CASE REPORT

Disseminated histoplasmosis presenting as multiple oral ulcers

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SUMMARY

A 61-year-old female with a history of advanced HIV disease and chronic hepatitis B was presented with an 8-week history of painful oral ulcers. She appeared systemically well but examination revealed multiple well-demarcated clean-based ulcers on the tongue and hard palate. Biopsy of one of the lesions showed numerous histiocytes containing intracellular yeast forms consistent with *Histoplasma capsulatum* var. *capsulatum*. Fungal blood cultures subsequently grew *H. capsulatum* var. *capsulatum*, confirming a diagnosis of disseminated histoplasmosis. She was treated with intravenous amphotericin B for 2 weeks followed by a prolonged course of oral itraconazole, with which her ulcers resolved completely and have not recurred. This case exemplifies how oral ulcers may be a manifestation of an underlying systemic disease and demonstrates the utility of biopsy in establishing a diagnosis.

BACKGROUND

Oral ulcers can be a protean and often vexing clinical presentation of systemic disease due to limited clinician exposure. The aetiology of oral ulcers represents a broad differential diagnosis. While ulcers may represent isolated oral disease, they may also be a manifestation of an underlying systemic condition. Mechanical trauma is the most common cause of oral ulcers. Viral infections such as HIV, Epstein–Barr virus (EBV), coxsackievirus, enterovirus and human herpes virus 8 (HHV-8) are also common culprits.¹ Additionally, neoplasm, aphthous ulcers, oral lichen planus, fungal infections, Behcet's syndrome, celiac disease, Sweet syndrome, pemphigus vulgaris, erythema multiforme and secondary syphilis should be considered.¹ Given the broad differential, any unexplained oral ulcers that do not resolve within 2 weeks should be considered for biopsy.¹ We present a case of unremitting oral ulcers in a patient with advanced HIV.

CASE PRESENTATION

A 61-year-old female with a history of advanced HIV disease and chronic hepatitis B was presented with painful oral ulcers. The oral ulcers began 8 weeks prior to admission, during which they had grown both in size and number. They were very painful to pressure and limited her ability to eat or drink fluids. She denied fevers, chills or rashes, and the review of systems was otherwise unremarkable. She reported intermittent compliance with scheduled medications, which included emtricitabine,

tenofovir and dolutegravir for HIV and atovaquone and azithromycin for prophylaxis against opportunistic infections. She denied medication changes, sick contacts or travel outside of Texas. Social history was notable for a 30 pack-year smoking history and active crack cocaine use.

On admission, she was afebrile (temperature 36.8°C) with blood pressure 160/86 mm Hg and heart rate 93/min. She was in apparent discomfort due to her oral lesions and was drooling profusely due to pain. Examination of the oropharynx revealed oral thrush and multiple clean-based ulcers on the tongue and hard palate (figures 1 and 2). There were no lesions on the lips, soft palate or gums. Pulmonary, cardiac, abdominal, neurological, skin and musculoskeletal exams were unremarkable.

INVESTIGATIONS

Laboratory analysis revealed a normal white blood cell count of $4.7 \times 10^9/L$ (normal $4\text{--}11 \times 10^9/L$) with low CD4 T-cell count of 88 cells/mL³ (normal 365–1437 cells/mL³). Hepatic enzymes were mildly elevated (aspartate transaminase 130 U/L (normal range 10–50 U/L), alanine transaminase 78 U/L (normal 10–50 U/L), alkaline phosphatase 152 U/L (normal 40–129 U/L)); total bilirubin and renal function were normal. Plasma HIV RNA was 216 copies/mL, and a hepatitis B viral load by PCR was >17 million IU/mL. Serum herpes simplex virus PCR, rapid plasma reagin, serum varicella PCR, serum cytomegalovirus PCR and serum cryptococcal antigen were negative. An admission chest X-ray was unremarkable. Fungal blood and bacterial blood cultures were negative at 48 hours of growth.

DIFFERENTIAL DIAGNOSIS

An infectious cause was principally suspected given the patient's immunocompromised state and clinical course with sudden onset and subacute progression. Infectious aetiologies including herpes simplex virus, cytomegalovirus, coxsackievirus (foot and mouth disease), enterovirus (herpangina), HHV-8, EBV, secondary syphilis, cryptococcosis, histoplasmosis and atypical lesions due to hepatitis B were leading considerations on the differential. Malignancies including oral Kaposi's sarcoma and non-Hodgkin's lymphoma in the setting of HIV infection were also considered. Additional aetiologies including chronic mechanical trauma, hepatitis B-associated cryoglobulinaemia, atypical presentation of

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Figure 1 Deep, well-demarcated, clean-based ulcers with rolled borders were present on the lateral and dorsal tongue.

levamisole-associated vasculitis, Behcet's disease, pemphigus vulgaris and HIV-associated aphthous ulcers remained in the differential.

TREATMENT

Given the diagnostic uncertainty, a biopsy of the tongue lesions was obtained. Findings were consistent with extensive but benign ulceration of the squamous epithelium; additionally, multiple intracellular yeast forms were observed (figures 3 and 4). A subsequent urine histoplasma antigen was markedly positive (>20 ng/mL (normal <1 ng/mL)), supporting the diagnosis of histoplasmosis.

The patient was started on a 14-day course of liposomal amphotericin B 3 mg/kg daily for disseminated histoplasmosis. Her oral lesions improved significantly and she was discharged on oral itraconazole (200 mg three times daily for 3 days, then 200 mg twice daily) with plans to complete at least 1 year of therapy. Four weeks after discharge, fungal blood cultures drawn on admission grew *H. capsulatum var. capsulatum*, confirming the uncommon diagnosis of disseminated histoplasmosis presenting as oral ulcers.

OUTCOME AND FOLLOW-UP

At clinical follow-up 6 weeks after initial presentation, the patient had self-discontinued itraconazole. Nevertheless, her oral lesions remained resolved. She was restarted on itraconazole and remains asymptomatic with no disease recurrence 7 months after diagnosis.

Figure 3 H&E stain at high power (400 $\times$) showing numerous histiocytes with multiple intracellular yeast forms consistent with *Histoplasma capsulatum var. capsulatum* (red arrows).

Figure 2 Multiple ulcerated lesions of the hard palate.

DISCUSSION

Infection with *H. capsulatum var. capsulatum* can manifest in a myriad of ways, ranging from asymptomatic self-limited disease to disseminated life-threatening infection. *H. capsulatum var. capsulatum* is a dimorphic fungus endemic in the Mississippi and Ohio River Valleys of the USA, as well as parts of Central America, South America, Asia and Australia.² Soil contaminated by bird or bat guano supports dense growth of *H. capsulatum var. capsulatum* that can persist many years after initial inoculation.³ Serological markers of disease have demonstrated that approximately 80% of young adults from the states bordering the Ohio and Mississippi Rivers have been previously exposed to the fungus.³

Despite high levels of endemic exposure, symptomatic infections are less common and estimated to occur in less than 1% of exposures in non-HIV infected individuals.⁴ The incidence prior to the highly active antiretroviral therapy (HAART) era in HIV-infected patients with AIDS from endemic areas was previously estimated at 2%–5% and up to 25% in select cities, reflecting the impaired cell-mediated immunity of these individuals.^{4,5} Prior studies observed disseminated infection in 95% of infections in patients with AIDS, with oral manifestations present in 25%–45% in the disseminated form of the disease.^{5,6} However, the true burden of HIV-associated histoplasmosis in the HAART era in the USA is not fully known since it is not a notifiable disease.⁷

Symptoms of acute pulmonary histoplasmosis include fever, chest pain, dry cough and malaise over a course of 1–2 weeks;

Figure 4 Gomori methenamine silver stain (200 $\times$) of squamous epithelium containing multiple histiocytes with intracellular yeast forms consistent with *Histoplasma capsulatum var. capsulatum*.

approximately 6% of patients may also develop rheumatologic manifestations including pericarditis, arthritis and erythema nodosum.^{3, 8} Pulmonary histoplasmosis can also present in a subacute fashion, with symptoms of several months' duration, or as a chronic illness with fevers, night sweats, weight loss, dyspnoea and pulmonary cavitory lesions.³ The presence of extrapulmonary disease implies disseminated infection. Symptoms of progressive disseminated histoplasmosis including diarrhoea, mucosal ulcers, skin lesions, hepatosplenomegaly and lymphadenopathy may be found on physical examination. Laboratory studies may show transaminitis, pancytopenia and significant elevations in serum lactate dehydrogenase and ferritin.⁴ Conversion from acute focal to progressive disseminated histoplasmosis occurs in approximately 0.05% cases, although immunosuppression confers a 10-fold higher risk.⁸

Positive histoplasma antigen levels in urine and plasma are sensitive markers for active infection, particularly disseminated disease, although cross-reactivity can occur in patients with infections due to blastomycosis, penicilliosis and paracoccidioidomycosis.^{8, 9} Serological tests for histoplasma antibodies also show cross-reactivity with antibodies to other endemic dimorphic fungi and are less sensitive than antigen detection, particularly in immunocompromised hosts.^{8, 10} Fungal cultures are positive in approximately 70%–75% cases of disseminated histoplasmosis.^{4, 9} Direct visualisation of organisms in infected tissue enables rapid and accurate diagnosis; however, obtaining tissue for this purpose carries risks and may not be feasible in some cases.

The recommended treatment for disseminated histoplasmosis is liposomal amphotericin B (3 mg/kg daily) for 1–2 weeks, followed by oral itraconazole (200 mg three times daily for

3 days, then 200 mg twice daily). Patients should receive at least 1 year of itraconazole and have proven biochemical and clinical symptom resolution prior to discontinuation of suppressive therapy. Additionally, HIV-infected individuals should have a CD4 T-cell count >150 cells/mm³ and be receiving suppressive antiretroviral therapy prior to discontinuation.¹¹

This clinical vignette describes a HIV-infected patient with an uncommon initial presentation of disseminated histoplasmosis with painful oral ulcers. Her case highlights the importance of early biopsy in cases of diagnostic uncertainty and demonstrates dramatic improvement of oral lesions with liposomal amphotericin B. Although disseminated histoplasmosis warrants long-term azole therapy, the patient was not compliant with outpatient therapy. Despite being currently symptom free, the literature suggests that she has at least a 10%–20% chance of relapse.^{4, 8, 10}

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Learning points

- ▶ Oral ulcers in a HIV patient have a broad infectious and non-infectious differential diagnosis, with disseminated histoplasmosis representing an uncommon aetiology.
- ▶ Biopsy for unexplained oral ulcers lasting longer than 2 weeks should be considered to facilitate diagnosis.
- ▶ Therapy for disseminated histoplasmosis typically involves sequential treatment with 1–2 weeks of liposomal amphotericin B followed by at least 1 year of oral azole therapy.

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