

Immune Reconstitution Inflammatory Syndrome: Cutaneous and Bone Histoplasmosis Mimicking Leprosy after Treatment

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Abstract

We present a case of disseminated histoplasmosis in a 12-year-old HIV infected boy. This is a rare presentation of *Histoplasma capsulatum* var. *capsulatum* which presented as Immune Reconstitution Inflammatory Syndrome with osteoarticular involvement. He was treated with fluconazole for five years and healed with shortening of all the digits.

Keywords: Cutaneous histoplasmosis; Immune reconstitution inflammatory syndrome; Bone

Introduction

Histoplasmosis is caused by *Histoplasma capsulatum*. It is a mycosis endemic to certain areas of America, Africa and Asia [1]. *Histoplasma capsulatum* var *duboisii* is the species that causes African histoplasmosis, which is endemic in sub-Saharan Africa. It is estimated that 95% of *Histoplasma capsulatum* infections are asymptomatic [2] and those that are symptomatic present with non-specific clinical features [2]. *Histoplasma capsulatum* has emerged as an important opportunistic infection among Human Immunodeficiency Virus (HIV) infected patients in endemic areas. Wheat et al. [3] reported that, there was a rising incidence of disseminated histoplasmosis among AIDS patients in endemic areas after a 5-year follow-up.

Case Report

A 12-year-old boy was previously treated in another hospital for persistent spiking fever and cough for one month. He had slightly painful swollen joints and hyperpigmented nodules on the face and on the lower limbs. He was treated for pulmonary tuberculosis and juvenile rheumatoid arthritis without any improvement and was referred to our hospital. He presented with persistent fever, chills, and headache. An Enzyme Linked Immunoassay test for HIV was positive with a CD4 count of 3/mm³. He was started on stavudine, lamivudine and efavirenz and continued with anti-tuberculosis treatment. After six weeks, he was re-admitted with persistent fever of 39°C and severe wasting. The joint swelling and pain had worsened bilaterally especially on the wrists and the proximal and distal inter-phalangeal joints. The skin lesions had also worsened with widespread involvement of the face extending to the scalp. The trunk, the lower and the upper limbs were also affected. Morphologically, the lesions were elevated, umbilicated nodules and hyperpigmented plaques on the back and the right leg. There were no respiratory symptoms and chest X-ray was normal. The full blood picture showed Hemoglobin 12.7 g/dl, Platelets 376,000/mm³, leucocytes 3780/mm³. The liver and the kidney function tests were within normal ranges. Blood slide for malarial parasites was negative, X-ray of the hands and the elbows showed soft tissue swelling, shortening and broadening of the digits with osteolytic changes involving metaphysis and epiphysis of the phalanges and the distal radius and ulna (Figure 1). Coarse trabeculations were also noted in the carpal bones. X-ray of the elbow showed severe narrowing of the joint space with periarticular lytic changes.

A biopsy of the skin lesions showed diffuse infiltrate mainly of

macrophages, few polymorphs and presence of small, round basophilic cytoplasmic organelles with surrounding halo (Figure 2) which was highlighted by methenamine silver stain (Figure 3) diagnostic of *Histoplasma capsulatum* var. *capsulatum*. The CD4 count increased to 484/mm³ within three months. The final diagnosis was a Disseminated Histoplasmosis presenting as an Immune Reconstitution Inflammatory Syndrome (IRIS).

He was started on Itraconazole (100 mg daily), while continuing with antiretroviral therapy. A rapid response was noted within one month with reduced fever, reduction of skin lesions and joint swelling and minimal pain. After six weeks his treatment was stopped by his family and he reappeared at the clinic after two months with worsening of the skin lesions and increased joint swelling. Fluconazole (200 mg daily) was commenced with good clinical improvement.

A follow-up over 5 years showed a stable CD4 above 600/mm³,



Figure 1: X-ray of the hands showing osteolytic lesions and destruction of epiphyseal plates.

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Received May 09, 2012; Accepted June 07, 2012; Published June 11, 2012

Citation: Kiprono SK, Masenga JE, Philemon RN, Chaula BM, Naafs B (2012) Immune Reconstitution Inflammatory Syndrome: Cutaneous and Bone Histoplasmosis Mimicking Leprosy after Treatment. J Clin Exp Dermatol Res 3:145. doi:10.4172/2155-9554.1000145

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softening of nodules (Figure 4) and depression of the skin lesions with anetoderma-like features, shortening of all the digits (Figures 5,6) and deformity of the elbows joints.

An X-ray of the hands showed widening and shortening of the bones, normal joint spaces and no osteolytic lesions. Biopsy of the anetoderma-like lesions showed no active infiltration and the culture was negative. Fluconazole was stopped and no clinical features of relapse were noticed at six months follow-up.

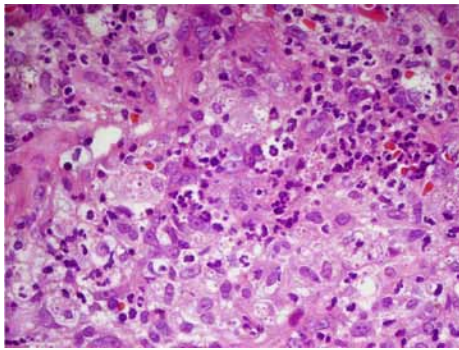


Figure 2: Hematoxylin and eosin stain (X20) of skin biopsy showing suppurative granulomatous infiltrate with intra-cytoplasmic basophilic granules with surrounding halo without Giant cells.

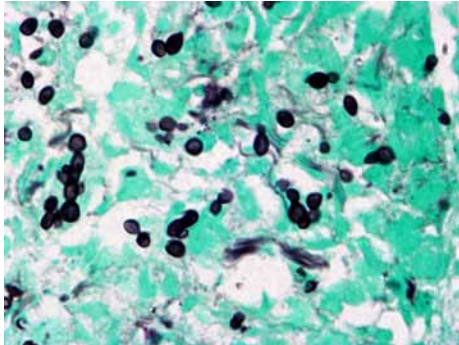


Figure 3: Skin biopsy showing the intra-cytoplasmic granules staining positive with methenamine silver stain (X40).



Figure 4: Umbilicated soft nodular lesions on the chin of the 18years boy after 6years of Fluconazole treatment.



Figure 5: Soft, shorter and thicker fingers without loss of sensation after treatment for Histoplasmosis.



Figure 6: Shortening of the toes which is more pronounced on the big toes after treatment for Histoplasmosis.

Discussion

Histoplasma capsulatum is a dimorphic fungus that usually parasitizes the reticuloendothelial system, thereby involving many organs such as the spleen, the kidney, the central nervous system (CNS) and the skin [3]. Histoplasmosis is mainly acquired through inhalation whereby the lungs are frequently affected. Most individuals with histoplasmosis are asymptomatic. Those who develop clinical manifestations are usually immunocompromised or were exposed to an unusually large inoculum. *Histoplasma* infection may remain latent, but further dissemination may occur with impaired cell-mediated immunity. Clinically histoplasmosis is subdivided into five forms; acute pulmonary, acute disseminated, chronic pulmonary, chronic disseminated and primary cutaneous [4].

Chronic disseminated histoplasmosis caused by *Histoplasma capsulatum* var. *capsulatum* is the most common type among AIDS patients. The disseminated form presents with constitutional symptoms, which include fever, cough, weight loss, malaise, and dyspnea [3]. A highly variable presentation is noted due to the multiple organ involvement.

Among patients with chronic disseminated histoplasmosis, cutaneous lesions are relatively rare and if they are present they indicate a severely disseminated disease. It was estimated that only 6% of the patients with disseminated histoplasmosis will have cutaneous involvement [3-5]. The clinical presentation of the cutaneous histoplasmosis is highly variable and there are no pathognomonic features of this disease. The clinical manifestations usually include nodules, papules, and ulcerations.

This patient's disease is peculiar because of the joint and the bone

involvement. There are only a few case reports of histoplasmosis involving the joints reported in English literature [6-8]. Simon et al. [9] reported a case of African histoplasmosis caused by *Histoplasma capsulatum* var. *duboisii* with multiple osteoarticular lesions and lymphadenopathy in an immunocompetent African patient. Bone histoplasmosis presents with destructive lesions observed in X-ray [10], which clinically resemble rheumatoid arthritis. *Histoplasma capsulatum* var. *duboisii* infections usually settle in the metaphyses of the long bones, the small bones of the hand and the flat bones. The earliest lesion is a small lytic area, which may resemble lesions of multiple myeloma or skeletal metastases. Similar osteoarticular features was seen in this case, however this was *Histoplasma capsulatum* var. *capsulatum*. To our knowledge, this is the first case of *Histoplasma capsulatum* var. *capsulatum* described with multiple bone and joint involvement resulting in an early closure of the epiphyseal plates and therefore, shortening of the digits due to impaired growth. Despite an extensive disease, the chest X-ray was normal, a feature which has been observed in 40-50% of the disseminated histoplasmosis infection in immunocompromised patients [11].

Successful treatment of HIV-infected patients with antiretroviral therapy can induce the IRIS [12]. Two different pathogenic mechanisms explain the occurrence of IRIS. These are paradoxical reaction to antigens of microbiologically inactive infectious agents despite effective anti-infectious therapy and unmasking of an active infection [13]. Nacher et al. [14] reported that patients taking Highly Active Antiretroviral Therapy (HAART) were likely to develop disseminated histoplasmosis than untreated patients. This suggests that immune reconstitution after HAART reveals undiagnosed latent disseminated histoplasmosis. The exacerbation of skin and joint symptoms after starting HAART may be due to exaggerated cell-mediated response identical to a pattern commonly seen in type 1 lepra reaction giving rise to swelling of the skin and a reactive arthritis.

Ampotericin B and Itraconazole are the antifungal agents that were noted to be effective in the treatment of histoplasmosis [15]. The availability and the cost of these medications are limiting factors in resource limited settings. This patient was treated successfully with fluconazole after a relapse with itraconazole interruption. Fluconazole was used because its availability and affordability. However, reports indicate that a high proportion of patients failed fluconazole therapy than those treated with itraconazole [16]. Fluconazole was found to induce resistance during therapy [16]. There was no relapse after stopping maintenance treatment after the rise of the CD4 count to more than 500/mm³. Treatment should be continued until clinical and laboratory findings are normal. However 10-15% of patients will experience relapse [17]. Longer therapy and probably a lifelong suppressive therapy were proposed in patients whose immunosuppression cannot be reversed [15]. The minimum required CD4 count reconstitution to stop maintenance therapy in disseminated disease involving the bone needs further research.

The aftermath of disseminated histoplasmosis on digits resemble leprosy, but without the loss of sensation. The stigmata associated with leprosy in endemic areas are compounded by stigma associated with HIV infection and therefore, this patient requires continuous counseling.

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