

Disseminated Histoplasmosis Due to *Histoplasma duboisii*: Two Cases at the Treichville University Hospital, Ivory Coast

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Abstract

Introduction: Disseminated histoplasmosis is a neglected tropical disease that is poorly documented in Côte d'Ivoire. The authors report two cases of disseminated African histoplasmosis in HIV-negative local patients residing in Côte d'Ivoire. **Case Report:** The patients were adults aged 46 and 31. Clinical examination revealed inflammatory swelling of the left shoulder in one patient, and left hip pain accompanied by fever and progressive weight loss in the other. Imaging studies showed osteolysis of the humeral head, iliac wings, and sacrum, associated with abscesses in the periarticular muscles and the left iliopsoas muscle. A diagnosis of histoplasmosis was suspected based on positive tests (lateral flow assay and enzyme immunoassay) for *Histoplasma* urinary antigen and direct examination revealing large, thick-walled yeast cells. Culture and genomic sequencing of the recovered strain confirmed the organism to be *Histoplasma capsulatum* var. *duboisii*. Specific treatment was initiated, consisting of intravenous liposomal amphotericin B followed by itraconazole. Clinical outcomes were favorable in both cases. **Conclusion:** These two cases underscore the importance of evaluating histoplasmosis in patients presenting clinical features suggestive of tuberculosis, even when mycobacterial investigations are negative, to reduce diagnostic delay.

Keywords

Disseminated Histoplasmosis, Urinary Antigen Histoplasma, Côte d'Ivoire

1. Introduction

African histoplasmosis is a deep-located fungal infection caused by *Histoplasma capsulatum* var. *duboisii* [1]. Although ubiquitous, with a higher prevalence in West and Central Africa, World Health Organization classifies African histoplasmosis as a neglected tropical disease (NTD) [2] [3]. Indeed, in sub-Saharan Africa, histoplasmosis appears to be substantially underdiagnosed, owing to limited clinician awareness, the marked clinical overlap between its disseminated form and tuberculosis, and constrained diagnostic capacity [4]-[7]. We report two cases of generalized African histoplasmosis observed in the Infectious and Tropical Diseases Department of the University Hospital Center (CHU) of Treichville.

2. Cases Presentation

1) Case 1

Mr. KG, a 46-year-old man with a medical history significant for well-controlled type 2 diabetes mellitus and pulmonary tuberculosis treated 20 years earlier, was admitted for evaluation of an inflammatory swelling of the left shoulder that had been progressing over a three-month period. This presentation occurred in the context of a low-grade fever, without chills or night sweats, and was not accompanied by any other associated symptoms. He had received analgesics and non-steroidal anti-inflammatory drugs, without clinical improvement.

On admission, physical examination showed a patient with an overall good appearance, afebrile with stable hemodynamic parameters. Inspection revealed a diffuse, tense swelling of the left shoulder. Palpation demonstrated increased local warmth and tenderness, associated with painful restriction of shoulder mobility, with pain rated at 6/10 on the numerical rating scale.

In addition, cervical lymph nodes and a mobile, non-tender left axillary lymph node was palpated. Peripheral pulses were preserved, and examination of the remaining systems was unremarkable.

A standard radiograph (**Figure 1**) of the left shoulder (taken one month after the onset of symptoms) showed an irregular and eroded appearance of the inferior glenoid cavity of the scapula. A computed tomography (CT) scan of the left shoulder revealed significant osteolysis of the humeral head and part of the scapula, with areas of hypodensity within the periarticular muscles, suggestive of an abscess (**Figure 2**).

Magnetic resonance imaging (MRI) enabled better characterization of the periarticular shoulder muscle abscesses (**Figure 3**).

Laboratory evaluation showed a normal white blood cell count and normochromic normocytic anemia, with a hemoglobin level of 10.5 g/dL. C-reactive pro-

tein (CRP) was elevated at 46 mg/L. Blood glucose was 1.28 g/L, and glycated hemoglobin (HbA1c) was 8.4%. HIV serology was negative.

Ultrasound-guided aspiration of the abscesses yielded purulent fluid containing more than 2000 leukocytes/mm³, with 92% polymorphonuclear neutrophils.

Standard bacteriological tests, polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* (MTB), and parasitological examination of the fluid sample were negative. Testing for *Histoplasma* urinary antigen was positive with both kits (*Histoplasma* Urine Antigen LFA® and Clarus *Histoplasma* GM EIA®).

As for the mycological examination of the pus, direct examination revealed large yeasts (around 12 µm in diameter) with thick, refractile walls, giving a pseudo-encapsulated appearance suggestive of *Histoplasma capsulatum* var. *duboisii*. The culture of pus specimens was positive, with macroscopic and microscopic examination of the colonies confirming that they were a strain of *Histoplasma* spp. Macroscopically, the colonies were downy and buff-brown in colour. Microscopic examination revealed filaments bearing small spores (2 - 3 µm) and large, round, sometimes pear-shaped (20 µm) chlamydospores with thick, spiny walls.

Furthermore, genome sequencing of the strains confirmed the species as *Histoplasma duboisii*.

Histopathological examination of the osteo-muscular and lymph node tissue fragments demonstrated granulomatous inflammation composed of epithelioid histiocytes and multinucleated giant cells containing yeast-like organisms. These organisms were round to oval and exhibited a thick, refractile capsule, findings suggestive of *Histoplasma capsulatum* var. *duboisii*. A diagnosis of disseminated histoplasmosis (osteoarticular the left shoulder and lymph node) due to *Histoplasma capsulatum* var. *duboisii* was thus made.

The treatment administered consisted of liposomal amphotericin B at a dose of 3 mg/kg/day administered by slow intravenous infusion via syringe pump for 14 days during hospitalization. The initial course was promising, marked by a progressive regression of symptoms until their complete disappearance. This was followed by oral administration of itraconazole 200 mg twice daily for 12 months, resulting in a favorable outcome and the patient's successful return to work and social life.



Figure 1. A standard radiograph of the left shoulder showed an irregular and eroded appearance of the inferior glenoid cavity of the scapula (black arrow).

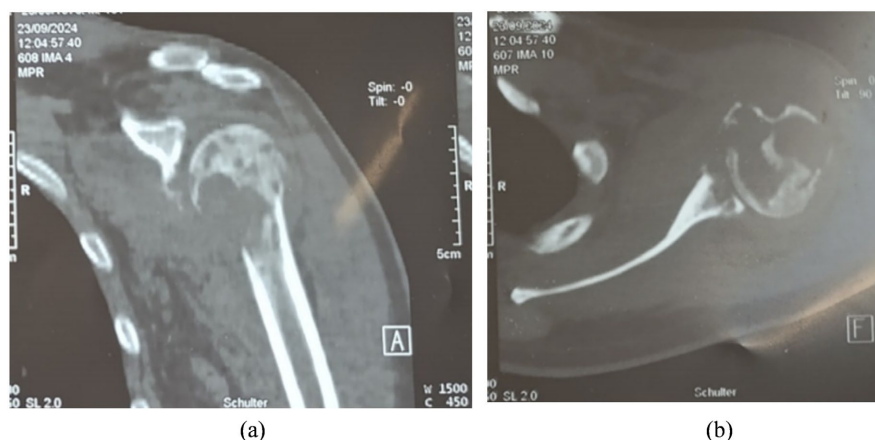


Figure 2. (a) CT scan of the left shoulder, bone window, coronal and (b) axial views: osteolysis of the humeral head (black arrow) and of the glenoid fossa of the scapula (white arrow).

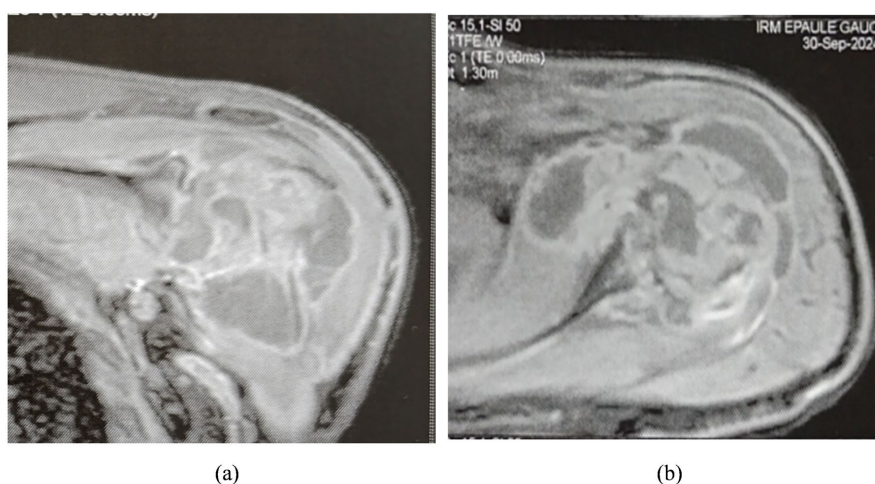


Figure 3. (a) MRI of the left shoulder coronal; (b) axial T1 sequence with gadolinium injection: multiple area of low signal with peripheral enhancement within the periarticular muscles of the left shoulder in favor of an abscess (white star).

2) Case 2

Mr. DD, a 31-year-old man with hemoglobin AC disease was admitted for chronic inflammatory pain of the left hip, associated with fever up to 39°C, deterioration in general condition, and a 20 kg weight loss over a 9-month period. These symptoms were accompanied by multiple firm, painful, inflammatory cutaneous nodules of varying size, adherent to the deep planes, located on the upper limbs and trunk (**Figure 4**).

Physical examination revealed tenderness on palpation of the inguinal regions and left gluteal area, as well as painful restriction of hip mobility, more marked on the left side. Cervical and inguinal lymphadenopathy were also noted.

Laboratory investigations showed marked leukocytosis at 33,810 cells/mm³, predominantly neutrophilic (83%), along with severe microcytic hypochromic anemia (hemoglobin: 6.6 g/dL). HIV serology was negative. Pelvic computed to-

mography demonstrated osteolytic lesions involving the iliac wings and sacrum, associated with abscess formation in the left iliopsoas muscle (Figure 5).

In view of this clinical presentation, the main diagnostic considerations were bifocal tuberculosis with osteoarticular and cutaneous involvement, and hematologic malignancy.

Drainage of these abscesses yielded approximately 800 milliliters of purulent fluid. Various bacteriological tests (standard and PCR for *Mycobacterium tuberculosis*) were performed and were negative. The blood smear and bone marrow aspirate were unremarkable. The lymph node aspirate showed a purulent smear with rare giant cells.

Antituberculosis treatment was initiated, along with corticosteroid therapy. The initial course was favorable (first two months of antituberculosis treatment), marked by the absence of fever, considerable regression of subcutaneous nodules and lymphadenopathy, a decrease in pain, and a weight gain of 7 kg. However, starting in the third month of antituberculosis treatment, a resurgence of symptoms was noted, characterized by an increase in the intensity of hip pain, an increase in the size of the nodules, and a recurrence of fever to 39°C. This resurgence necessitated further investigations, including urine tests for histoplasmosis (*Histoplasma* Urine Antigen LFA® and Clarus *Histoplasma* GM EIA®), which were positive. Mycological examination of the pus and skin specimen revealed large yeasts (around 12 µm in diameter) with thick, refractile walls, giving a pseudo-encapsulated appearance suggestive of *Histoplasma capsulatum* var. *duboisii* in direct examination. In culture of pus specimens, macroscopically, the colonies were downy and buff-brown in colour. Microscopic examination revealed filaments bearing small spores (2 - 3 µm) and large, round, sometimes pear-shaped (20 µm) chlamydospores with thick, spiny walls (Figure 6). Genome sequencing of the strains confirmed the species as *Histoplasma duboisii*. The possibility of tuberculosis was ruled out. The diagnosis of disseminated histoplasmosis (osteoarticular, lymph node and cutaneous), due to *Histoplasma capsulatum* var. *duboisii*, was therefore made.



Figure 4. Skin nodules located on the right forearm (a); the trunk (b); left forearm (c).

The treatment consisted of intravenous administration of liposomal amphotericin B at a dose of 3 mg/kg/day for two weeks as an induction therapy in a hospital setting. Patient DD developed an immuno-allergic reaction including a fever of 38.8°C with chills, urticaria, chest discomfort, tachypnea, and tachycardia. These symptoms occurred during the liposomal amphotericin B infusion. An emergency intravenous injection of 100 mg of hydrocortisone and one gram of paracetamol every 8 hours were administered, which controlled the reaction. After two weeks, oral maintenance therapy with itraconazole, at a dose of 200 mg twice daily, was initiated for 12 months. The clinical course was favorable.



Figure 5. (a) CT scan of the pelvis, bone window; (b) parenchymal window in axial section: osteolysis of the left iliac bone and sacrum (black arrow); hypodense formation within the left iliac muscle suggesting an abscess (white arrow).

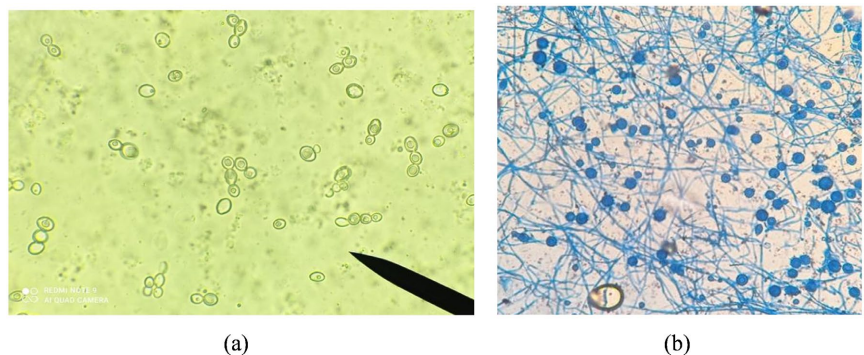


Figure 6. (a) Large, thick-walled yeasts (*Histoplasma capsulatum* var. *duboisii* yeasts (×400); (b) Microscopic appearance in lactophenol blue (×400) with filaments bearing small spores (2 - 3 μm) and large, round, sometimes pear-shaped (20 μm) chlamydospores with thick, spiny walls.

3. Discussion

We report two cases of disseminated histoplasmosis caused by *Histoplasma capsulatum* var. *duboisii* in young HIV-negative indigenous adults. These cases highlight the diagnostic difficulty and prolonged clinical courses often associated with histoplasmosis. Extrapulmonary involvement, particularly affecting the skin, bones, and lymph nodes, is common in African histoplasmosis [8]. Missed diagnostic

opportunities during medical consultations have been reported in 82.9% of cases [9]. In our patients, the diagnosis of histoplasmosis was established only after delays of 3 and 9 months, respectively, during which the second patient had received antituberculosis therapy. These delays are comparable to those described in other studies [9] [10].

The clinical presentation is highly polymorphic and frequently mimics tuberculosis. In one series, 80 cases of fungal infection were initially misdiagnosed as tuberculosis because of overlapping manifestations, including fever, asthenia, night sweats, abdominal pain, abdominal distension, cutaneous lesions, lymphadenopathy, hepatomegaly, and splenomegaly [8].

The most frequent symptoms were abscessed lesions, lymphadenopathy, and osteoarticular infections. Our two patients were not infected with HIV. Oladele *et al.* noted that over the past six decades, out of 470 cases of Histoplasmosis, 62% were HIV negative in Africa [11].

A definitive diagnosis was achieved using the rapid and non-invasive urine histoplasma test. The rapid urine antigen (LFA) test used in our patients was the “*Histoplasma* Urine Antigen, LFA” test (MiraVista Diagnostics, Indianapolis, USA) (reported sensitivity and specificity: 93.18% and 96.97%, respectively). Bansal *et al.* noted that the *histoplasma* antigen test tripled the diagnosis of histoplasmosis [12]. These two observations clearly illustrate the value of urine *Histoplasma* antigen tests, which allowed for the suspicion of histoplasmosis. Indeed, clinician training in the diagnosis of histoplasmosis, coupled with the introduction of antigen tests, has led to a sevenfold increase in the diagnosis of this disease in certain regions of Colombia [13]. The widespread availability of these urine tests in our work setting will allow clinicians to refine their management and reduce diagnostic errors. *Histoplasma* antigen is present in the urine of approximately 90% of patients and in the serum of approximately 80% of patients [14]. Histopathology confirmed the diagnosis of histoplasmosis due to *Histoplasma capsulatum* var. *duboisii* in our two cases. Histopathology is the predominant diagnostic method in 87.9% of cases [1].

Treatment is medical and relies on antifungals. Liposomal amphotericin B and itraconazole are the best therapeutic options for managing histoplasmosis. Fungal clearance is achieved more rapidly with liposomal amphotericin B compared to itraconazole in the treatment of histoplasmosis [15], therefore liposomal amphotericin B is recommended in severe forms of histoplasmosis [16]. The initial strategy involves administering liposomal amphotericin B at a dosage of 3 mg/kg/day as a 2-hour intravenous infusion using a syringe pump for two weeks.

Our two patients benefited from this liposomal amphotericin B induction protocol for treatment.

One patient developed an immuno-allergic reaction following administration of liposomal amphotericin B. Indeed, parenteral administration of this product can cause immediate reactions (shock, hypothermia, with chills) [17]. Better tolerance of this drug requires the intravenous administration of acetylsalicylic acid

and corticosteroids.

This treatment was well tolerated in the second patient, and clinical improvement was observed in both cases. Oral itraconazole, at a dose of 200 mg twice daily, was subsequently administered for 12 months [18]. Both patients had a favorable outcome, with complete clinical recovery and return to work.

4. Conclusions

African histoplasmosis remains a poorly understood and underdiagnosed mycosis in our setting. Its broad clinical spectrum, combined with limited access to appropriate diagnostic modalities, frequently delays accurate diagnosis and optimal management. The nonspecific nature of its clinical presentation makes differentiation from tuberculosis particularly challenging.

Management relies primarily on antifungal therapy, the accessibility and availability of which should constitute a public health priority.

It is therefore essential to improve recognition of this disease in order to enhance understanding of its diagnostic features and ensure early, appropriate treatment. The development and wider implementation of rapid diagnostic tools in the African context could substantially contribute to this objective.

Ethical Consideration

The patients gave their consent for the writing and publication of the study.

Informed Consent

Informed consent was obtained from the patients for the publication of the case study details.

Author Contributions

All the authors participated intellectually in the preparation and revision of the manuscript before its submission.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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