Case Report

Primary Cutaneous Coccidioidomycosis in a Human Immunodeficiency Virus-Positive Patient: Case Report and Literature Review

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Abstract

Coccidioidomycosis is a recognized opportunistic infection among persons infected with human immunodeficiency virus (HIV). Compared with immunocompetent persons, HIV-infected patients are at risk of symptomatic and progressive disease since the control of coccidioidal infection requires intact cellular immune function. We report a case of a 28-year-old HIV positive woman, who presented with 3 months' history of widespread pruritic hyperpigmented nodular skin lesions. The histopathological evaluation of excisional biopsy was consistent with cutaneous coccidioidomycosis. Chest X-ray showed no lesion in the lung. Abdominopelvic ultrasound revealed no abnormality. The patient had end-stage HIV disease (AIDS) with CD4 lymphocyte cell count of 66 cells/μL, and HIV-1 RNA viral load of 128,763 copies/ml. Even though up to 50% of patients with coccidioidomycosis could develop cutaneous involvement, this tends to occur following pulmonary and or systemic disease. Primary cutaneous coccidioidomycosis is rare, and this possibility should be considered in the evaluation of HIV-positive patients, even in nonendemic areas of the world.

Keywords: *Coccidioides*, cutaneous coccidioidomycosis, human immunodeficiency virus infection

Introduction

Coccidioidomycosis is a systemic fungal infection caused by two species: *Coccidioides immitis* and *Coccidioides posadasii*.[1] It is endemic in the Western hemisphere, particularly between the 40° latitudes North and South. It is almost exclusively prevalent in the semiarid to arid life zones of the Southwestern United States, North of Mexico, and in Central and South America.[2] Primary pulmonary involvement, usually acquired through inhalation of arthroconidia is the most common form of coccidioidomycosis. In the general population, up to 60% of cases of pulmonary coccidioidomycosis are asymptomatic, and the remaining 40% are symptomatic, and often present with pulmonary with or without systemic manifestations.[3] About 1% of infected persons develop disseminated disease, which can involve the skin, joints, bones, central nervous system, or other organs.[3,4] Human immunodeficiency virus (HIV)-infected patients are at increased risk of disseminated infection and dissemination has been shown to be due to a defect in T-cell function.[5] A prospective study conducted in 1988 at an HIV clinic in a coccidioidal endemic region indicates a cumulative incidence of active coccidioidomycosis of 25% during 41 months of follow-up, corresponding to an annual incidence of 7.3%.[6] In contrast, a retrospective review at the same clinic during antiretroviral therapy (ART) era from 2003 to 2008 showed an annual incidence of only 0.9%, and a decrease in the severity of disease compared to the previous study.[7] Studies in HIV patients have also demonstrated a high proportion of patients with pulmonary involvement, often with bilateral lung lesions, and a high mortality rate of 40%–80%, suggesting coccidioidomycosis as an opportunistic fungal infection.[6-8] Cutaneous coccidioidomycosis in the form of a nonpruritic papular rash, erythema nodosum, and erythema multiforme have been documented in 50% of symptomatic pulmonary infection.[9] However, primary cutaneous coccidioidomycosis

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without pulmonary or systemic involvement is extremely rare, with fewer than 26 cases reported in the literature since 1926 to date.[10-12] The primary cutaneous disease results from direct traumatic inoculation of the organism into the skin from an external source.[12] Cutaneous lesions due to coccidioidomycosis include papules, nodules, gummas, pustular acneiform, ulcerated and verrucous plaques, scars, abscesses, and fistulae.[9-12] HIV-infected patients are at an increased risk of wide spectrum of dermatosis due to qualitative and quantitative defects in cellular immunity.[8,13] Distinguishing cutaneous coccidioidomycosis from the myriad of other HIV-related dermatological manifestations can be a herculean task, and may therefore pose diagnostic challenges especially when a patient is seen outside the endemic regions of the world.[4,9,14] We report this case of primary cutaneous coccidioidomycosis, and review the existing literature.

Case Report

We present a 28-year-old HIV-positive woman who had been on ART with Zidovudine (AZT), Lamivudine (3TC), and Nevirapine for 5 years. She presented with 3 months' history of widespread hyperpigmented nodular skin lesions of various sizes as depicted in Figures 1a, 2a and 3a. It was associated with pruritus, low-grade pyrexia, anorexia, and progressive weight loss but she had no associated cough or difficulty in breathing. She is a resident of Northeastern Nigeria and had no travel history significant for possible exposure to coccidioidomycosis. She was evaluated for possible HIV-associated dermatoses. Her hemoglobin concentration was 10.6 g/dl; erythrocyte sedimentation rate was 64 mm/h, CD4T lymphocyte cell count was 66 cells/μL and HIV-1 RNA viral load of 128763 copies/mL despite good compliance with ART. Her chest radiography was essentially normal without any focal lesions. Renal and liver function tests were essentially within normal limits. Histopathology of biopsied representative lesion from the skin showed numerous *Coccidioides* spherules as shown in Figure 4a and b, consistent with cutaneous coccidioidomycosis. Her ART was switched to second-line medications, AZT, 3TC/Tenofovir (3TC/TDF) and Atazanavir/Ritonavir. Oral fluconazole at a dose of 200 mg twice daily for 6 months resulted in resolution of the lesions as shown in Figures 1b, 2b and 3b. We describe a case of primary cutaneous coccidioidomycosis in a patient with AIDS and without prior pulmonary or systemic involvement by disease.

Figure 1: Facial lesion (a) before therapy, (b) after therapy

Discussion

Cutaneous coccidioidomycosis is associated with a variety of clinical manifestations. Skin manifestations can be seen in different scenarios of coccidioidal infection: (1) part of the acute pulmonary infection, "acute pulmonary exanthema;" (2) disseminated infection (secondary cutaneous infection); or, in rare occasions, (3) primary infection due to direct inoculation as primary cutaneous infection, as in this case.[9,15]

In immunocompetent individuals, almost two-third of cases are asymptomatic; the remaining one-third presents with either a self-limited pulmonary syndrome that resembles community-acquired pneumonia, chronic progressive pulmonary coccidioidomycosis or disseminated disease beyond the thoracic cavity.[15] Conversely, HIV-infected patients are at risk of symptomatic disease as the control of coccidioidal infection depends on a specific cellular immune response.[7] Reports from coccidioidomycosis endemic region showed an increase in the incidence of symptomatic diseases among persons infected with HIV-1 in the early period of the HIV pandemic.[6] The introduction of potent ART has significantly reduced the incidence of symptomatic coccidioidomycosis in HIV-infected patients.[7] Several published case studies have described the clinical manifestations of coccidioidomycosis in patients with HIV infection.[6-8,13] A study has established factors associated with the development of symptomatic coccidioidomycosis in a cohort of HIV patients. The factors include blood CD4 lymphocyte count <250 cells/μl and a diagnosis of AIDS.[13] Specific *in vitro* cellular responsiveness to coccidioidal antigen is lost when the CD4 cell count drops to <250 cells/μL.[5,8,13] The association between HIV infection and symptomatic coccidioidal disease suggests the need to consider coccidioidomycosis regardless of the

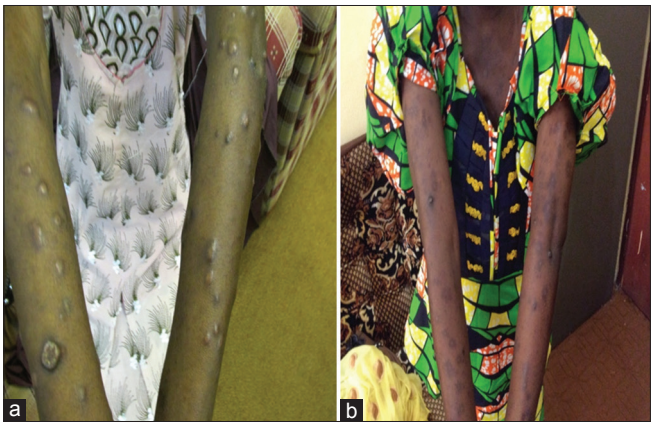

Figure 2: Lesions on the upper limb, (a) before therapy (b) after therapy

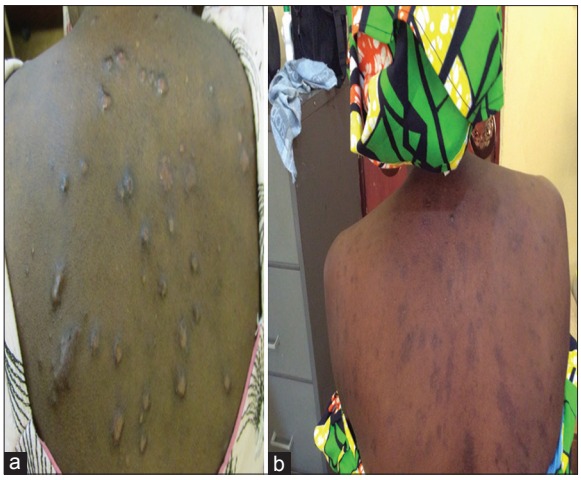

Figure 3: Lesions on the back (a) before therapy (b) after therapy

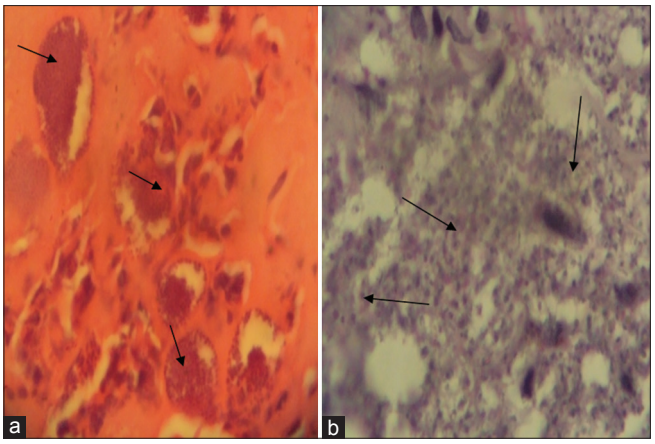

Figure 4: Photomicrograph of coccidioidomycosis showing (a) intact spherules, as shown by arrows (H and E, ×200), (b) numerous coccidioides spherule (arrows) (PAS, ×400)

geographic locale of any immunosuppressed HIV-infected patient presenting with the compatible syndrome. Other factors responsible for increased incidence among both the immunocompromised and immunocompetent population include a growing population, migration of susceptible people to endemic areas, increased longevity, soil disturbance due to construction work and businesses, and climate changes.[2,3,15]

The mainstay of diagnosis for coccidioidomycosis is serologic testing, histopathological identification, and culture. Isolation of the fungus or histological identification from tissues or clinical specimen remains the gold standard for establishing the diagnosis of coccidioidomycosis.[16] Serologic testing is less reliable for patients with HIV infection than for immunocompetent patients. Two previous studies reported sensitivity of serologic test for detecting coccidioidomycosis of 68% and 74%, respectively.[17,18] The finding indicates that serologic test is a valuable screening tool for coccidioidomycosis, but it is not very sensitive.[17,18] *Coccidioides* species can also be detected in tissue or clinical samples using a variety of standard histochemical staining techniques, including the hematoxylin and eosin stain. Staining methods, such as periodic– acid Schiff, Papanicolaou, and Gomori methenamine stains, are useful for rapid detection of *Coccidioides* species in the cytology of respiratory secretions.[19] However, such stains are only positive in ~40% of cases that are confirmed by culture.[20] Papanicolaou and Gomori methenamine stains have been shown to be more sensitive in detecting fungi from clinical specimen than the traditional potassium hydroxide stain.[20] The diagnosis could also be established by culture of clinical samples obtained from suspected coccidioidal infection. Unlike other pathogenic fungi, *Coccidioides* is frequently isolated from infected samples within 5 days, even when plated onto routine bacteriologic culture medium and incubated at 37°C.

Formulating treatment guidelines for each clinical manifestation of coccidioidomycosis in patients with HIV infection remains a herculean task due to paucity of controlled trials and profound variability in treatment outcome.[19,20] Evidence indicates the superiority of the use of a combination of an azole antifungal and amphotericin B, in patients without impairment of renal function despite theoretical concerns that amphotericin B could be nephrotoxic and antagonistic to antifungal activity.[21] HIV-infected patients with symptomatic coccidioidomycosis should be offered antifungal therapy. Amphotericin B or the newer lipid formulations of amphotericin has been shown to be effective for serious coccidioidal infection, despite safety concerns about their nephrotoxicity. The administration of amphotericin B through continuous infusion is associated with reduced renal toxicity than bolus intravenous route.[22] The intravenous amphotericin B therapy can be administered daily at the dose of 0.25–0.5 mg/kg body weight in 500 ml of water with 5% dextrose and infused over a 2-h period. Amphotericin B medication is then discontinued after 500–1000 mg has been administered, and triazole therapy can be continued alone.[22,23] A placebo-controlled study that included HIV-infected patients compared fluconazole to itraconazole and found that itraconazole was slightly superior, particularly regarding bone and joint disease.[24] Reports have also demonstrated efficacy with voriconazole when other therapies have failed.[25] Although there are several potential interactions between antifungal agents and ART, no dosage adjustment is usually required. Neither fluconazole nor voriconazole appears to affect or be affected by concomitant HIV protease inhibitor therapy.[26,27] However, levels of itraconazole (but not its metabolite hydroxyitraconazole) are increased when administered with the combination HIV protease inhibitor lopinavir/ritonavir,[28] and a reduced dosage may be used. Tenofovir has been associated with reduced renal function;[29] it should be used with caution in patients also receiving amphotericin B. Because the critical factor in the control of coccidioidomycosis is cellular immune function, the institution of effective ART should be done contemporaneously with the initiation of antifungal therapy, if possible.[21] For those with disseminated disease, prolonged and even life-long antifungal therapy is the rule. The presentation, management, and outcome of coccidioidal meningitis in persons with HIV infection are not different from those for persons without

HIV infection.[24,25] However, meningitis is distinct from other forms of coccidioidal infection. First, it does not respond to intravenous amphotericin B. Because of this, therapy must include a triazole antifungal. Failure of triazole therapy may necessitate the initiation of intrathecal amphotericin B therapy.[20-22] Previous case–control study suggests that HIV-infected patients with oropharyngeal candidiasis treated with fluconazole residing in the coccidioidal endemic zone had a slightly reduced risk of developing coccidioidomycosis.[25,30]

Conclusion

We report a case of primary cutaneous coccidioidomycosis, a rare form of the disease without pulmonary involvement in an HIV-positive patient. High index of suspicion and appropriate evaluation of cutaneous lesions in HIV patients is necessary for early diagnosis and institution of specific treatment.

Recommendation

Cutaneous coccidioidomycosis should be considered, regardless of the geographic locale of any immunosuppressed HIV-infected patient presenting with the compatible syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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