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Disseminated Histoplasmosis Presenting as Skin Nodules

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Authors' contributions

This work was carried out in collaboration between all authors. Author BBA did the histopathology of the patient, collected data regarding the patient. Author DRA managed the literature searches. Author MM wrote the first draft of the article. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aim: We present a case of histoplasmosis presenting with skin nodules and lymphadenopathy from a non endemic area.
Case Presentation: A 60-year-old male presented with multiple skin nodules and lymphadenopathy.
Discussion: Histoplasmosis is a rare fungal infection caused by dimorphic fungus *Histoplasma capsulatum*, occurring in AIDS patients and other immunocompromised individuals. It usually causes pulmonary infection, following which dissemination to the other parts of the body can occur through lymphatics and bloodstream. Skin lesions mimicking tuberculosis or malignancy can be presenting feature of disseminated histoplasmosis in 10% of patients. Histoplasmosis is endemic in Central and South America and Africa. In India it is endemic in east Indian states.
Conclusion: Due to non specific clinical presentations, low clinical suspicion especially from non endemic areas and lack of proper diagnostic facilities, a diagnosis of histoplasmosis is not sought. Delay in diagnosis often leads to delayed treatment increasing morbidity and mortality.

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Keywords: Histoplasmosis; disseminated; skin nodules; AIDS.

1. INTRODUCTION

Histoplasmosis, also known as Darling's disease, is a rare fungal infection caused by the fungus *Histoplasma capsulatum* frequently associated with AIDS and other immunocompromised patients. *H. capsulatum* is an intracellular organism parasitizing the reticuloendothelial system involving the spleen, liver, kidney, central nervous system and other organs. Disease caused by *H. capsulatum* occurs in three forms: (i) primary acute pulmonary form, (ii) chronic pulmonary and (iii) disseminated form [1].

Disseminated histoplasmosis is the most common manifestation associated with AIDS [2]. Cutaneous involvement is reported in nearly 10% of HIV-associated histoplasmosis cases [3]. Primary cutaneous infection of the skin is rare and usually cutaneous involvement is the manifestation of disseminated disease [3].

Histoplasmosis is endemic in central eastern United States, especially the Ohio and Mississippi River Valleys, in Central and South America, and Africa [4]. In a study done in United States incidence rates of Histoplasmosis varied from 3.3 to 12.4/105 person-years in different regions of the country [5]. Histoplasmosis is rarely reported from India. Panja and Sen first reported histoplasmosis from India in 1954 [6]. It is considered to be endemic in East Indian states like West Bengal [7]. There are sporadic case reports from South India as well [8]. India being a non endemic area, incidence studies have not been done. However sporadic cases have been reported from various parts of the country. On the basis of histoplasmin skin testing a positivity rate of 12.3% was reported in India and a positivity rate of 9.4% was reported in another study [7,9].

We report a case of disseminated histoplasmosis in a 60-year-old male who presented with papulonodular skin lesions and generalized lymphadenopathy.

2. PRESENTATION OF CASE

A 60-year-old male patient presented in the outpatient department of Postgraduate Institute of Medical Sciences Rohtak, Haryana, India with the complaints of papulonodular skin lesions on chest wall and back with multiple swellings gradually increasing in size in cervical, axillary and inguinal regions for the past 6 months (Fig. 1). The swellings were painless and were associated with mild fever occurring on and off. There was history of loss of appetite and weight. There was no history of cough or respiratory distress.

On examination the patient was afebrile, pulse rate, respiratory rate and blood pressure were within normal limits. Multiple papulonodular skin lesions of 1−2 cm in diameter were seen on the chest wall and back. Bilateral cervical, axillary and inguinal lymph nodes were enlarged ranging in size from 1−4 cm. The lymph nodes were discrete, firm, non tender and mobile. Non tender hepatosplenomegaly was also seen.

On investigation, his hemoglobin was 10.1 gm/dl, total leucocyte count was 6800/µl, differential leucocyte count was neutrophils 83, lymphocytes 12, monocytes 2, eosinophils 2 and basophils 1. The erythrocyte sedimentation rate was 70 mm

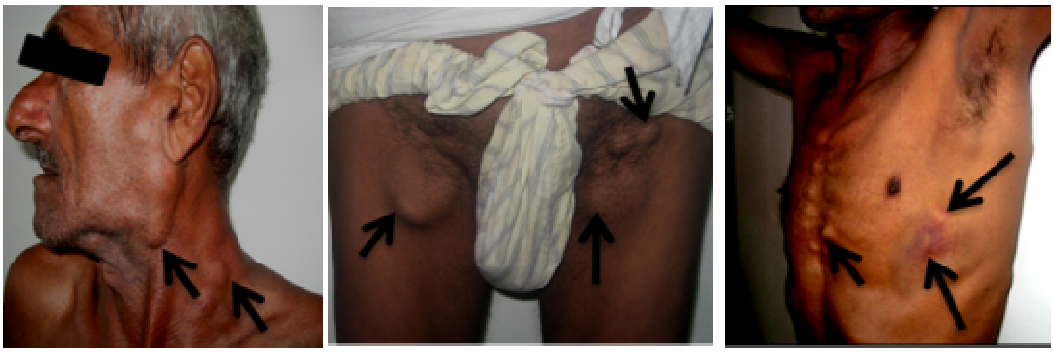

Fig. 1. Photograph of the patient showing nodules on the cervical region, inguinal region and chest wall

in the first hour. Liver and kidney function tests were within normal limits. The patient was tested for HIV infection as per NACO guidelines and was found to be positive. CD4 lymphocyte count of the patient could not be done. Chest X-ray showed mediastinal lymphadenopathy. Abdominal ultrasonography revealed hepato-splenomegaly and enlarged intraabdominal lymph nodes.

A diagnosis of tuberculous lymphadenopathy was made. Skin and lymph node biopsy was done and was subjected to histopathological examination. Histopathological examination of skin and lymph node biopsy revealed numerous foamy macrophages parasitized with small round to oval yeast cells surrounded by a clear halo (Fig. 2). Few extracellular yeast cells were also seen. Periodic Acid-Schiff staining revealed pink to purplish red fungal wall with pale coloured protoplasm filling the cells. Gomori methenamine silver staining showed the presence of black budding yeast cells (Fig. 3). The histological picture was compatible with diagnosis of histoplasmosis. The patient was started on induction therapy with oral itraconazole 200 mg thrice a day for 3 weeks and was switched to oral itraconazole 200 mg twice daily therapy after that. After two months of therapy the patient showed some reduction in lymph nodes and skin nodules. However, the patient was lost to follow up after that.

3. DISCUSSION

Histoplasmosis is caused by the dimorphic fungus, *H. capsulatum*, which is an intracellular fungus parasitizing the cells of reticuloendothelial system and involvings the spleen, liver, kidney, central nervous system and other organs. The organism exists as asaprophyte in nature and has been isolated from soil. Bird and bat excrement enhances the growth of the organism in soil by accelerating sporulation. Its spores are infectious to humans by the airborne route.

While infection in the immunocompetent individuals is subclinical or mild self limited pulmonary illness, in immunocompromised individuals it presents with life-threatening disseminated illness [10]. Disseminated histoplasmosis has emerged as an important opportunistic infection in endemic areas. Disseminated form of histoplasmosis generally presents with non specific clinical presentations like fever, weakness, weight loss, hepatosplenomegaly and mucocutaneous lesions [2]. Skin lesions in histoplasmosis can be primary or more commonly secondary to disseminated disease. Skin lesions may be the initial manifestation of histoplasmosis in about 10% of cases and serve as marker for AIDS in the areas endemic for histoplasmosis [3]. Skin lesions range from papules, plaques, nodules to erosions and ulcers, molluscum like lesions, keratotic plaques and acneiform eruptions [11].

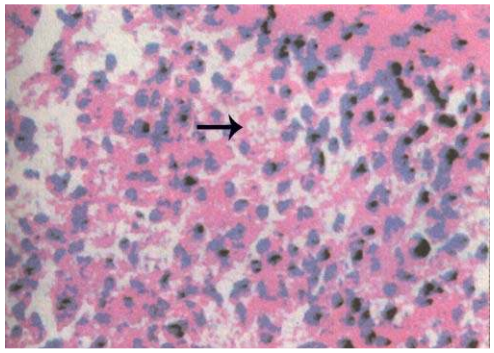

Fig. 2. Section of skin stained with hematoxylin and eosin showing *Histoplasma capsulatum* surrounded by a clear halo filling the cytoplasm of phagocytes (X400)

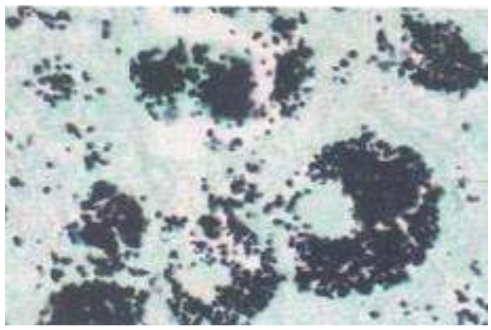

Fig. 3. Section of skin stained with Gomori methanamine silver staining showing black budding yeast cells (X100)

In the present case the patient had all the manifestations of disseminated histoplasmosis along with papulonodular skin lesions. However, due to marked generalized lymphadenopathy and the area being non endemic for histoplasmosis a clinical diagnosis of tuberculous lymphadenopathy was made. Since the clinical features simulate other febrile illnesses, the clinical suspicion is low in non endemic areas and standard diagnostic tests for histoplasmosis are not well established, a diagnosis is usually arrived at accidently. Most of the times the initial diagnosis is either tuberculosis or malignancy [10].

Generally, by the time histoplasmosis affects HIV-positive patients, other opportunistic infections would have already occurred and the HIV status of the patient would have been known [12]. However in the present case HIV status of the patient became apparent only after a diagnosis of histoplasmosis was made.

Histopathological examination of biopsy specimens from the skin lesions and lymph nodes remains the mainstay of diagnosis, as the presence of small yeast cells budding on a narrow base in the tissue itself provides a conclusive evidence of the disease. However, the presence of budding yeast cells may be confused with yeast cells of *Penicillium marneffi*, *Cryptococcus neoformans, Candida spp*. especially *C. glabrata* which does not show pseudohyphae, *Sporothrix schenckii* and *Coccidioides immitis*. Yeast forms of *Penicillium* shows septate appearance, whereas *Histoplasma* shows budding yeasts. Cryptococci are larger in size 5−10μm as compared to yeast cells of *Histoplasma* which are 2-4 μm in diameter. Mucicarmine staining for capsular material may be used to distinguish between the two. *C. glabrata* shows more size variability than histoplasmosis and a halo around the yeast is not appreciated. In *Sporothrix schenckii* infection the yeast cells are fewer and a mixed granulomatous and suppurative reaction is seen in tissues rather than a pure granulomatous reaction which is seen in histoplasmosis. Endoconidia of *Coccidioides immitis* are rounder, do not bud and are accompanied by a spherule.

3.1 Treatment

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily), induced a more rapid and complete response, lowered mortality, and reduced toxicity [13]. According to guidelines published by Infectious Diseases Society of America (IDSA guidelines), for moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) (A-I) [14]. Step-down therapy to oral itraconazole, 200 mg 3 times daily for 3 days, and then 200 mg twice daily, should be given for a total of at least 12 months [14]. For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended (A-II) [14]. The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption, but it is less well tolerated than the capsule formulation, which should be given with food. Because of potential drug interactions between itraconazole and both protease inhibitors and efavirenz, it is advisable to obtain serum levels of itraconazole after 2 weeks of therapy. A randomly obtained serum level of at least 1.0 μg/mL is recommended and levels >10 μg/mL are unnecessary [15]. Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4 count >300 cells/mm3, should be managed in a manner similar to that used for a nonimmunocompromised host.

Our patient was started on oral itraconazole therapy only and for the first two months the patients improved but the patient was lost to follow up. The treatment modalities used in various studies have been essentially the same i.v. amphotericin B followed by oral itraconazole [16,17,18]. However different patients respond differently to therapy, therefore individual need based changes need to be done for proper management of patients [18].

4. CONCLUSION

Though histoplasmosis is rare opportunistic infection in India, it is being increasingly reported from non endemic areas also. Skin lesions are present in about 10% of AIDS patients with histoplasmosis, and may serve as marker for disseminated histoplasmosis. A differential diagnosis of disseminated histoplasmosis should always be kept in mind in immunocompromised patients presenting with skin lesions, even from the non endemic areas for early diagnosis and proper management.

CONSENT

All authors declare that ‘informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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