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Tonsillar ulceration as manifestation of disseminated African histoplasmosis in an immunocompetent Portuguese host

L. Cardoso[a,*], C. Silva[a], N. Marques[b], C. Veríssimo[c]

[a] Department of Otolaryngology, Centro Hospitalar e Universitário de Coimbra, 3000-075 Coimbra, Portugal
[b] Department of Infectious Diseases, Centro Hospitalar e Universitário de Coimbra, 3000-075 Coimbra, Portugal
[c] Department of Parasitology and Mycology, Instituto Nacional de Saúde Doutor. Ricardo Jorge, 1600 Lisboa, Portugal

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ABSTRACT

Histoplasmosis is a systemic mycosis caused by Histoplasma capsulatum. Rare in Europe but endemic in some regions of Brazil, United States, Africa and Asia. Most of the cases are asymptomatic. Disseminated form is defined by the presence of an extra-pulmonary focus, particularly associated with immunosuppression. We report a case of an unilateral persisted tonsillar ulceration, in an immunocompetent Portuguese host, as manifestation of disseminated African histoplasmosis 45 years later after living 3 years in Africa.

1. Introduction

Histoplasmosis is a systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic fungus, first described in 1906 by Samuel Darling in Panama [1,2]. It has been isolated from soil contaminated with bird or bat droppings in endemic areas such as Brazil, North/Central of United States, central/western Africa and parts of Asia; it´s rare in Europe and frequently associated with patients from endemic areas who seek care in Europe or visited those countries in the past [3–8]. There are two varieties of *H. capsulatum* that are pathogenic to humans: *H. capsulatum* var. *capsulatum* and *H.* var. *capsulatum duboisii*. Less common, *H. capsulatum* var. *duboisii* is the etiologic cause for African histoplasmosis [3,5]. In var. *capsulatum,* most of the cases are asymptomatic, and those with symptoms usually present with self-limited respiratory infection. Variety *duboisii* has tropism for lymph nodes, skin, and bones and is classically associated with cutaneous lesions (nodules, ulcers) and osteolytic bone lesions, especially affecting the skull, ribs, and vertebrae [6]. The disseminated form is defined by the presence of an extra-pulmonary focus, particularly on those with risk factors: immunosuppression, transplantation, chronic renal disease, prolonged use of corticosteroids and acquired immune deficiency syndrome [7,9]. One third of disseminated disease presented oropharyngeal involvement. The most common sites are tongue, palate and buccal mucosa [2]. We report a rare case of a disseminated African histoplasmosis in an immunocompetent Portuguese host presented with unilateral tonsillar ulceration and large inguinal lymphadenopathy 45 years after living in Africa.

2. Case

A 68 years-old Caucasian Portuguese male, presented at day 0 in the otorhinolaryngology emergency department with 2 months' sore throat, loss of weight (5 kg) and persisted tonsillitis after several treatments with antibiotics. He denied other complaints such as cough, dyspnea, nocturnal sweating, nausea, vomiting, diarrhea or headaches. Medical history included alcohol and tobacco abuse stopped 15 years ago; residency on a rural area with daily contact with birds, cats and dogs; malaria and typhoid fever during his first year of military service in Portuguese Colonial War in Africa (Angola) from 1969 to 1971; right inguinal hernia since 2005.

At admission, on day 0, a complete exam revealed a left tonsillar ulceration (Fig. 1A) with bilateral cervical infracentimetric lymphadenopathy and a 5 cm right inguinal lymphadenopathy, mobile and nontender (Fig. 1B).

At day 0, routine hematological parameters were normal; blood and urine cultures were sterile; c-reactive protein, erythrocyte sedimentation rate, serum levels of liver enzymes, bilirubin and lactate dehydrogenase were within reference ranges; serologic tests for human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, herpes simplex virus, *Borrelia burgdorferi*, *Brucella*, *Bartonella*, *Histoplasma* and interferon-gamma release assays were negative; previous contact/infection and immunity – immunoglobulin (Ig) M negative and IgG positive – were documented to *Chlamydia trachomatis*, epstein-barr virus, *Chlamydophila pneumoniae*, Cytomegalovirus, *Toxoplasma* and *Varicella zoster*; routine serologic antibodies for autoimmune diseases were also

* Corresponding author.

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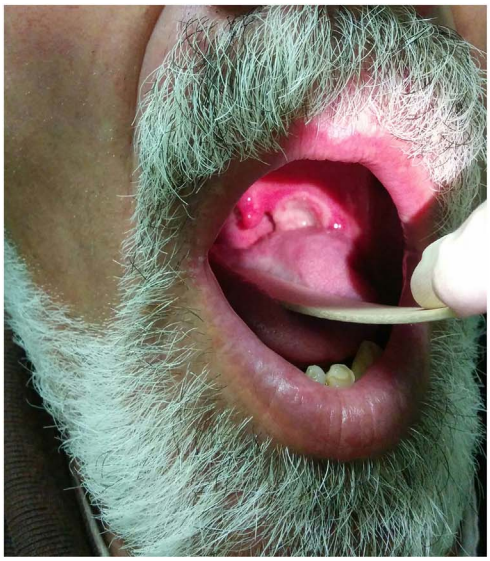

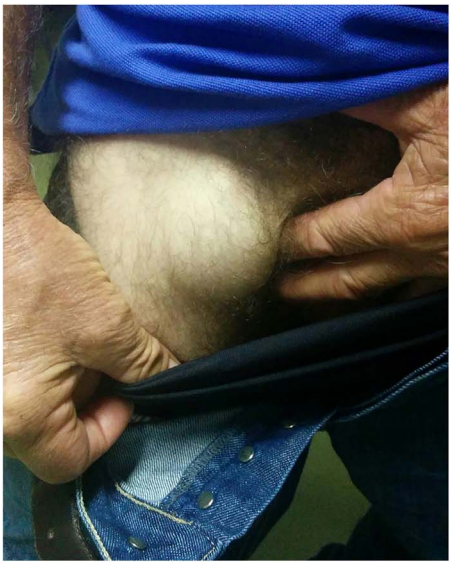

Fig. 1. A. Left tonsilar ulceracion; B. Right inguinal lymphadenopathy.

negative. Screening test for syphilis was positive.

Chest X-ray, cervical/thoracic computed tomography (CT) and upper gastrointestinal endoscopy were normal.

To exclude malignancy, on day 5, a biopsy of the ulcerated tissue was performed and direct examination revealed large narrow based budding yeast cells compatible with *Histoplasma* (Fig. 2). Culture of ulcerated tissue on Sabouraud dextrose agar at 30 °C revealed a white filamentous fungus one month after incubation (Fig. 3), the microscopic examination with lacto-phenol cotton blue preparation, showed septate hyphae and thick-walled tuberculated conidia. Genomic DNA was extracted and the internal transcribed spacer (ITS) region of ribosomal DNA (rDNA) was amplified using primer set ITS1 (5′TCCGTAGGTGAACCTGCGG3′) and ITS4 (5′TCCTCCGCTTATTGATATGC3′). The aligned sequence was compared with sequences deposited at GenBank database and showed > 98% similarity with *H. capsulatum* var. *duboisii* sequences, which is the value considered as an acceptable identification to species level. The isolate is deposited at GenBank database with the accession number KY420902.

Left inguinal lymphadenopathy was removed on day 33 and histopathologic study was positive for Periodic Acid Schiff (PAS) and Grocott's methenamine silver (GMS) stains and revealed ovoid yeast cells in direct histopathologic exam also compatible with histoplasmosis.

Patient was treated with Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscular each at 1-week intervals. After treatment, on day 30, Rapid Plasm Reagin for Treponema pallidum were negative but the tonsillar ulceration persists. On day 35, he started oral itraconazol 200 mg three-times-daily for the first 3 days and then 200 mg twice-daily for 12 months.

After 1 month of treatment, tonsillar ulceration healed completely with some retraction of the soft palate (Fig. 4) and there was no cervical lymphadenopathy palpable. Inguinal region also healed well. There was no sign of disease or side effects during the 12-month period of antifungal treatment. Six months after treatment, no recurrence was also detected.

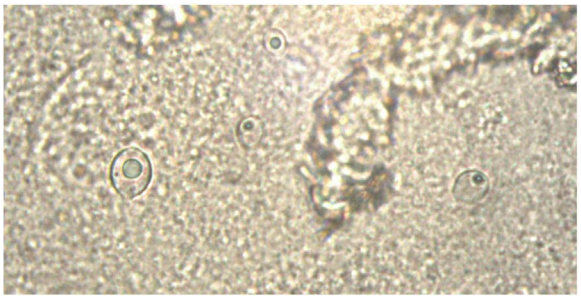

Fig. 2. *Histoplasma capsulatum var. duboisii* yeast in fresh exam from tonsillar tissue (400x).

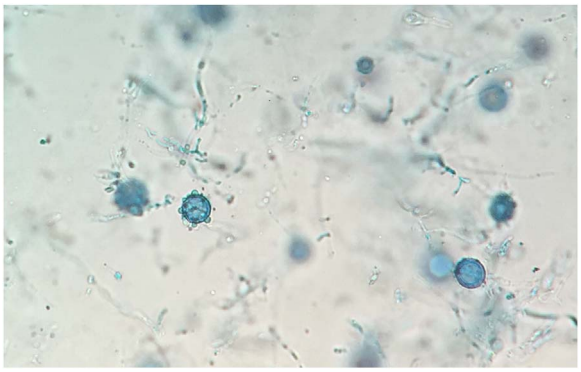

Fig. 3. Septate, hyaline hyphae with large thick-walled spherical macroconidia. Lactophenol cotton blue from the culture plate −400x.

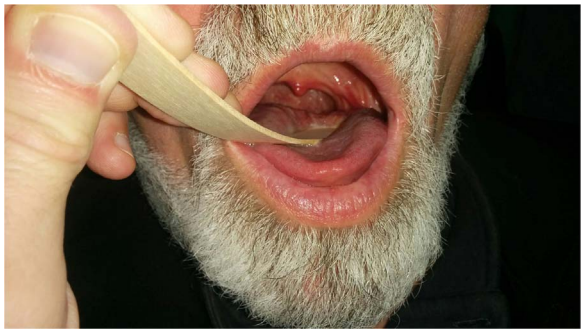

Fig. 4. Oral cavity: 1 month after treatment.

3. Discussion

Oral ulcerations have many different etiologies and it can be a challenge to diagnose and manage. Their cause can range from minor irritation to systemic diseases (viral, bacterial, fungal or autoimmune) and malignancies. Malignancy must be excluded, particularly in solitary persisted ulceration, in patients with history of alcohol and smoking

behavior. A biopsy is mandatory. Oral histoplasmosis is unusual and is typically associated with immunosuppression status, especially in patients with AIDS and/or active pulmonary tuberculosis. Oral lesions can be the presentation of disseminated disease.

There are several cases worldwide reported with oral histoplasmosis in immunocompetent patients [7,9–19]. In Portugal, only one case was published about an oral histoplasmosis in a hemodialysis patient with persisted fever [9].

Our case illustrates a two-month persistent tonsillar ulceration as a manifestation of disseminated African histoplasmosis in an immunocompetent Portuguese patient who lived three years in Africa 1969–1971) and had an inguinal lymphadenopathy misdiagnosed as inguinal hernia for years. *H. capsulatum var. duboisii* is not endemic in Europe and the patient might acquire the infection in Africa. This patient also had a positive screening for syphilis that mislead/delay the diagnosis and treatment for histoplasmosis.

The definitive diagnosis of histoplasmosis requires isolation of the *H. capsulatum* on specific culture media or visualization in direct examination using specific fungal staining techniques: PAS or GMS. Non-culture methods have also been developed and include antibody or antigen detection, although there is an increase in false-negative results in the disseminated form of histoplasmosis [5]. In our patient, the immunodiffusion antibody detection was negative; in our experience this method is less sensitive for detection of the *Histoplama capsulatum duboisii*.

Until the azole era began in the 1990s, amphotericin B deoxycholate was the only therapeutic option. Nowadays, patients who are not severely ill, can be treated with oral itraconazole, 200 mg twice daily for 6–12 months and some authors advocate 200 mg 3 times a day for the first 3 days. Fluconazole is less effective than itraconazole and it's considered to be a second-line agent [1,10].

Despite the rarity of the disease in Europe, clinicians should be aware of the possibility of histoplasmosis in cases of tonsillar ulceration specially in travelers or immigrants from sub-Saharan West and central Africa.

Conflict of interest

There are none.

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