CASE REPORT

Disseminated histoplasmosis: missed opportunistic infection in a HIV-infected patient

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SUMMARY

Oral ulcers are common in HIV-infected patients, with a broad differential, including viral, bacterial, fungal, mycobacterial and neoplastic aetiologies. We present a case of a patient with AIDS with oral ulcer, which was a cutaneous presentation of disseminated histoplasmosis. Our patient responded excellently to treatment.

BACKGROUND

Oral ulcers are common in HIV-infected patients, with a broad differential including viral, bacterial, fungal, mycobacterial and neoplastic aetiologies. Histopathological examination can be invaluable in making a definitive diagnosis and directing specific treatment.

CASE PRESENTATION

A 28-year-old man presented with a painful ulcer at the left angle of the mouth, left submandibular swelling, fever, anorexia and a 6 kg weight loss over 2 months. Throughout this time period, the ulcer had gradually increased in size, spreading over the left buccal mucosa and causing severe deglutitory pain. He denied any symptoms of cough with expectoration, dyspnoea or haemoptysis.

The patient reported being diagnosed with HIV 1 year ago and was not on antiretroviral therapy; most recent CD4 cell count showed a downtrend from 212 to 138 cells/mm³ over 2 months. He reported a history of high-risk heterosexual behaviour. One month prior to presentation, the patient had been hospitalised with left submandibular lymphadenopathy and had received a diagnostic fine needle aspiration at an outside institute. Smear results showed granulomas without any definite evidence for caseous necrosis, cultures were pending and he was empirically started on isoniazid, rifampicin, ethambutol and pyrazinamide. Despite treatment however, symptoms continued to worsen.

The patient had no history of latent or active tuberculosis, had not been incarcerated. Purified protein derivative was never performed previously. The patient had no other significant medical history and no personal history of any oral or genital ulceration. He was a daily tobacco chewer for the past 10 years and denied other substance misuse.

Physical examination revealed cachexia however he was not acutely ill looking with a weight of 49 kg (body mass index 22 kg/m²). Blood pressure was normal, temperature 38.4°C and heart rate 130 bpm. Oral examination was significant for an

irregularly bordered, tender, indurated 6×10 cm blackish ulcer at the left angle of the mouth extending into the oral cavity with moderate amount of yellowish discharge and slough at the ulcer base. A 3×3 cm, tender, mobile left submandibular lymph node was appreciated. Multiple subcentimeteric deep cervical nodes were also noted. Non-tender hepatosplenomegaly was present on abdominal examination. The remainder of the examination was normal.

INVESTIGATIONS

Complete haemogram and differential was normal. Complete metabolic panel was normal except for an alkaline phosphatase of 1215 IU/mL. Venereal Disease Research Laboratory (VDRL) and markers for acute hepatitis were negative. Chest X-ray was suggestive of mediastinal widening and lung parenchyma did not show any infiltrates or opacity. Abdominal ultrasound showed hepatosplenomegaly with extensive periportal and mesenteric lymphadenopathy. CT of the abdomen confirmed these findings without additional abnormalities.

Scraping of oral mucosa was performed. Histopathological examination (figure 1) of stained smear showed epithelioid granulomas with eosinophilic intramicrocytic granules resembling signet rings, due to the double wall of *Histoplasma capsulatum*. Staining with Gomori methanamine silver stain outlined the double wall of histoplasma. Lymph node biopsy showed similar histology. The interim culture for *Mycobacterium tuberculosis* from lymph node were negative.

TREATMENT

A diagnosis of AIDS with disseminated histoplasmosis (DH) was thus established. Antitubercular agents were stopped and the patient received intravenous amphotericin B followed by 12 weeks of maintenance therapy with itraconazole. On completion, marked clinical improvement was noted. He gained 3 kg, his ulcer size diminished by 70% and alkaline phosphatase decreased to 665 IU/mL. Highly effective antiretroviral therapy was then started with zidovudine, efavirenz and lamivudine after completion of induction therapy with amphotericin B, and continued on fluconazole 400 mg for maintenance treatment.

OUTCOME AND FOLLOW-UP

The patient was followed up at the end of 1 and 3 months. There was a complete resolution of his symptoms, itraconazole was stopped and the patient was continued on zidovudine, efavirenz and

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Figure 1 (A) Granulomatous reaction with macrophages having intracellular and extracellular histoplasma. (B) Single macrophage showing many intracellular vacuoles containing body stained, that is, histoplasma. (C) Single macrophages showing many intracellular histoplasma. (D) Gomori methanamine silver stain showing the double wall of histoplasma.

lamivudine. There were no symptoms or signs to suggest any opportunistic infection or relapse of histoplasmosis.

DISCUSSION

H capsulatum is a deep fungal mycosis of immunocompetent and immunocompromised hosts.¹ *H capsulatum* var *capsulatum* is endemic in the Ohio River and Mississippi River Valleys of the USA, whereas *H capsulatum* var *dubosii* is endemic in Africa.² Clinical manifestations of histoplasmosis are of three main types: pulmonary, progressive DH (PDH) and chronic cavitary forms.

1. Criteria confirming the diagnosis of histoplasmosis

- Fungal stains of tissue specimen with Gomori methanamine silver stain demonstrating double wall of the yeast phase of this organism;
- Culture from blood, bone marrow, lymph node, cerebrospinal fluid and respiratory secretions. Although culture is sensitive, it takes 4 weeks for an organism to grow in vitro;
- Antigen detection tests from blood and urine. Rapid diagnosis can be established but has a high false positive rate, hence these are helpful in monitoring therapeutic response and relapse of infection.^{3 4}

2. Criteria supporting the diagnosis of histoplasmosis

- Bone marrow involvement is suggested by cytopaenia with a decreased reticulocyte count. Elevated alkaline phosphatase levels are seen in patients with liver infiltration. Lactate dehydrogenase and ferritin levels are elevated in patients with DH;
- Chest radiograph patterns include reticulonodular pattern, diffuse interstitial pattern and mediastinal lymphadenopathy.

DH is a serious opportunistic infection in patients with AIDS and should be considered in all patients with AIDS with a low CD4 count, general ill health and elevated liver enzymes. The

1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults describes histoplasmosis, disseminated or extrapulmonary as one of the conditions included in the 1993 AIDS Surveillance Case Definition.⁵

Treatment in patients with AIDS comprises induction and maintenance phases. Duration of therapy varies based on acute (6–12 weeks) or chronic disease (1 year). Liposomal amphotericin B is used for induction therapy with or without glucocorticoids for 1–2 weeks. Liposomal amphotericin B has been more effective than the deoxycholate formulation for treatment of PDH in patients with central nervous system involvement. Itraconazole (200 mg twice daily) for 12 weeks is the antifungal of choice for the maintenance phase.¹ Posaconazole, voriconazole and fluconazole are acceptable alternatives for patients who cannot take itraconazole.²

Learning points

- ▶ *Histoplasma capsulatum* is in differential of oral ulcers in patients with HIV infection.
- ▶ Biopsy of atypical oral ulcer is important in identifying opportunistic infection in patients with HIV infection.
- ▶ Know the treatment of histoplasmosis in an immunocompromised host.

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