Medical Mycology Case Reports 32 (2021) 43–46

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Case Report

Histoplasmosis in an off-trail Hiker receiving ustekinumab: Implications for Preventive and diagnostic strategies for patients receiving anti-IL-12/23 therapy

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ARTICLE INFO

Keywords:
Histoplasmosis
Ustekinumab
Immunosuppression

ABSTRACT

Ustekinumab, an IL-12/23 inhibitor, is an important agent in treatment of inflammatory bowel disease and psoriasis. Clinical trials have not demonstrated significantly increased infection risk with ustekinumab. We report a case of disseminated histoplasmosis in the setting of ustekinumab and methotrexate following a hike in the Catskill Mountains, a region not commonly associated with *Histoplasma encapsulatum*. To our knowledge, this is the first reported case of newly acquired histoplasmosis complicating treatment with ustekinumab.

1. Introduction

Since 1998, biological agents have become a critical part of the management of inflammatory bowel disease because of their remarkable efficacy [1,2]. As immunomodulators, however, these medications can potentiate serious immunologic reactions, infections, and malignancies. The TNF-α antagonists, for example, clearly increase the risk for serious infection and a recent meta-analysis suggests that this risk is higher when these agents are used in combination with more traditional agents, such as thiopurines or methotrexate [3].

By comparison, while the FDA label indicates that ustekinumab "may increase the risk of infections or reactivation of latent infections," several large randomized trials and long term follow-up studies of patients receiving ustekinumab have not demonstrated an increased risk of infection [4–9]. Unlike the TNF-α antagonists, there is no boxed warning for the development of histoplasmosis. We report herein the first case to our knowledge of newly acquired disseminated histoplasmosis in a young man with ulcerative colitis and atopic dermatitis who was receiving ustekinumab and methotrexate. The case carries valuable implications for diagnosis and treatment of histoplasmosis in patients who are receiving ustekinumab.

2. Case

2.1. Presentation

A 35-year-old man presented in June with fever, drenching night sweats, weight loss, headache, and dyspnea while receiving ustekinumab for ulcerative colitis and methotrexate for atopic dermatitis [Day 0 = symptom onset]. He had been first diagnosed with ulcerative colitis ten years earlier and had failed multiple lines of treatment including mesalamine, 6-mercaptopurine, balsalazide, vedolizumab, and infliximab. Ustekinumab had been started two years prior with complete remission of disease. All remaining agents were discontinued in the following four months, and he continued on single agent therapy with ustekinumab thereafter. One year prior, he had been diagnosed with atopic dermatitis for which he received cyclosporine, which was cross tapered to methotrexate in the month prior to presentation.

He initially presented to multiple outpatient practices and the emergency department, where he was provided supportive care and a course of doxycycline for a potential tick-borne illness. Eventually he presented to an infectious disease specialist who recommended inpatient evaluation [Day 9]. At that outside hospital admission, he was found to be febrile to 38.6 °C and dyspneic with a complete blood count notable for a white blood cell count of $8 \times 10^3/\mu L$, hemoglobin of 12 mg/dL, and a platelet count of $309 \times 10^3/\mu L$. Serum aminotransferases

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https://doi.org/10.1016/j.mmcr.2021.03.004
Received 19 November 2020; Received in revised form 28 February 2021; Accepted 1 March 2021
Available online 13 March 2021

and lactate dehydrogenase (LDH) were also elevated. A non-invasive infectious diseases evaluation was negative, including blood cultures, tickborne disease serologies, and CMV and EBV PCR. Computed tomography revealed right-sided pulmonary nodules and a pleural-based mass, hilar and subcarinal lymphadenopathy, and hepatosplenomegaly. Immunosuppression was held at admission and supportive care was provided. Upon transfer to our hospital [Day 13], he was afebrile and breathing comfortably, but with persistent night sweats and palpable hepatosplenomegaly. His complete blood count showed a white blood cell count of $7.9 \times 10^3/\mu L$ with an automated differential of 58% bands, 21% neutrophils, and 12% monocytes, a hemoglobin of 12.5 gm/dL, and a platelet count of $239 \times 10^3/\mu L$.

Significant in the history were multiple environmental exposures. He had no recent international travel history or sick contacts, but as an avid outdoorsman, he had recently hiked extensively in the Catskill Mountains and kayaked on the Delaware River. He had also adopted a cat from a shelter within the past month. His most recent potential exposure occurred one week prior to the development of symptoms during an off-trail hiking and rock-climbing excursion in Millbrook, Duchess County, New York. On this off-trail hike, he remembered disturbing dirt, clambering between rocks, and inhaling soil near rocky overhangs.

2.2. Differential diagnosis

In this young man on multiple immunosuppressants presenting with fever, lung nodules, lymphadenopathy, and hepatosplenomegaly, the suspicion was highest for infectious and malignant etiologies. The initial differential diagnosis was broad–including common bacterial and viral infections, as well as less common mycobacterial, parasitic, actinomycotic, and fungal etiologies, such as *Aspergillus* spp., *Cryptococcus* spp., and *Nocardia* spp. related to his environmental exposures. Based on his off-trail hiking expeditions, we also included blastomycosis and histoplasmosis within the differential, cognizant that these infections are relatively uncommon in this geographic location (Fig. 1). With the history of a new cat in the household, we also considered bartonellosis and toxoplasmosis, which may present with lymphadenopathy. At this point, we also were unable to rule out lymphoproliferative disease, as there may be a minimally increased risk of these diseases in the presence of ustekinumab and methotrexate [10,11].

2.3. Investigations

To better characterize the lymphadenopathy and lung nodules observed on CT scan (Fig. 2, top), MRI was performed and demonstrated the continued presence of a right lower lobe lung nodule, hepatosplenomegaly, hilar lymphadenopathy, and abdominal lymphadenopathy as well as two indeterminate lesions in the liver consistent with

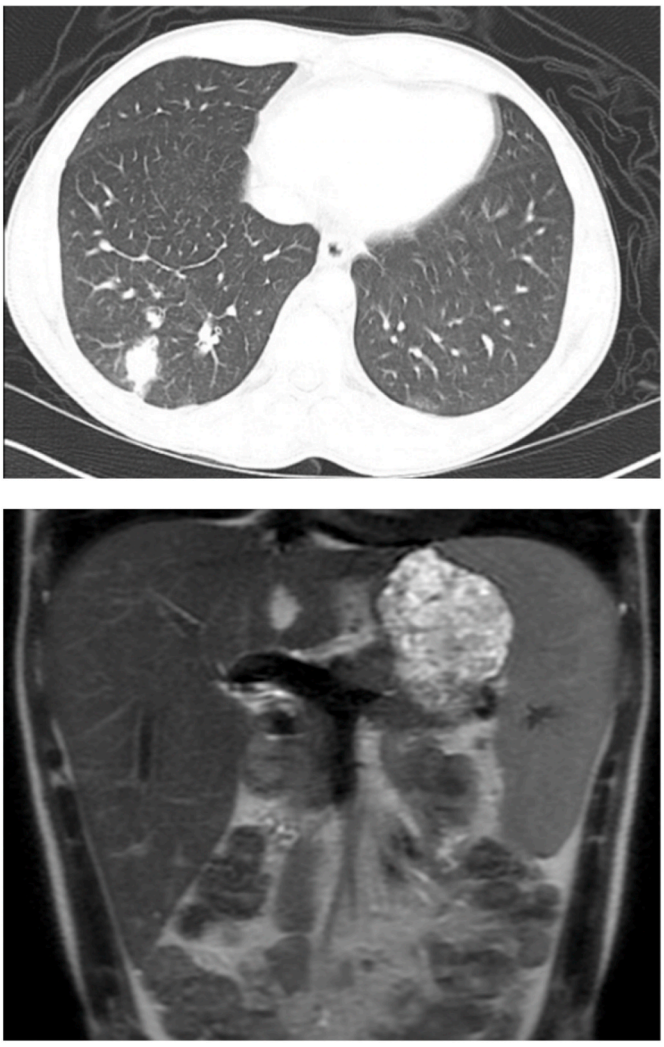

Fig. 2. Imaging of the chest and abdomen shows a clear lung nodule (CT, top panel) and presence of hepatosplenomegaly (MRI, bottom panel).

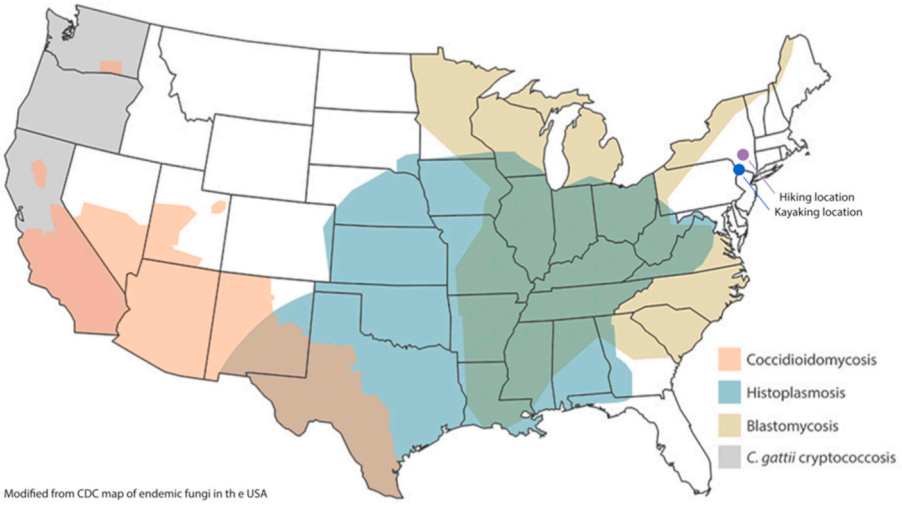

Fig. 1. Map of endemic fungi in the US & potential sites of exposure in this case.

hemangiomas (Fig. 2, bottom). These findings were concerning for an ongoing infectious or malignant process and were supported by an elevated LDH level of 556 U/L (normal 118–230). Procalcitonin was also mildly elevated at 0.32 ng/mL (normal <0.08). Serum (1 → 3)-β-D-glucan, *Histoplasma* urine antigen, *Cryptococcus* serum antigen, *Toxoplasma* serum PCR, *Bartonella henselae* IgG/IgM, QuantiFERON TB Gold, peripheral blood smears, HIV, *Legionella* urine antigen, *Streptococcus pneumoniae* urine antigen, and a respiratory viral panel were negative with exception of a positive *Mycoplasma pneumoniae* IgM antibody, which had been negative at the outside hospital. Blood cultures also continued to be negative. When imaging and bloodwork did not reveal the diagnosis, a fine needle aspiration (FNA) was performed of the pleural-based lung nodule [Day 15]. The FNA revealed non-necrotizing and necrotizing granulomas with narrow-based budding yeast, consistent with *Histoplasma capsulatum* (Fig. 3) [Day 17]. Four weeks later, fungal cultures from the tissue specimen incubated at 30° Celsius grew a mould confirmed as *Histoplasma capsulatum* by quantitative PCR of a unique region of the *H. capsulatum* gene encoding the M antigen (New York State Department of Health Wadsworth Laboratory) [10]. Altogether, the clinical scenario and culture results supported a diagnosis of disseminated histoplasmosis.

2.4. Treatment

After the tissue diagnosis, ustekinumab and methotrexate were discontinued, our patient's fever, dyspnea, and night sweats resolved, and the mildly elevated procalcitonin, LDH, and aminotransferase levels began to normalize. Given the clinical improvement, we debated the role of antifungal therapy. In anticipation of the patient needing to restart immunosuppressive therapy for his autoimmune conditions, we chose to initiate oral itraconazole [Day 17] at a loading dose of 200 mg three times daily for three days followed by 200 mg twice daily, which is first line therapy for pulmonary histoplasmosis and has been shown to be effective in mild disseminated histoplasmosis [12]. Unfortunately, one week into treatment, he developed a diffuse, pruritic, maculopapular drug rash necessitating a change to second line therapy with posaconazole 300 mg daily.

2.5. Outcome & follow-up

The patient tolerated posaconazole without further side effects and remained asymptomatic at three weeks post-discharge follow-up. Interval chest imaging demonstrated mild decrease in the size of the pulmonary nodule and a marked diminishment of previously noted mediastinal lymphadenopathy. Currently, the patient has completed 9 months of oral posaconazole and has restarted his treatment with methotrexate and ustekinumab.

3. Discussion

This is the first reported case to our knowledge of newly acquired histoplasmosis complicating treatment with ustekinumab. A few notable features of this case include the demonstration that [1]: histoplasmosis should be considered as a diagnostic possibility in areas outside of those in which it is widely endemic [2], immunosuppressive regimens including IL-12/23 blockade may contribute to histoplasmosis infection [3], direct tissue sampling can be key to diagnosis of *H capsulatum*.

Histoplasmosis is an endemic fungal infection in the United States with most infections occurring in the Ohio and Mississippi River valleys, where it is considered widely endemic. In a recent analysis, only 1.1% of histoplasmosis cases reported in the US occurred in the New England area [11]. Fewer than 50 cases were reported in New York State between 1938 and 2013, and New York was ranked among the states with the fewest outbreaks of histoplasmosis [12]; however, we hypothesize that our patient was exposed while hiking and rock climbing in the Catskill Mountains, where he inhaled organic particulate matter contaminated

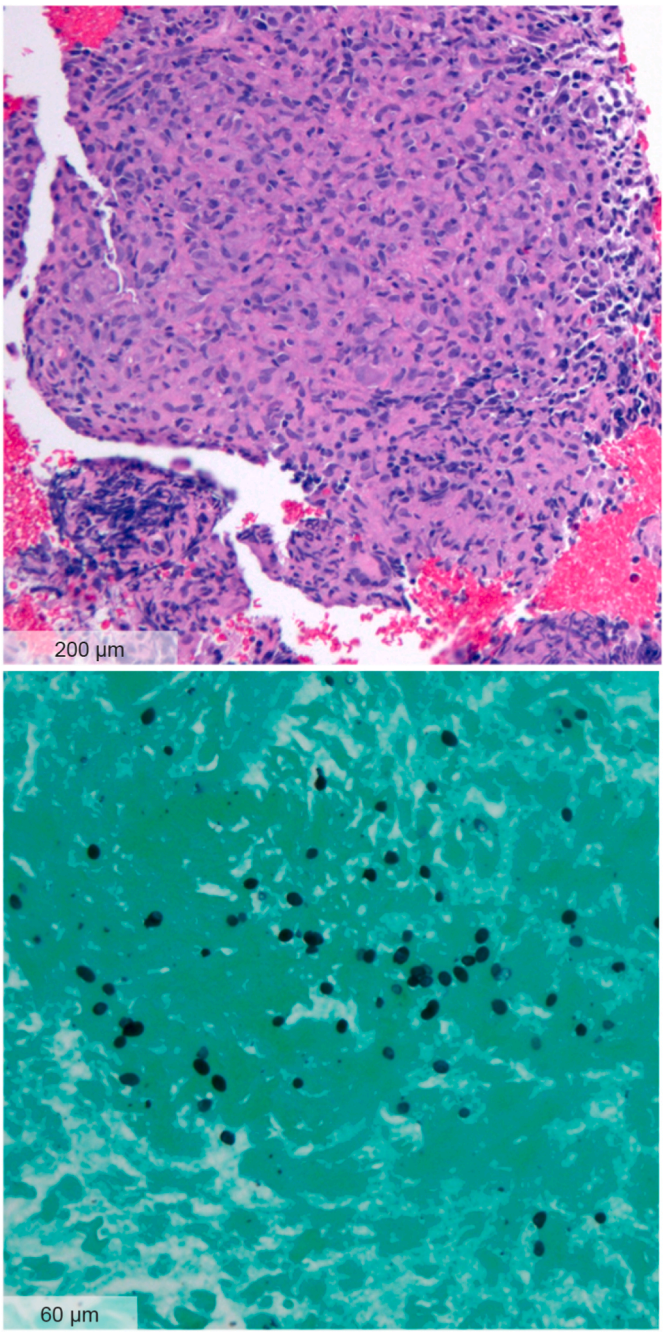

Fig. 3. Histology of fine needle aspirate of lung nodule showing non-necrotizing granulomas (hematoxylin & eosin stain, top panel) and small budding yeasts morphologically compatible with *H. capsulatum* (Gomori-methenamine silver stain; bottom panel).

with *H. capsulutum* microconidia. While reactivation of latent infection is possible, our patient did not have calcifications in the lung, liver, or spleen that would suggest previous infection, and prior experience with TNF-α inhibitors and autopsy studies of histoplasmosis suggest that infection from a new exposure is a more common mechanism of disease.

While the majority of immunocompetent individuals exposed to *H. capsulatum* are asymptomatic, some develop self-limited acute pulmonary histoplasmosis. Persons who are immunosuppressed, on the other hand, are at risk of disseminated and progressive disease [13]. In this case, it is notable that our patient was hiking with two other individuals, who were presumably exposed to the same aerosolized *H. capsulutum* microconidia found in organic particulate matter. Yet,

neither of them developed symptoms of either acute pulmonary histoplasmosis or disseminated histoplasmosis. Given the similar environmental exposures, we hypothesize that our patient's immunosuppressive therapy with ustekinumab and methotrexate increased his risk for development of histoplasmosis. Further supporting this hypothesis, our patient had improvement in his symptoms after immunosuppression was held, even before initiation of antifungal therapy. Ustekinumab is of particular interest in this combination because of its mechanism of action and because methotrexate alone has been demonstrated to have minimal increased infection risk [14].

As a critical mediator of the initial Th1 response, IL-12 has been shown to mediate a protective innate host response to histoplasmosis [15]. Ustekinumab, by inhibiting IL-12/23, disrupts the development of an effective Th1 response to *H. capsulatum* [16]. In comparison to anti-TNF-α therapy, however, which is a known important risk factor for histoplasmosis, ustekinumab appears to have a less profound effect of interfering with the host response to *H. capsulatum*. This may be because TNF-α is important for both the initial innate response to the fungus and the later interaction of the adaptive-enhanced innate response, while IL-12 is more relevant to the later response. This would be compatible with only one other ustekinumab-related case of histoplasmosis having been reported to date, and that case was in a patient who had evidence of infection prior to therapy and had also recently received infliximab (TNF-α blockade), azathioprine, and prednisone [17]. Given the theoretical risk of fungal infections like histoplasmosis with IL-12 blockade and the paucity of data in the clinical setting, further investigation would be beneficial in delineating the risk of immunosuppressive regimens containing ustekinumab.

Diagnostically, *H. capsulatum* can be difficult to identify. Urine antigenic testing, while simple and non-invasive, is positive in only 83% of acute and 92% of disseminated histoplasmosis; serum antigen testing has similar or slightly lower sensitivity but can provide additive benefit [18]. In this case, we only tested for the urine antigen, which was in fact negative. Serum (1 → 3)-β-D-glucan, which is positive in 87% of disseminated histoplasmosis, was also negative. In this setting, early tissue sampling was therefore critical to ascertaining the diagnosis.

Our experience with this case suggests that there should be appropriate suspicion for histoplasmosis even in areas where *H. capsulatum* is not considered widely endemic. This is particularly important in patients with potential environmental exposures and in those with predisposing immunosuppression. Proper counseling to avoid aerosolized soil can help to prevent infection, and timely identification facilitates appropriate immunosuppression management and support with antifungals.

Declaration of competing interest

There are none.

Acknowledgements

We thank our patient for the opportunity to be involved in his care and all members of the clinical care team. YH was supported by grants from the NIGMS and NCI of the NIH under award numbers T32GM007739 and F30CA203238.

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