made by the corresponding author Jacob Denton. Please let me know if you have any additional questions or concerns.

References

[1] Roy R, Alotaibi AA, Freedman MS. Sphingosine 1-phosphate receptor modulators for multiple sclerosis. CNS Drugs 2021;35(4):385–402. https://doi.org/10.1007/s40263-021-00798-w.
[2] Mehling M, Kappos L, Derfuss T. Fingolimod for multiple sclerosis: mechanism of action, clinical outcomes, and future directions. Curr Neurol Neurosci Rep 2011;11(5):492–7. https://doi.org/10.1007/s11910-011-0216-9.
[3] Ito JI. T cell immunity and vaccines against invasive fungal diseases. Immunol Investig 2011;40(7-8):825–38. https://doi.org/10.3109/08820139.2011.595472.
[4] Blair JE, Ampel NM, Hoover SE. Coccidioidomycosis in selected immunosuppressed hosts. Med Mycol 2018;57(Suppl._1). https://doi.org/10.1093/mmy/myy019.
[5] Bays DJ, Thompson GR. Coccidioidomycosis. Infect Dis Clin N Am 2021;35(2):453–69. https://doi.org/10.1016/j.idc.2021.03.010.
[6] Fisher MC, Koenig GL, White TJ, Taylor JW. Molecular and phenotypic description of Coccidioides posadasii sp. nov., previously recognized as the non-California population of Coccidioides immitis. Mycologia 2002;94(1):73–84.
[7] Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. Emerg Infect Dis 2017;23(2). https://doi.org/10.3201/eid2302.160505.
[8] Guo X, Ruan Q, Jin J, et al. Disseminated coccidioidomycosis in immunocompetent patients in non-endemic areas: a case series and literature review. Eur J Clin Microbiol Infect Dis 2022;41(6):925–39. https://doi.org/10.1007/s10096-022-04447-y.
[9] Diaz JH. Travel-related risk factors for coccidioidomycosis. J Travel Med 2018;25(1). https://doi.org/10.1093/jtm/tay027.

[10] Scotto R, Reia A, Buonomo AR, et al. Risk of invasive fungal infections among patients treated with disease modifying treatments for multiple sclerosis: a comprehensive review. Expert Opin Drug Saf 2021;20(8):925–36. https://doi.org/10.1080/14740338.2021.1918673.
[11] Porwal MH, Salter A, Patel D, Obeidat AZ. Alopecia in multiple sclerosis patients treated with disease modifying therapies. J Cent Nerv Syst Dis 2022;14:11795735221109674. https://doi.org/10.1177/11795735221109674 [Published 2022 Jun 23].
[12] Scotto R, Reia A, Buonomo AR, et al. Risk of invasive fungal infections among patients treated with disease modifying treatments for multiple sclerosis: a comprehensive review. Expert Opin Drug Saf 2021;20(8):925–36. https://doi.org/10.1080/14740338.2021.1918673.
[13] Abrahamowicz AA, Chow EJ, Child DD, et al. Disseminated histoplasmosis in a patient with multiple sclerosis treated with fingolimod. Neurol Neuroimmunol Neuroinflamm 2021;8(3). https://doi.org/10.1212/nxi.0000000000000966.
[14] McGinley MP, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions. Lancet 2021;398(10306):1184–94. https://doi.org/10.1016/s0140-6736(21)00244-0.