Our Dermatology Online

Case Report

Acute cutaneous disseminated histoplasmosis and secondary syphilis as an initial presentation in an HIV patient

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ABSTRACT

Herein, we report a case of cutaneous disseminated histoplasmosis associated with secondary syphilis in a 32-year-old male with a history of progressive weight loss of 30 kgs and HIV diagnosis for five months. He presented with a generalized dermatosis with a predominance on the face, trunk, and upper limbs, consisting of multiple papules, nodules, and plaques of 1 month of evolution. During the diagnostic approach, viral load above 400,000 copies/ml, CD4 count of only 1 cell/μL, and histopathological features of histoplasmosis along with disseminated disease, in addition to a positive PCR test for syphilis. The treatment for syphilis was penicillin G-benzathine for three weeks and, for histoplasmosis, amphotericin B for twenty-one days and itraconazole for one year. The patient was considered clinically and microbiologically cured of both conditions.

Key words: Acquired immunodeficiency syndrome, Human immunodeficiency virus, *Histoplasma capsulatum*, *Treponema pallidum*, Cutaneous disseminated histoplasmosis, Secondary syphilis

INTRODUCTION

Histoplasmosis is a systemic fungal infection caused by a dimorphic fungi *Histoplasma capsulatum* that occurs primarily in immunocompetent and immunocompromised patients. In patients with acquired immunodeficiency syndrome (AIDS), histoplasmosis is the most common endemic mycosis and is an AIDS-defining disease and a leading cause of death in people living with HIV/AIDS, with mortality rates ranging from 13% to 48% [1,2].

Histoplasmosis may be asymptomatic or may cause self-limiting flu-like symptoms or pneumonia in immunocompetent individuals. Although, under immunosuppressive conditions such as AIDS patients, it occurs as acute progressive disseminated histoplasmosis or severe pneumonia. Most cutaneous disseminated cases do not have obvious pulmonary involvement, yet it is believed that they may spread to the skin from an initial pneumonic focus. It is important to note that there are no pathognomonic lesions due to the polymorphic nature of cutaneous histoplasmosis, which usually occur on the face and neck, yet may occur in any clinical topography, including palms and soles, as well as in all mucous membranes (oral, anal, and genital) [1,3]. The dissemination of the disease to various organs and systems, such as the heart, adrenal glands, eyes, meninges, has been reported. Most cases are fatal, especially those associated with AIDS [3,4].

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Herein, we present a case of cutaneous disseminated histoplasmosis (CDH) and secondary syphilis in an immunocompromised patient with a recent diagnosis of HIV.

CASE REPORT

A 32-year-old male presented with a generalized dermatosis predominantly on the face, trunk, and upper limbs, consisting of multiple papules, nodules, and plaques of 1 month's evolution. On interrogation, the patient reported progressive weight loss of 30 kg and an HIV diagnosis five months previously on antiretroviral therapy (ART) with Triumeq (Dolutegravir, Abacavir, Lamivudine).

A dermatological examination revealed a generalized dermatosis with the involvement of the palms and soles, consisting of multiple papules, nodules, and erythematous plaques with scaling on the surface, some ulcerated or with central umbilication, some with a warty appearance and some with necrotic areas and crusts on the surface (Fig. 1).

The rest of the physical examination revealed whitish plaques compatible with oral candidiasis in the oral cavity adhering to the hard palate and 2 cm of hepatomegaly and splenomegaly in the abdomen, without other relevant findings.

The clinical diagnosis of CDH was suspected based on the cutaneous findings and complementary studies were requested. The hemogram revealed pancytopenia (normocytic anemia, normochromic WHO grade III (Hb: 6.10 g/dL), leukopenia at the expense of lymphopenia (0.3 thousands/µL), and thrombocytopenia (146000/µL). He also had hypoalbuminemia (1.6g/dL), elevated liver enzymes (serum glutamic-oxaloacetic transaminase: 172 units/L, serum glutamic-pyruvic transaminase: 134 units/L), and elevated alkaline phosphatase: 307 units/L. Viral load resulted with 479,063 copies/mL and CD4 T lymphocyte count with only 1 cell/µL. Acute phase reactants were elevated (ESR 73 mm/hr, CRP 12.99 mg/dL). A simple chest CT scan was performed, which highlighted a ground glass nodule in the peripheral field of the right lower lobe and a left basal consolidation.

Multiple cultures and stains were performed in search of fungi and mycobacteria (members of the *Mycobacterium tuberculosis* complex and non-tuberculosis *Mycobacteria*) in different tissues and

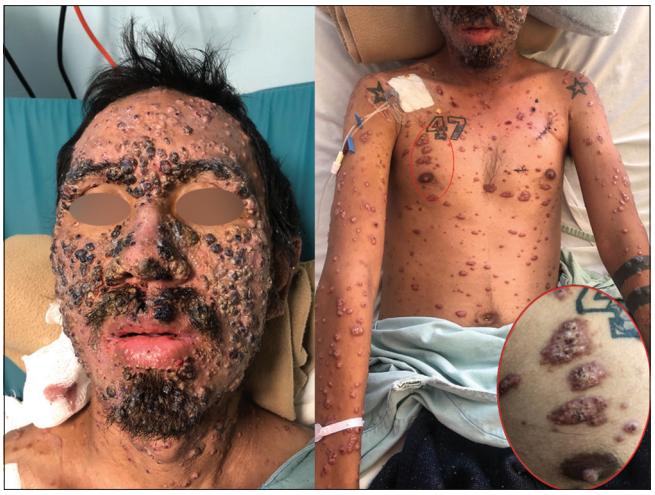

Figure 1: Left: Nodules and papules, some umbilicated and others with crusts and/or necrosis in a patient with CDH & secondary syphilis. Right: Multiple erythematous nodules and plaques, some umbilicated and others with crusts and scales located on the anterior and posterior thorax and arms.

secretions, among which only the urinary antigen for *Histoplasma* was positive (greater than 15 ng/m). Intracellular yeasts were also observed in a smear taken directly from the skin nodule by Wright staining. PCR for *Treponema pallidum* in the blood was also found to be positive.

A skin biopsy report showed that, in the cytoplasm of histiocytes and giant cells, yeast structures with capsule-like reinforcement and peripheral clear spaces were identified (Fig. 2). Therefore, the diagnosis of HCD and secondary syphilis was established.

The patient received initial antifungal treatment with amphotericin B deoxycholate 1.0 mg/kg/day for fourteen days and maintenance with itraconazole 200 mg three times a day for three days and then 200 mg twice a day for one year. Penicillin G benzathine 2,400,000 IU IM was administered weekly for three weeks to treat syphilis. The lesions disappeared completely one year after treatment (Fig. 3). The patient was considered clinically and microbiologically cured of both conditions.

DISCUSSION

With the increasing number of patients with AIDS, a number of unusual clinical manifestations are being observed, and it is important to be aware of them. Immunocompromised patients with disseminated histoplasmosis usually present with other symptoms such as fever, fatigue, anorexia, and weight loss and

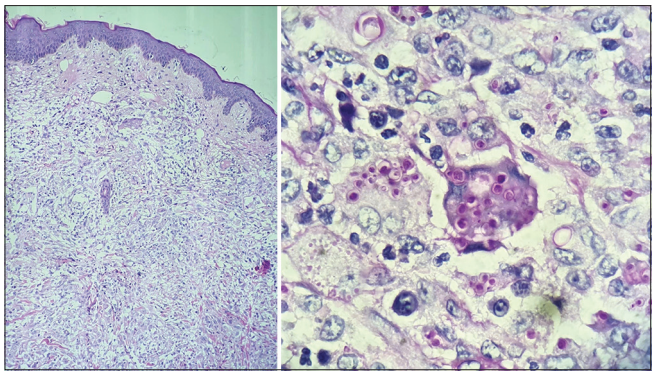

Figure 2: Skin biopsies. Left: Panoramic: Dense granulomatous chronic inflammatory infiltrate consisting of lymphocytes, plasma cells, histiocytes, and giant cells multinucleated (H&E, 10x). In the granulomatous process with histiocytes and giant cells, yeast cells with capsule-like reinforcement (PAS, 80x).

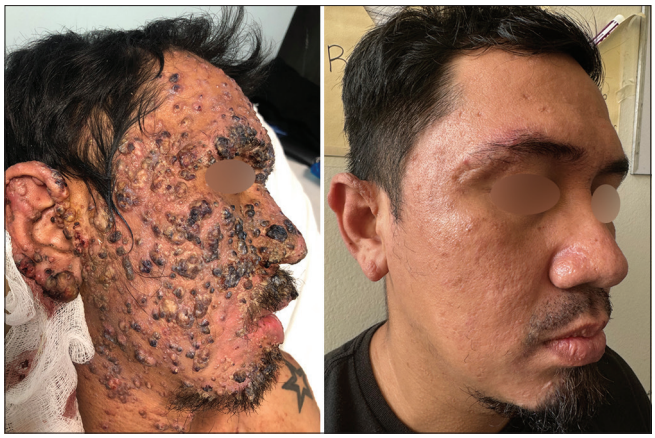

Figure 3: Left: Basal process with nodular and papular lesions on the face. Right: Resolution of lesions after one year of treatment.

even with such an overwhelming infection manifested by shock and multiple organ failure [1]. Physical examination demonstrates hepatosplenomegaly and diffuse lymphadenopathy in half of the patients [5].

The cutaneous lesions of histoplasmosis are non-specific and highly polymorphic, making diagnosis by physical examination virtually impossible. Immunosuppressed patients, including HIV-infected patients, may present with mucocutaneous ulcers or erosions, as well as multiple erythematous papules or nodules with desquamation or crusting, or some may even present with a mollusk-like appearance or necrotic areas. Other manifestations may include abscesses, ulcers, cellulitis, purpuric lesions, and panniculitis, including palmo-plantar lesions (also common in secondary syphilis) [3,6,7].

On the other hand, malignant syphilis is an uncommon form of secondary syphilis associated with HIV infection. The clinical presentation is characterized by necrotic nodules and generalized ulcerated lesions similar to those of histoplasmosis [8]. Thus, although the biopsy diagnosis is compatible with histoplasmosis, it cannot be excluded that some of the dermatologic lesions present in the patient were also due to syphilis [9]. Therefore, in our patient, the lesions of both diseases could coexist.

According to a study on patients living with HIV in Europe, 38.5% of the patients with histoplasmosis had a concomitant opportunistic infection, the most common being invasive candidiasis, *Pneumocystis jirovecii* pneumonia, and mycobacterial infection, and only one patient was found with syphilis [4].

General laboratory studies may reveal pancytopenia and elevated liver enzymes and markers of inflammation, including ESR, C-reactive protein, and ferritin [5]. Adequate diagnosis for histoplasmosis includes culture, biopsy, tissue histochemical stains, body fluid aspiration cytology smears, and antigen and antibody testing (serology). Culture is the gold standard for diagnosis, yet it takes days or even weeks to test positive and is, therefore, impractical as a criterion for initiating treatment [2,3,10].

However, in acute or progressive CDH in AIDS, because of the high fungal burden, blood culture and antigen testing are highly positive (95% and 86%, respectively) and serology is low (83% in immunosuppressed patients compared to 100% in non-immunosuppressed patients) [2,3].

Antigen detection tests have higher performance in diagnosing disseminated histoplasmosis in people living with HIV, with a sensitivity of 95% and a specificity of 97%. Antibody testing had a specificity of 100% and a sensitivity of 58%, probably because these individuals are highly immunosuppressed. Molecular testing by DNA detection has shown high diagnostic accuracy (sensitivity of 95%, specificity of 99%), yet the limitation is the lack of cost-effectiveness [10].

In patients with HIV/AIDS, it may be clinically simulated by deep fungal infections (Cryptococosis, *Talaromycosis-marneffei*, coccidioidomycosis, leishmaniasis and pneumocystosis), so it is important to differentiate it early to initiate targeted treatment. It is usually associated with advanced immunosuppression in AIDS, with CD4 counts less than 150 cells/µL [2]. It is important to highlight that our case had a viral load

of almost 480 thousand copies and one CD4, which implies a state of severe immunosuppression, and that explains the reason for the widespread development of both diseases.

In terms of treatment, severe disease should be treated with 1–2 weeks of induction therapy with liposomal amphotericin B, followed by itraconazole monotherapy for 12 months [10]. The liposomal amphotericin B is preferred to deoxycholate because it has been shown to have higher response rates (88% vs. 64%) and to be associated with fewer side effects. The standard dose of liposomal amphotericin B is 3 mg/kg/day, with a range of 3–5 mg/kg/day, for two weeks, and upon completion of the initial amphotericin B therapy, patients should be placed on oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily) for a total of at least twelve months [11-13]. The patient was treated according to the latest treatment guidelines and showed adequate clinical evolution.

Relapse rates may be as high as 90% in those who do not receive maintenance therapy. Relapse most commonly occurs 6 to 18 months after the discontinuation of induction therapy [12,14].

Conditions for discontinuing itraconazole therapy in AIDS patients with disseminated histoplasmosis on antiretroviral therapy include the following: patient has completed at least 12 months of itraconazole, fungal blood cultures are negative, serum and urine antigen levels are less than 4 U/mL (less than 2 ng/mL in recent studies), CD4 count is greater than 150 cells/mm [5,11-13].

CONCLUSION

The cutaneous manifestations of CDH are highly variable and even more so when they are associated with syphilitic secondary symptoms. In this case, we emphasize dermatological lesions that may not be characteristic of the disease. However, we must analyze the clinical context of the patient and suspect it early, since there are multiple differential diagnoses to which patients with HIV and a low CD4 count are susceptible. This case was an excellent example of the first manifestations in the debut of HIV-AIDS. They may be associated with various infections such as histoplasmosis (common in tropical areas), syphilis, and other sexually transmitted infections.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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