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Case Report

Disseminated histoplasmosis mimicking post-vaccination side effects in an immunocompromised person with multiple sclerosis

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Abstract

We describe the case of a gentleman with relapsing-remitting multiple sclerosis and chronic lymphocytopenia secondary to treatment with fingolimod who presented with disseminated histoplasmosis after receiving the third dose of the Moderna coronavirus disease 2019 (mRNA-1273) vaccine. Following the vaccination the patient noted fatigue which worsened over time along with gradual weight loss. A few months later he noted low-grade fever and finally shortness of breath. A diagnosis of disseminated histoplasmosis was performed based on urine, blood, and imaging data. He responded well to prolonged antifungal treatment. Fingolimod was discontinued and replaced with glatiramer acetate. He has been clinically stable until the time of this report, 33 months following symptom onset.

Keywords: Case report, lymphocytopenia, multiple sclerosis, histoplasmosis, fingolimod, COVID-19, COVID-19 vaccine

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Introduction

Fingolimod is a highly efficacious treatment for people with relapsing-remitting multiple sclerosis (RRMS). It binds to the sphingosine-1-phosphate (S1P) receptor and acts by leading to lymphocyte sequestration inside the lymphoid organs.[1,2] This results in fewer circulating lymphocytes, potentially increasing the risk of infections.

Histoplasma capsulatum is an endemic dimorphic fungus that may cause an acute or chronic pulmonary disease, mediastinitis, or disseminated disease. The most important risk factor for the development of disseminated histoplasmosis is immunosuppression.[3]

We report the case of a gentleman with RRMS treated with fingolimod for about 6.5 years, who presented with disseminated histoplasmosis. Symptoms started immediately after the Moderna Coronavirus disease 2019 (COVID-19) (mRNA-1273) vaccination, in the setting of chronic lymphocytopenia.

Case report

A 58-year-old gentleman with no significant past medical history was diagnosed with MS at the age of 46 in 2012 when he presented to an outside hospital with subacute onset of left lower extremity weakness. The diagnosis of MS was supported by magnetic resonance imaging (MRI) and cerebrospinal fluid data. After treatment with steroids, he started subcutaneous injections of glatiramer acetate. In January 2014, due to injection fatigue, he switched treatment to *per os* (PO) dimethyl fumarate which he discontinued a year later due to reported increased fatigue as a side effect. In January 2015 he started fingolimod 0.5 mg PO daily.

He established care in our institution in November 2016 when he presented with clinical and radiological stability from disease onset. While under our care, yearly MRIs, semiannual neurological assessments, and annual ophthalmologic and dermatologic evaluations were performed. Hepatic function tests (HFTs) and complete blood cell (CBC) counts with cell differential

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were also routinely evaluated. While HFT and CBC remained consistently within the normal range, the absolute lymphocyte counts (ALC) were persistently low (Figure 1). For this reason, his fingolimod dose was repeatedly adjusted from 0.5 mg daily to 0.5 mg every other day depending on the ALC (Figure 1).

In 2021 (March, April, and September), the patient received three doses of the Moderna COVID-19 vaccine (mRNA-1273).[4] At the time of these vaccinations, he was taking 0.5 mg fingolimod every other day. A few days after the third dose, he noted the onset of a new fatigue, which was initially thought to be a side effect of the COVID-19 vaccine.[4] This fatigue persisted and worsened over time. In late November, he was noted to have a low-grade fever and to have lost 15 pounds of body weight. Thus, he called our clinic in early December to report his concerns. This prompted blood work for CBC with cell differentials and a complete metabolic panel. Elevated levels of calcium (13.9 mg/dL; normal limits: 8.4–10.5 mg/dL) and alkaline phosphatase (189 units/L; normal limits: 40–150 units/L) were detected. He was referred to the emergency room (ER) and subsequently hospitalized. Laboratory investigations showed low parathyroid hormone levels (8 pg/mL; normal limits: 16–77 pg/mL). A chest-abdomen-pelvis computerized tomography (CT) returned unremarkable. He received intravenous (IV) fluids and his calcium level normalized. He was discharged home with the diagnosis of hypercalcemia due to increased intake of supplements and dehydration. A plan was made to assess the etiology of his low-grade fever with an outpatient workup.

Over the following days, however, fatigue, muscle aches, and low-grade fever persisted. A urine search for the antigen for *histoplasma* was performed and found to be positive. The notification of this blood result coincided with the subacute development of a new shortness of breath, in early January 2022. He was advised to visit the ER where a chest CT showed diffuse ground glass opacity with patchy consolidation in the lung bases, suggesting fungal or viral pneumonia (Figure 2). Blood culture was positive for *histoplasma.* Viral hepatitis panel, serum cryptococcus and blastomyces antigen, bacterial blood cultures, and COVID-19 test were negative. The patient had hypercalcemia (12.0 mg/dL), elevated aspartate

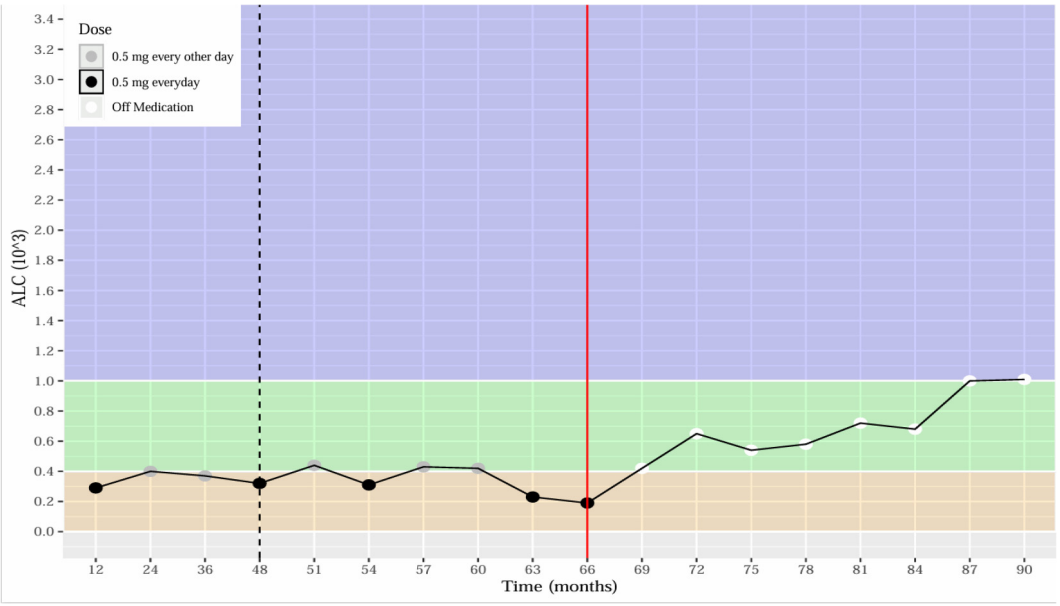

Figure 1. Changes in the absolute lymphocyte count (ALC) over time: The figure depicts the ALC change over time. The graph covers the period of this patient's care in our institution from January 2016 (12 months after the start of fingolimod) until his last blood draw in January 2024 (21 months after stopping fingolimod). We present yearly values for the first four years and quarterly values thereafter. The dotted line demarcates this change. The purple band indicates normal ALC values; the green band indicates values between 400 and 1000 cells/mm^3; the orange band indicates values between 200 and 399 cells/mm^3; the grey area indicates levels of ALC <200 cells/mm^3. The red line indicates the time of the diagnosis of histoplasmosis, at which point in time fingolimod was discontinued. The dose of fingolimod the patient was taking at each blood draw is displayed as colored dots. The grey dots represent every other day regimen, the black dots represent the everyday regimen, and the white dots represent the ALC value obtained when the patient was off the medication.

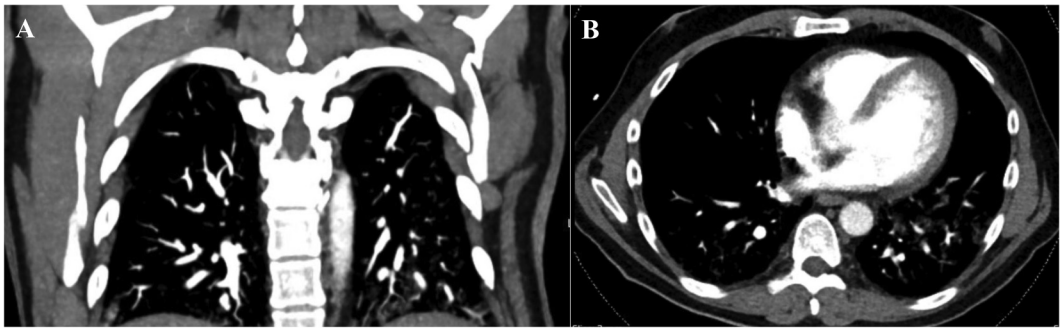

Figure 2. Chest computerized tomography appearance of the disease: Coronal (A) and axial (B) images of the chest computerized tomography obtained following presentation to the emergency room showed diffuse ground glass opacity with patchy consolidation in the lung bases. The findings are non-specific but concerning for viral or fungal pneumonia.

aminotransferase (56 units/L; normal limits: 5–40 units/L), alanine transaminase (59 units/L; normal limits: 0–55 units/L), and alkaline phosphatase (190 units/L) and reduced platelet counts (80×10^3/mcL; normal limits; 135–371/mcL). IV fluids along with amphotericin-B 3 mg/kg IV daily were started and maintained for 3 days. As his condition rapidly improved, he switched to PO itraconazole at the dose of 200 mg three times daily and was subsequently discharged. He continued PO itraconazole at the dose of 100 mg twice daily for 12 months. Fingolimod was discontinued and replaced with glatiramer acetate. Urine histoplasma was monitored serially until found to be negative in February and August 2023 (six months following antifungal treatment discontinuation).

At the time of this manuscript draft, 33 months from symptom onset, his MS has remained clinically and radiologically stable, as his repeated MRI showed in March 2024. The ALC values are up-trending, and nearly close to normal limits (Figure 1).

Discussion

Serious infections during treatment with fingolimod are rare, ranging between 1% and 2% with no reported cases of histoplasmosis in phase-III clinical trials.[5,6] A single case of disseminated histoplasmosis[7] and one of cutaneous histoplasmosis[8] have been described in the literature (Supplemental Table 1). Fingolimod acts as an agonist of S1P, and it results in rapid internalization and sustained loss of the receptor expression. The loss of S1P receptors results in impaired ability of lymphocyte migration to the tissues leading to an increased susceptibility to infections.[1,2]

Fever, fatigue, and weight loss are the main symptoms of histoplasmosis; laboratory findings include elevated alkaline phosphatase, high lactate dehydrogenase, and C-reactive protein as well as hypercalcemia.[3] Despite none of these laboratory findings being highly specific, their occurrence along with the symptoms in an immunocompromised patient should raise the suspicion for histoplasmosis.

The aspect that distinguishes our case from previous ones is the onset of symptoms immediately following the third COVID-19 vaccine, resembling possible side effects of it. His fatigue started nearly concomitantly with the third COVID-19 vaccine. It persisted for months with a worsening pattern alongside weight loss which the patient noted only later. While initially attributed to lingering vaccination side effects, in retrospect, we argue that in this immunocompromised person with MS, this worsening fatigue could have been due to the start of infection with histoplasmosis. A post-vaccination response likely partially overlapped with the onset of infectious symptoms and this temporal coincidence delayed the search for diagnostic alternatives for the patient's fatigue.

One may also argue that the immunological response to COVID-19 vaccination in this immunocompromised patient might have favored the occurrence of histoplasmosis. Although several alterations in the immune system have been shown to occur up to four weeks after the administration of the COVID-19 vaccine,[9] there is insufficient evidence in this case to draw any firm conclusions regarding a pathogenic link between the vaccine administration and the occurrence of disseminated histoplasmosis.

Conclusions

Our report informs clinicians of the rare possibility of serious infections in the setting of fingolimod-induced immunosuppression. It also suggests the importance of timely investigations of alternative diagnoses for

post-vaccination-like symptoms in people with MS and immunosuppression. Taking into consideration the high efficacy of fingolimod in reducing MS clinical and MRI activity[1] as well as the safety and benefit of COVID-19 (and other) vaccines among people with MS on disease-modifying agents,[10] our report should certainly not discourage clinicians from using fingolimod or vaccinations while caring for people with MS. Our case also increases our knowledge of possible long term-side effects of S1P-inhibitors now that this class of medication is entering its second decade in the market.

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Author Contributions

AAT and FB were involved in conceptualization, data curation, formal analysis, investigation, and methodology; AAT was involved in writing the original draft; FB was involved in project administration, resources, software, validation, visualization, supervision, and reviewing & editing the manuscript; SA was involved in reviewing & editing the manuscript.

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Ethical approval

Not applicable.

Data availability statement

Data associated with this manuscript is available from the author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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