



Disseminated histoplasmosis in a patient with chronic lymphoedema

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ABSTRACT

A 54 year-old man with lymphopenia secondary to lymphatic filariasis was admitted with dry cough, fever and wasting syndrome. He was diagnosed with sarcoidosis and therapy with corticosteroid was initiated. The patient evolved with worsening of the symptoms. *Histoplasma* species was recovered in lung biopsy tissue, lung tissue culture, and bone marrow aspirate. The authors describe the first case of disseminated histoplasmosis secondary to lymphatic filariasis, followed by a literature review. 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Histoplasmosis is a fungal infection acquired by the inhalation of *Histoplasma capsulatum* conidia from the environment [1]. This dimorphic fungus has a worldwide distribution, and it is endemic in the American continent, including central areas of the USA and large parts of Latin America [1]. Even though histoplasmosis is endemic in Brazil, the diagnosis is usually performed in late stages of the disease, and the frequency of disseminated histoplasmosis is likely to be underestimated [2].

Histoplasmosis is usually asymptomatic and may be a self-limiting disease. However, disseminated infection may occur, mostly in lymphopenic patients, being HIV/AIDS and induced immunosuppression by TNF- α inhibitors the two main risk factors [3]. Here we report the first case of disseminated histoplasmosis secondary to lymphatic filariasis resulting in marked lymphopenia.

2. Case

A 54 year-old man was admitted to a hospital elsewhere (Day 0) presenting with dry cough, fever and wasting syndrome. Over the previous weeks he had noticed episodes of night sweats, weight loss (~8 kg), fatigue and abdominal pain. His medical history was marked by a chronic and extensive lymphoedema (elephantiasis supposedly due to *Wuchereria bancrofti* infection), involving lower limbs and the scrotum. This condition started when he was a teenager and persisted along his life, resulting in recurrent episodes of cellulitis and bacteraemia.

Physical investigation did not demonstrate skin lesions or oral ulcers. There were no alterations on pulmonary exam, but abdominal physical examination demonstrated a diffuse discomfort during palpation but no signs of organomegalies or peritoneum inflammation.

A primary investigation with chest X-ray was normal. A chest and abdominal computed tomography were performed, demonstrating, respectively, multiple small micronodules in the lungs (Fig. 1) and enlarged adrenal glands with mild increase of the liver and spleen (Fig. 2). Laboratory studies revealed anaemia and leukopenia.

During the following days, the patient persisted febrile and demonstrated clinical deterioration (Day 4). A video-assisted thoracoscopic biopsy was performed, revealing a non-necrotic granulomatous disease. Tissue was negative for acid fast bacilli and fungi. A bone marrow aspiration was also performed. Under the hypothesis of sarcoidosis, steroids were initiated (prednisone 40 mg/daily) and the patient was released from the hospital in a better clinical status. However, after a few days of clinical improvement, the patient deteriorated dramatically, and he was readmitted to the hospital in severe shock (Day 14). Lung biopsy was reviewed by an experienced pathologist and a necrotic granuloma was observed. Typical small oval budding yeasts of *Histoplasma* species were seen in tissue and the fungus was later identified on culture of lung tissue and bone marrow aspiration. The patient was found to have a low CD4 count (198 cells/mm³) due to chronic loss of lymphocytes.

Therapy with liposomal amphotericin at 3 mg/kg was initiated and maintained for 3 weeks. The patient had a dramatic improvement of his symptoms and was discharged from the hospital on itraconazole 400 mg

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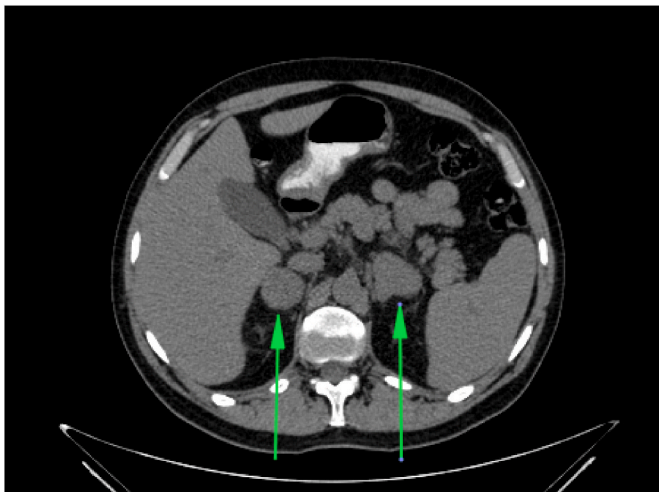


Fig. 1. Abdominal computed tomography revealing enlarged adrenal glands (arrows).



Fig. 2. Chest computed tomography showing the presence of diffuse micronodules in the lungs.

daily, and completed 1 year of antifungal therapy, with no evidence of relapse. He was also put on primary prophylaxis with trimethoprim-sulfamethoxazole, due to the low CD4 count. Few weeks after hospital discharge, his spouse reported the presence of a bird nest out of a window close to an air conditioner at the patient's house (Fig. 3). Culture of organic material found on the nest revealed growth of *Histoplasma capsulatum*.

3. Discussion

The majority of cases of disseminated histoplasmosis (DH) reported in the literature involve patients living with HIV/AIDS [1,4]. After inhalation of fungal propagules, most people, particularly healthy individuals, remain asymptomatic or developed mild symptoms such as cough, fever, and chest pain [5]. However, immunocompromised patients are at least 10 times more likely to manifest symptomatic disease and develop DH than the general population [3] and the risk of an immunocompromised patient to evolve with disseminated course may be as high as 95%. It is interesting to note that 90% of disseminated histoplasmosis occur in patients with CD4 counts <200 cells/mm³ [5].

Even though DH is infrequent in the bone marrow transplant population, DH is a challenging condition to solid-organ transplant recipients, since T-cell immune dysfunction can be significant especially



Fig. 3. Bird nest found near the air conditioning of patient's bed.

among cases of renal and liver transplant [6–8]. Amongst patients under treatment with tumor necrosis factor (TNF) blockers, DH is the most common opportunistic infection with a mortality rate of 20% [9]. The disseminated form has also been described in immunocompetent hosts.

In the present case, the patient's medical history was marked by a chronic lymphoedema, secondary to lymphatic filariasis. This chronic disease is characterized by the accumulation of interstitial fluid in tissues due to damaged lymphatic vessels, leading to swelling, and dysfunction of the limbs. Patients in this condition often exhibit impaired immune function due to pathological features which includes oedema, dermal fibrosis and formation of fat tissue, predisposing them to a variety of infections [10]. Nevertheless, there has been no report of DH related to lymphopenia secondary to lymphatic filariasis.

Clinical findings of DH frequently consist of systemic symptoms including fever, fatigue, weight loss, night sweats, progressive shortness of breath, and diarrhea if the gastrointestinal system is affected [7,11]. Physical examination may reveal lymphadenopathy, hepatomegaly, or splenomegaly with skin lesions. In some patients, mucous membrane ulcerations can also be present [12].

Disseminated infection can also present with specific symptoms and signs related to organ involvement. The most common sites of extrapulmonary dissemination are the liver, spleen, gastrointestinal tract, and bone marrow; dissemination to these sites occurs in 33–66% of cases. Less common sites include skin, adrenal glands, central nervous system, and heart, in 10–20% of cases [3]. Some patients have adrenal insufficiency caused by diffuse infiltration and necrosis of the adrenal glands. This includes Addison's disease and computed tomography scan shows markedly enlarged adrenals, often with necrosis in the central area. In the case reported by the authors, the patient presented extrapulmonary involvement, since both adrenal glands were increased, and the patient presented hepatosplenomegaly. Severe disease can present as sepsis syndrome with hypotension, disseminated intravascular coagulation, renal failure, and acute respiratory distress [7]. Even though skin or mucosal involvement were not reported by the medical team, the patient informed having developed oral ulcers and disseminated skin lesions during course of disease.

Laboratory changes are common in DH and may reveal elevated liver enzymes (especially alkaline phosphatase), increased lactate dehydrogenase, ferritin and pancytopenia, being highly suggestive of disseminated disease. However, none of which are specific for diagnosis [7].

Pulmonary involvement occurs in 50–90% of patients and is characterized by diffuse reticulonodular, interstitial, or millitary infiltrates. In individuals residing in endemic areas, pulmonary nodules seen on chest imaging are common findings, being histoplasmosis an important cause of noncancerous granulomatous nodules and masses [3].

Occasionally, the initial radiograph may be normal.

Many of the manifestations are similar to those of sarcoidosis and a mistake in diagnosis can be disastrous if the patient is treated with immunosuppressive medications, resulting in increased morbidity and mortality [7,13]. In this case, our patient was discharged on corticosteroids under the initial hypothesis of sarcoidosis and, although his initial clinical improvement, he deteriorated on the following days. Therefore, particularly in endemic areas, histoplasmosis must be excluded before treating patients with presumed sarcoidosis since progressive dissemination may occur.

Diagnostic assays are essential to improving the care of patients with advanced disease who are under a higher risk of developing disseminated histoplasmosis. The gold standard for diagnosing histoplasmosis is identification of the pathogen in conventional laboratory tests (culture, histopathology and special stains). Therefore, diagnosis may require invasive medical procedures to obtain tissues [14]. The *Histoplasma* antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), a non-invasive diagnosis method, is particularly useful for the diagnosis of DH and has a high sensitivity using urine samples (95%) [14]. However, its availability is very limited in South and Central America. In Brazil, only 16% of reference centers have access to *Histoplasma* antigen detection [15]. For that reason, diagnosis is usually delayed, as reported in our case. In the absence of antigen detection, diagnosis of histoplasmosis in Latin America typically takes 14–21 days (time for cultures to turn positive) and case-fatality is above 40% [15].

Antifungal therapy is always indicated for disseminated histoplasmosis because untreated disseminated disease is usually fatal. Liposomal amphotericin B 3.0 mg/kg for two weeks is the preferred treatment for severe or moderately severe disease, since a clinical trial demonstrated the benefit of this intervention, in comparison to amphotericin B deoxycholate [16].

4. Conclusion

Although most cases of DH occur in HIV/AIDS patients, it can be present in other immunosuppressive conditions. The authors describe the first case of disseminated histoplasmosis secondary to filariasis-induced lymphopenia. However, in Brazil, diagnosis is challenging due to limited access to diagnostic assays. Antigen detection could improve the diagnostic capacity and improving clinical outcomes, including mortality.

Ethical form

The authors have obtained written and signed consent to publish the case report.

Declaration of competing interest

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