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Disseminated Histoplasmosis in Central California Seen in an Immunocompromised Patient

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Abstract

Histoplasma capsulatum is a dimorphic fungus found in certain parts of North, Central, and South America. Transmission is primarily through airborne inoculation from inhaled fungal microconidia. Histoplasmosis is typically a self-limited mycosis; however, in patients with immunodeficiency, disseminated disease can occur and may lead to high disease burden. This report studies a case of disseminated histoplasmosis in a patient newly diagnosed with human immunodeficiency virus. His presentation on admission was consistent with infectious pulmonary granulomatous disease, and further imaging and laboratory results showed evidence of multi-organ involvement. It is likely his presentation in Central California was a reactivation infection after inoculation in Central America many years ago.

Keywords

Histoplasma capsulatum, histoplasmosis, disseminated, HIV, immunocompromised, granulomatous hepatitis, bone marrow involvement, California, coccidioidomycosis

Introduction

Histoplasma capsulatum is a dimorphic fungus found in the central and eastern United States, most commonly in the Ohio and Mississippi river valleys. It is also seen in other regions of the Americas, such as Central and South America.[1] Transmission is primarily through airborne inoculation as patients usually contract the fungus from inhaled microconidia.[1] Between 1938 and 2013, there were 105 reported outbreaks of histoplasmosis in various settings in the United States and Puerto Rico.[2] Histoplasmosis is very much low burden, and for a vast majority of cases in immunocompetent patients, this mycosis is self-limiting. However, in patients with immunodeficiency, disseminated disease is common and can lead to an appreciable increase in morbidity and mortality.[1] Reactivation of latent organisms is the most common etiology of infection in patients with immunodeficiency, and endemic regions see the highest rates of diagnosis compared with the general population.[3] However, cases in nonendemic regions occur rarely and are worth studying as they can contribute to larger-scale disease epidemiology. This report studies a case of disseminated histoplasmosis in a male patient newly diagnosed with human immunodeficiency virus (HIV); his presentation was notable as he was diagnosed in Central California, a nonendemic area that more commonly sees coccidioidomycosis.

Case Description

A 53-year-old man with no past medical history presented to the emergency department with cough, fever, fatigue, and profuse sweating for 1 month. The patient's fatigue had eventually progressed to weakness, and he soon required a wheelchair for mobility. Otherwise, he denied any headaches, shortness of breath, focal weakness, dizziness, hyperreflexia, ataxia, abdominal pain, nausea, vomiting, or diarrhea. Social history revealed the patient immigrated from Mexico in 1993 to the San Joaquin Valley in Central California and never returned. He had worked as a farmer in Kern County for the past 20 years; he denied working around farm animals nor living around bats or birds. He also denied any recent travel history or sexual activity with men. He denied intravenous drug use, but stated he had been accidentally stuck by needles in the past. He also denied smoking or alcohol use.

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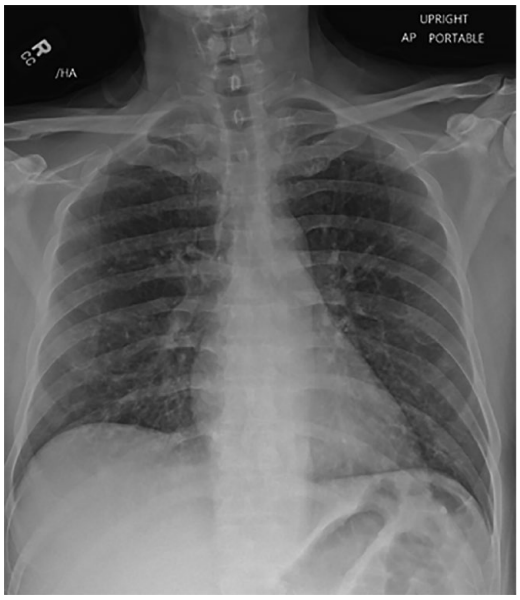

Figure 1. Chest x-ray showing diffuse pulmonary nodules.

In the emergency department, the patient was febrile at 38.5 °C, blood pressure was 100/63 mm Hg, heart rate 104 beats/minute, respiratory rate 18 breaths/minute, and SpO_2 98%. He was bedbound, severely diaphoretic, and seen hiccupping. Head and neck examination was not significant for lymphadenopathy or jugular venous distension. Respiratory examination was significant for diminished vesicular sounds anteriorly and bilaterally but no adventitious sounds. Cardiovascular examination revealed discernible heart sounds with regular rate and rhythm and no murmurs, gallops, or rubs. Blood counts did not show leukocytosis nor bandemia, though he had notable normocytic anemia (hemoglobin 10.4 g/dL, hematocrit 30.7%, and mean cell volume 87.5 fL) and thrombocytopenia (platelets 112×10^9/L). Hypoalbuminemia (albumin 2.5 g/dL) and elevated liver function tests were also noted (aspartate transaminase [AST] 349 U/L, alanine transaminase [ALT] 262 U/L, and alkaline phosphatase [ALP] 285 U/L). HIV and syphilis screens were reactive. His chest x-ray showed diffuse pulmonary nodules (Figure 1). Computed tomographic (CT) scans of his chest, abdomen, and pelvis showed numerous bilateral ill-defined nodules in the lungs with a posterior peripheral predominance (Figure 2). The CT scans were also showing diffuse paraesophageal, peritoneal, and retroperitoneal adenopathy (Figure 3). This patient was originally admitted for concern of disseminated coccidioidomycosis and was started on 800-mg fluconazole empirically. Diagnostic bronchoscopy was done on the day of admission to expedite diagnosis given his immunosuppression from HIV. Airway examination was unremarkable, but the bronchoalveolar lavage (BAL) Gram stain results were significant for intracellular

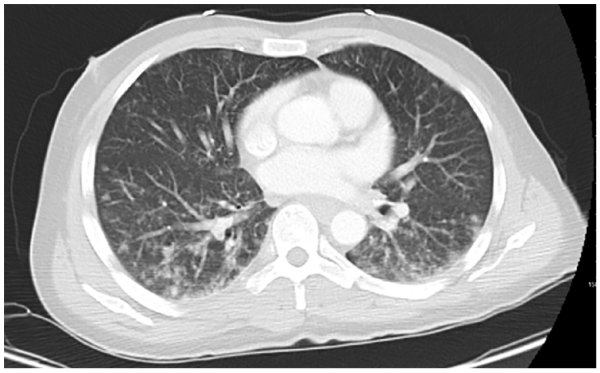

Figure 2. Computed tomography of the chest showing numerous bilateral ill-defined nodules in the lungs with a posterior peripheral predominance.

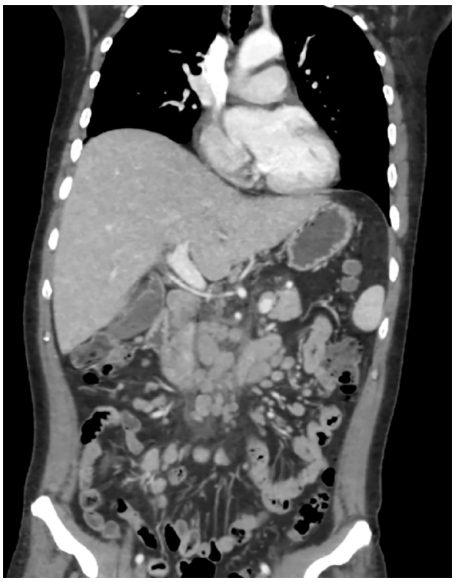

Figure 3. Computed tomography of the abdomen showing diffuse paraesophageal, peritoneal, and retroperitoneal adenopathy.

organisms resembling *H. capsulatum* (Figures 4-5) and potassium hydroxide (KOH) prep test was positive for fungal elements. Later, lactate dehydrogenase levels resulted 1090 U/L and ferritin >40 000 ng/mL. Coccidioidomycosis serology and QuantiFERON Gold testing also came back negative.

Fluconazole was discontinued and induction therapy was begun with Amphotericin B 3 mg/kg intravenous daily for 2 weeks. After that, therapy with itraconazole 200 mg three times a day was begun for 3 days as a loading dose, followed by 200 mg twice a day maintenance therapy for at least 1 year along with immunity reconstitution with HIV therapy. Throughout his 7-day hospital stay, the patient's symptoms

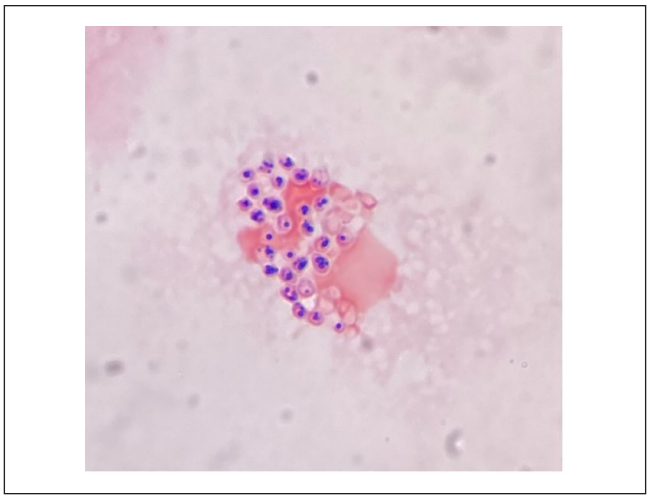

Figure 4. Bronchoalveolar lavage Gram stain showing intracellular elements resembling *Histoplasma capsulatum*.

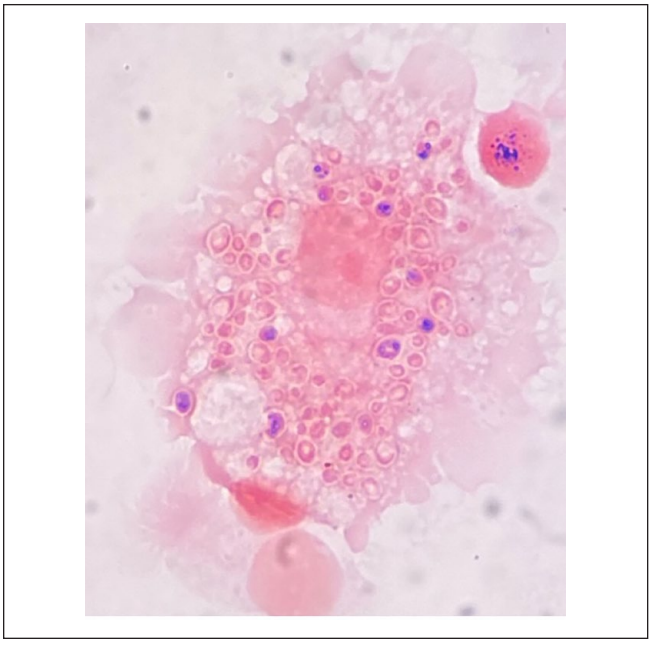

Figure 5. Bronchoalveolar lavage Gram stain showing intracellular elements resembling *Histoplasma capsulatum*.

largely subsided while on antifungal induction therapy, and tolerated Amphotericin B well without concerning adverse effects. His fever subsided within 2 days. He had begun ambulating to and from the bathroom without difficulty. He denied any sweating symptoms after 3 days in the hospital. Of note, his pancytopenia had remained by discharge (hemoglobin 9.8 g/dL, hematocrit 29.7%, and platelets 64×10^9/L). The patient's liver function tests also remained elevated at discharge (AST 99 U/L, ALT 166 U/L, ALP 688 U/L). He was discharged on day 8 of Amphotericin treatment with a plan for daily outpatient administration to complete the 14-day course. His CD4 count later resulted <20 cells/μL and viral load 465 000 copies/mL; since discharge, he has started antiretroviral therapy for AIDS with bictegravir-emtricitabine-tenofovir alafenamide (50 mg/200 mg/25 mg 1 tablet by mouth once daily) and sulfamethoxazole/trimethoprim (800 mg/160 mg 1 tablet by mouth once daily). He had also received treatment for syphilis with penicillin G benzathine (2.4 million units intramuscular injection). His latest follow-up 4 months after discharge is showing improved CD4 count to 111 cells/μL and viral load 58 copies/mL; he continues to be compliant with medications and has no report of returning symptoms.

Discussion

This patient's presentation was consistent with an infectious pulmonary granulomatous disease, and his HIV screen was positive on admission. His immunocompromised state is an ideal background for usually benign organisms such as *H. capsulatum.* Moreover, disseminated histoplasmosis was apparent in this patient due to evidence of multi-organ involvement—with his pancytopenia (suggesting bone marrow infiltration), transaminitis (suggesting granulomatous hepatitis), and generalized lymphadenopathy in the abdomen.[4]

Histoplasma capsulatum is a dimorphic fungus well documented in academic literature; it is one of the most endemic mycoses in the United States.[2] Disease incidence typically occurs in the eastern United States, and many studies have documented organism exposure rates between 60% and 90% in the general population.[5] Prevalence estimations in Latin America are also very common, showing population exposure rates of more than one-third in some studies.[6] However, patients with compromised immunity are more likely to witness symptomatic pulmonary or disseminated disease, which requires prompt antifungal induction therapy. In such cases, Amphotericin B is usually recommended as initial treatment; it acts by directly binding to ergosterol on fungal cell membranes and formation of pores that cause cell leaking—and ultimately cell death.[7] Long-term management after initial Amphotericin B treatment includes itraconazole.[8] Itraconazole is a broad-spectrum antifungal agent that inhibits its fungal cell membrane ergosterol synthesis by inhibiting lanosterol 14-α-demethylase, the enzyme responsible for converting lanosterol to ergosterol.[9]

This case report highlights the rare incidence of progressive disseminated histoplasmosis in an area that is not typically endemic to this pathogen. On admission, his presentation showed evidence of a fungal disease process but was akin to native fungal infections more commonly found in this region such as coccidioidomycosis, especially from his occupation as a migrant farm worker in the dry, arid environments of Central California.[10] However, his negative results on coccidioidomycosis serological testing and BAL Gram stain results provided clear evidence of a completely different

fungal pathogen. It is more likely his case was due to latent pathogen reactivation after exposure many years ago in his native country.

Histoplasmosis is a well-documented opportunistic infection in the setting of HIV, sometimes even representing the first disease manifestation of the virus.[11] In endemic regions, symptomatic disease is typically from exogenous exposure, and HIV-related histoplasmosis in these regions is not uncommon. One study conducted in patients from Kansas City, an endemic region, showed the incidence rate in HIV-related histoplasmosis to be 4.7%—with the vast majority of these individuals presenting with multi-organ involvement.[12] However, presentation in nonendemic regions may occur as well, though rarely. In these cases, it is likely the fungus is a reactivation of latent, endogenous pathogens.[11] In our case, the patient immigrated from Mexico in 1993 and lived in central California for almost 20 years without returning. He probably contracted the fungus in his native country, which had stayed dormant in his system for many years until he was infected with HIV.

Conclusion

This case of progressive disseminated histoplasmosis is unique in the geographic setting of Central California. Prevalence of this fungus in the western United States is rare, but has resulted in symptomatic disease in an individual with HIV. His presentation likely represents reactivation of endogenous disease foci in the setting of immunodeficiency. This is especially interesting as clinicians in central California largely attribute symptoms and findings of fungal infection to coccidioidomycosis.

Declaration of Conflicting Interests

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Disclaimer

Views expressed in this article are our own and not the official position of the institutions listed.

Prior Presentation of Abstract Statement

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Ethical Approval

Ethical approval to report this case was obtained from the Kern Medical Institutional Review Board (IRB # 22088).

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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