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Disseminated histoplasmosis with oral involvement and co-infection with Pneumocystis in a patient with HIV: A case report

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ABSTRACT

Oral manifestations of disseminated histoplasmosis are rare but can present in immunocompromised individuals. We report a case of disseminated Histoplasmosis presenting with presumed oral involvement and *Pneumocystis jirovecii* pneumonia in a seropositive HIV individual. A 32-year-old male with HIV presented to the emergency department for a two-week history of abdominal pain and a tongue ulcer in the setting of significant weight loss, blood-tinged sputum, and non-adherence with antiretroviral therapy for three years. Physical exam revealed a verrucous ulcer on the lateral aspect of the tongue. CT scan of the chest revealed diffuse bilateral pulmonary nodules and ground glass opacities. At presentation, his CD4 + count was 12 cells/mm^3. During his hospitalization, he developed acute hypoxic respiratory failure requiring non-invasive ventilation. His urine histoplasma antigen was positive at greater than 25 ng/mL and liposomal amphotericin was started. Shortly thereafter, *Pneumocystis jirovecii* PCR on bronchoalveolar lavage returned positive prompting additional therapy with trimethoprim-sulfamethoxazole. At discharge, the patient had no respiratory symptoms and near-resolution of his tongue ulcer.

Introduction

Despite the introduction of antiretrovirals (ART), opportunistic infections (OIs) continue to be reported in people living with HIV (PLWH) [1]. Histoplasmosis is an opportunistic infection with protean clinical manifestations caused by *Histoplasma capsulatum*, a dimorphic fungus that is distributed worldwide but endemic to North America and Central America [2]. There are increasing reports of infections in patients with no known exposures to areas of endemicity, suggesting an evolving epidemiology of *Histoplasma* beyond previously described geographic distribution [3]. It is the most common endemic mycosis in the United States and the most common opportunistic infection among HIV patients in Latin America [4]. This is a case presentation highlights the importance of gastrointestinal manifestations of histoplasmosis as well as the diagnostic challenges occurring in the setting of multiple, simultaneous OIs in a single individual.

Case presentation

A 32-year-old male presented to the emergency department in June 2023 with a two-week history of abdominal pain and tender tongue lesion. His abdominal pain was associated with night sweats, vomiting, non-bloody diarrhea, and a 40-pound weight loss in the past year. He additionally reported a minimally productive cough with blood-tinged sputum and a painful shallow ulcer on the lateral aspect of his tongue for the last two weeks.

He was originally from Oaxaca, Mexico and immigrated to the United States in 2013. He reported a diagnosis of HIV in 2018 treated with ART until 2020, when he returned to Mexico and lost access to ART. He returned to New Jersey in 2021 but did not resume ART. His last CD4 + count and viral load were unknown.

He reported no sick contacts, no recent travel since 2021, and no contact with animals. He had stopped using tobacco one year prior and denied a history of alcohol or intravenous drug use. He was heterosexual and denied a history of sexually transmitted infections. He was never incarcerated and reported stable living conditions. At the time of

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admission, he worked in a pizzeria in New Jersey. Aside from the HIV diagnosis, he had no other health issues or prior hospitalizations.

On physical examination, he was ill-appearing, diaphoretic and lethargic. He was febrile to 103.2 F, tachycardic to 144, with an oxygen saturation of 88% on room air. Additional vital signs on arrival included blood pressure of 112/47 mmHg, and respiratory rate of 20/min. He had mild oral thrush and a solitary tender shallow ulcer with raised irregular borders on the lateral aspect of his tongue (Fig. 1). He had no lymphadenopathy, hepatosplenomegaly, or rash. On pulmonary exam, he had scattered rales bilaterally with decreased breath sounds in all lung fields.

Investigations

Initial laboratory tests showed hemoglobin of 16 g/dL (13.2–16.6), white cell count of 8.2×10^3/uL (4.0 - 10.0), an absolute neutrophil count of 7.96×10^3/uL (1.8 - 7.4), an absolute lymphocyte count of 0.08×10^3/uL (0.95 - 3.07) and a platelet count of 44×10^3/uL (140 – 440). His hepatic function panel revealed an elevated aspartate aminotransferase of 134 U/L (10 – 55), alanine aminotransferase of 82 U/L (10 – 50), and alkaline phosphatase of 122 U/L (45 – 115).

Lactate dehydrogenase was elevated at 827 U/L (125 – 220). Arterial blood gas performed while the patient was receiving 4 L/min of oxygen showed a pH of 7.47, pCO_2 of 31.0 mmHg, pO_2 of 153.0 mmHg, and HCO_3 of 22.6 mmol/L. His CD4 + count was low at 12 cells/mm^3 (424 – 1509) and viral load was elevated at 548,000 cp/mL. A chest X-ray showed a diffuse, micronodular, miliary pattern and a thoracic CT revealed diffuse small bilateral pulmonary nodules with central ground-glass opacities (Figs. 2a and 2b).

Differential diagnosis

In the setting of advanced HIV and a miliary pattern of infiltrates on his thoracic CT, the two leading diagnoses of concern were *Pneumocystis jirovecii* pneumonia (PJP) and pulmonary tuberculosis. Other infectious causes included on the differential were viral pneumonia, Legionnaire's disease, non-tuberculosis mycobacterial infection, and infection due to endemic mycoses such as histoplasma or coccidioidomycosis. His oral ulcer was thought to be due to herpes simplex virus, syphilis, oral candidiasis, or malignancy.

Hospital course

He was initially treated with ceftriaxone and azithromycin to treat community-acquired pneumonia, and oral fluconazole for presumed oral candidiasis. On day 1 of hospitalization, due to high clinical suspicion for PJP, intravenous trimethoprim-sulfamethoxazole (TMP-SMX) (15 mg/kg/day) and prednisone were added. On day 2 of hospitalization, due to worsening dyspnea and hypoxia (90% on 6 L of oxygen), he was upgraded to the intensive care unit and placed on non-invasive ventilation for respiratory support. Induced sputum for *Pneumocystis jirovecii* polymerase chain reaction (PJP PCR) and acid-fast bacillus (AFB) stain and bacterial culture were all negative. Due to the severity of hypoxia and initially negative infectious work-up, on day 3 of hospitalization bronchoscopy was performed with bronchoalveolar lavage (BAL), and a BAL specimen was sent for PJP PCR. BAL fluid was negative for AFB stain, however, urine histoplasma antigen obtained on day 1 of hospitalization returned positive at > 25 ng/mL on day 5 of hospitalization.

Additional infectious work-up was negative including legionella urine antigen, legionella sputum culture, serum cryptococcal antigen, and serum cytomegalovirus detection by PCR. Serum Beta-D-Glucan was positive at 208 pg/mL (normal < 60 pg/mL) (Table 1).

Given his positive urine histoplasma antigen in the context of his tongue lesion, pulmonary nodules on imaging, transaminitis, and gastrointestinal symptoms, he was diagnosed with disseminated histoplasmosis. He was started on liposomal amphotericin B (3 mg/kg/day) on day 5 of hospitalization. TMP-SMX and prednisone were discontinued, given the alternative diagnosis of histoplasmosis as well as the negative PJP PCR on induced sputum. However, on day 8 of hospitalization, PJP PCR on BAL from bronchoscopy performed on day 3 of admission resulted as positive. Given the positive PJP PCR on BAL and the continuous need for supplemental oxygen via high-flow nasal

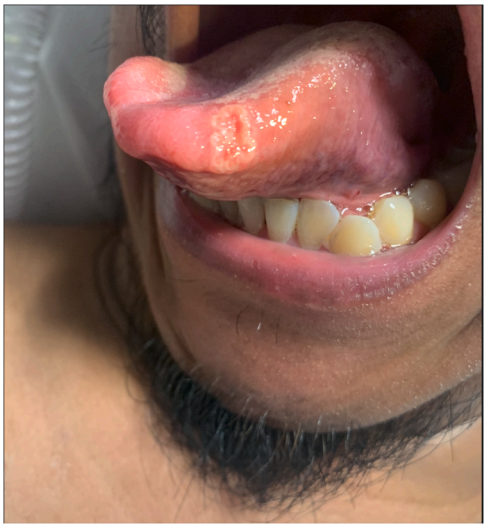

Fig. 1. Tender shallow tongue ulcer with raised irregular edges on lateral border of tongue.

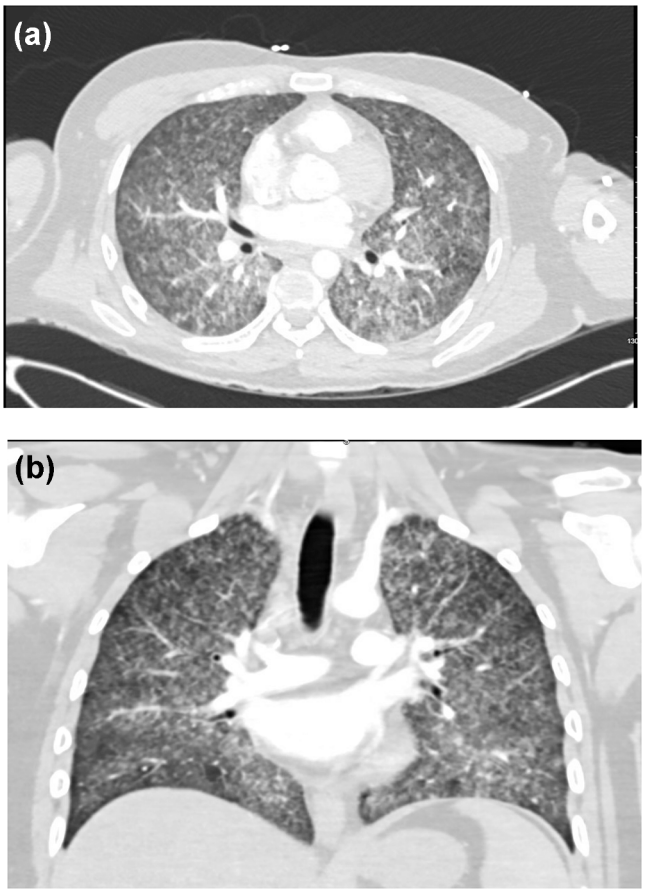

Fig. 2. a and b: CTA chest cross-sectional view (a) and coronal view (b) with diffuse extensive symmetrical tiny nodules with central subtle ground glass opacities.

Table 1
Summary of tests.

Day of hospitalization test was obtained	Test	Results
Day 0	T-cell (CD4)	12 cells/mm^3 (424 −1509)
	HIV−1 Viral Load	548,000 copies/mL
	Legionella antigen, urine	Negative
	QuantiFERON-TB Gold	Negative
	1,3-Beta-D-Glucan	208 pg/mL (<60)
	LDH	827 U/mL (125 −220)
Day 1	Aspergillus galactomannan, serum	Not detected
	Histoplasma antigen, urine	Detected at > 25 ng/mL
	Streptococcus pneumoniae antigen, urine	Negative
Day 2	PJP PCR, induced sputum	Negative
	AFB culture, induced sputum	Negative
	Bacterial culture, induced sputum	Normal respiratory flora
Day 3	PJP PCR, BAL	Positive
	Bacterial culture, BAL	Normal respiratory flora
	Legionella culture, BAL	Negative
	AFB culture, BAL	Negative
	CMV PCR, serum	Not detected
Day 4	Cryptococcus antigen, serum	Not detected

cannula with no improvement, he was restarted on therapeutic PJP treatment and concurrent disseminated histoplasmosis therapy with amphotericin.

By day 10 of hospitalization, his respiratory status improved, and he no longer needed supplemental oxygen. He experienced significant improvement in his tongue ulcer and began to tolerate food and oral medications, so biopsy was not pursued. At discharge, on day 17 of hospitalization, the patient had near complete resolution of his oral ulcer and had no respiratory symptoms. He was discharged on oral TMP-SMX, adjunctive steroids, and 200 mg of itraconazole twice daily to complete the remainder of his treatment course. For PJP treatment, he was planned for oral TMP-SMX and steroids for 21 days. While his histoplasmosis treatment course entailed itraconazole for at least 12 months.

Discussion

The patient described in this case presented with a tender tongue lesion and hypoxia and was found to be co-infected with *Histoplasma* and *Pneumocystis jirovecii.* This case illustrates the diagnostic challenge in a patient with advanced HIV presenting with multiple opportunistic infections simultaneously. When treating a highly immunocompromised host, Hickam's Dictum applies, which states that "*patients can have as many diseases as they damn well please*" [5]. This is not uncommon in patients with advanced HIV.

Nodules in a miliary pattern on a CT chest in an immunocompromised HIV patient have a wide differential. Pulmonary infections of concern in this population include *Pneumocystis jirovecii* pneumonia, *Mycobacterium tuberculosis*, non-tuberculous mycobacterium, and other fungal infections such as cryptococcosis, histoplasmosis or coccidiomycosis [6]. The presence of multiple OIs at once presents a diagnostic challenge and highlights the importance of microbiological identification. *Pneumocystis jirovecii* and *Histoplasma capsulatum* are respiratory fungal pathogens that primarily target the lung and present similarly with fever, non-productive cough, and dyspnea in infected patients. Similar cases of co-infection with histoplasmosis and pneumocystis in immunocompromised individuals, though rare, have been reported in the medical literature [7–15]. This is the first case to our knowledge of co-infection with disseminated histoplasmosis with oral involvement and pulmonary pneumocystis.

In HIV-infected patients with CD4 + counts below 200/mm^3, histoplasmosis often presents as a progressive disseminated disease with extrapulmonary manifestations [16]. Clinical manifestations of disseminated histoplasmosis depend on the genetic variation among different strains, the host's immune system, and the burden of inhaled spores [17]**.** Dissemination into the gastrointestinal tract often involves the colon and terminal ileum leading to abdominal pain and inflammatory diarrhea [18]. Oral manifestations of histoplasmosis are associated with the disseminated form and can occur anywhere in the oral mucosa but most commonly are found on the palate, buccal mucosa, and tongue [19]. These lesions appear as granular or verrucous ulcerations surrounded by irregular erythematous or white areas [17]. It is important to differentiate oral ulcers caused by histoplasmosis from those caused by other etiologies, such as malignancies, autoimmune diseases, and other infections. Other potential infectious etiologies include herpes simplex virus, *Treponema pallidum, Blastomyces dermatitidis, and Cryptococcus neoformans* [16]. Biopsy of the oral ulcer with pathology evaluation is an efficient way to diagnose a patient with oral manifestations of histoplasmosis in conjunction with laboratory tests confirming disseminated disease [17]. Antigen detection by enzyme immunoassay from body fluid of infected patients is commonly used; urine has a sensitivity of 95–100% and serum has a sensitivity of 92–100% [16]. There have been case reports of oral manifestations of histoplasmosis among immunodeficient and rarely, immunocompetent individuals [17, 19]. *Pneumocystis jirovecii* Pneumonia (PJP) is the most common opportunistic infection in persons with HIV [19]. PCR assay on induced sputum for *Pneumocystis jirovecii* has a sensitivity of 95%, whereas BAL specimens for *Pneumocystis jirovecii* PCR have a sensitivity approaching 100% [20]. Therefore, a negative induced sputum PCR should not rule out PJP pneumonia in a patient in whom there is high clinical suspicion and additional testing such as bronchoscopy with BAL should be performed to confirm the presence or absence of PJP, as well as to exclude other potential causes of pneumonia, including other OIs.

In HIV patients with low CD4 + counts presenting to the hospital with concerns regarding infection, as observed in this case, it is crucial to consider concurrent OIs in the differential diagnosis. The patient in this case was diagnosed with disseminated histoplasmosis with oral involvement and pulmonary pneumocystis. Although no biopsy was performed for his oral lesion, it was presumed to be due to histoplasmosis based on compatible clinical picture and clinical response to targeted histoplasmosis therapy. A high index of suspicion should be maintained for patients who have resided in areas of high endemicity, as early diagnosis and prompt initiation of directed therapy can significantly improve outcomes.

CRediT authorship contribution statement

S. Ajao: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **N. Damle:** Writing – original draft, Writing – review & editing. **M. Zhao:** Writing – review & editing. **G. Ferreira:** Writing – review & editing. **K. Kaye:** Conceptualization, Supervision, Writing – review & editing. **J. Mills:** Conceptualization, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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