Case Study

Disseminated Histoplasmosis in an Immunocompetent Host Presenting as Pyrexia of Unknown Origin (PUO)

Sanjay Pandit[1], Pratap Singh[2], Naresh Kumar[3], Shivani Bansal[4], Rashmi Jain Gupta[5]

Abstract

Histoplasmosis is a progressive granulomatous disease caused by intracellular dimorphic fungus *Histoplasma capsulatum*. The fungus present in the soil infects through inhalational route and can manifest as any of the three main types-acute primary pulmonary type, chronic cavitatory or progressive disseminated. In disseminated histopasmosis (DH), the fungus is detected from more than one location in the body. This is the rarest form of all three types and is usually present in immunocompromised individuals. We report the case of a 27-year-old immunocompetent patient who presented with prolonged fever, weight loss, pain abdomen and skin lesions. She was found to have hepatosplenomegaly and pancytopenia. Biopsy from skin lesions and bone marrow stained positive for *H. capsulatum* sp. She was treated with amphotericin B for 28 days, followed by oral Itraconazole for 6 months, leading to complete resolution of the disease. This case is interesting due to the presence of disseminated histoplasmosis in an immunocompetent host with prominent skin lesions.

Keywords: Histoplasmosis, Immunocompetent

Introduction

Two varieties of the fungi Histoplasma are known to infect humans, namely: *Histoplasma capsulatum* var. *capsulatum* and *H. capsulatum* var. *Duboisii*. It is a dimorphic fungus which exists as a mycelial (mold) form in the soil under ambient conditions and converts into a yeast form once it enters the human body. The *microconidia* of the mycelial form are believed to be infective due to their size of 2-5 µm, which allows them to lodge in terminal bronchioles and alveoli.[1] It is a systemic fungal disease of worldwide occurrence with cases being reported from everywhere except Antarctica. In India, most of the cases have been reported from Assam and West Bengal, which are considered endemic for histoplasmosis. Three large studies conducted from Delhi and South India reported an occurrence of 37, 24 and 19 cases of DH respectively in a 10-year follow-up period.[2-4]

[1,2]Associate Professor, Department of Medicine, [3]Associate Professor, [4]Ex-Senior Resident, Department of Skin & Venereal Diseases, Maulana Azad Medical College, New Delhi.
[5]Senior Specialist, Department of Pathology, Lok Nayak Hospital & MAMC, New Delhi.

Correspondence: Dr. Naresh Kumar, Maulana Azad Medical College, New Delhi.

E-mail Id: drnareshmamc@gmail.com

Orcid Id: http://orcid.org/0000-0003-4581-609X

How to cite this article: Pandit S, Singh P, Kumar N et al. Disseminated Histoplasmosis in an Immunocompetent Host Presenting as Pyrexia of Unknown Origin (PUO). *J Adv Res Med* 2017; 4(1&2): 10-13.

ISSN: 2349-7181

The disease in many cases may be asymptomatic or it may manifest clinically as: acute primary pulmonary type, chronic cavitatory or progressive disseminated type. The progressive disseminated type also known as the progressive disseminated histoplasmosis (PDH) is usually associated with risk factors like age >55 years or immunosuppressison and is the rarest of all types. It can present clinically as acute, subacute or chronic types depending upon the duration and type of symptoms and the extent of organ involvement by the fungus. We hereby report a case of subacute PDH with diffuse cutaneous and bone marrow involvement in an immunocompetent individual from the non-endemic region of North India.

Case report

A 27-year-old lady, a resident of western part of Uttar Pradesh in India, was admitted with complaints of fever for one year, progressive weight loss for six months with multiple skin lesions on face and both arms for the last three months (Fig. 1a and 1b). On examination, she had pallor, tachypnea (respiratory rate-32 breaths/min), tachycardia (heart rate: 130 beats/min) and blood pressure of 100/62 mmHg. On systemic examination, she had liver palpable 4 cm below costal margin and spleen was palpable 6 cm below costal margin. There were no palpable lymph nodes. Multiple papulo-nodular lesions were present on face and both arms. There were no oral ulcers. Patient was worked up along the lines of pyrexia of unknown origin.

On investigation, hemogram revealed pancytopenia (Hb-8.6 gm%, TLC-2400/cmm, platelets-96,000/cmm). Blood glucose, liver and renal function tests, and chest X-ray were found to be normal. CT scan of chest was also done, which was completely normal. Mantoux test, blood and urine cultures were negative. ELISA for HIV was non-reactive with a CD4 count of 694, bone marrow aspirate from sternum on Giemsa staining revealed normocellular marrow, normal M:E ratio, normal trilineage hematopoiesis with increase in plasma cells and histiocytes. Numerous 2-4 µm oval to round bodies with eccentric to central nuclei and a perinuclear vacuole were identified within the histiocytes. These bodies were identified extracellularly, also which was suggestive of histoplasma. Bone marrow biopsy revealed similar findings on H&E stain. Special staining with Grocott silver stain confirmed the diagnosis of histoplasma (Fig. 2). Biopsy was also done from skin lesion which revealed similar findings, showing a large number of fungal spores of *H. capsulatum* inside histiocytes and scattered extracellularly. The patient was treated with injectable Amphotericin B during hospital stay. She became afebrile and showed marked improvement in skin lesions after two weeks of treatment. Skin lesions got completely resolved and hepatosplenomegaly completely regressed by six weeks (Fig. 3a & 3b). She was then put on oral Itraconazole (400 mg per day) for one year and followed in outpatient department. Response to the therapy was satisfactory and the patient completely recovered from the disease.

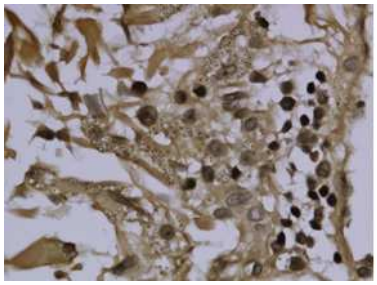

Figure 1

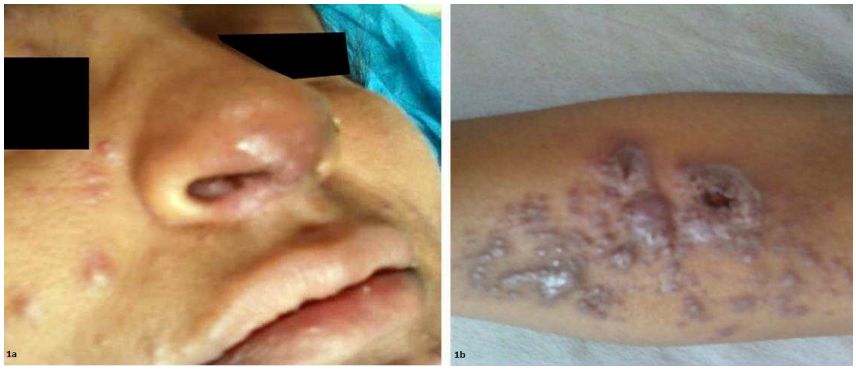

Figure 2

ISSN: 2349-7181

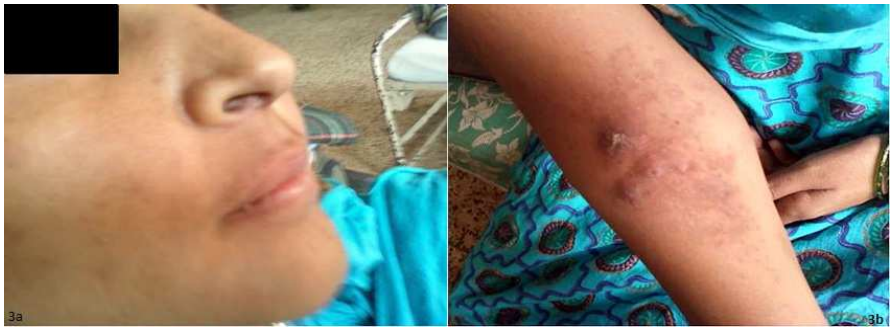

Figure 3

Discussion

Disseminated histoplasmosis is rare in an immunocompetent individual. Major risk factors for it include AIDS with CD4 count of less than 150 cells/µL, use of corticosteroids, hematologic malignancy, and solid organ transplantation. Patients receiving tumor necrosis factor antagonists (e.g., Etanercept, Infliximab) are also at an increased risk for DH. People involved in various types of occupations involving exposure to soil rich in bird excretions like agriculture, outdoor construction and rehabilitation of buildings inhabited by birds have been found to be at a higher risk of getting infected.[1] Differential diagnosis of histoplasmosis includes leishmaniasis, tuberculosis, toxoplasmosis, other fungal infections like cryptococcosis, candidiasis and coccidioidomycosis.

In only one of the three large case series of DH published from India, the one from CMC Vellore had reported four cases of DH out of a total of 19 in immunocompetent individuals.[3] In this series, only two of the 19 cases studied had skin involvement in the form of nodules and papules and out of them *H. capsulatum* could be demonstrated in only one patient. In another recent case series from India published in 2015, seven cases of DH in immuncompetent patients were reported over a period of five years and out of them only one had skin involvement in the form of ulcerated nodular lesions in which the fungus was demonstrated.[5]

The patient discussed here was not having diabetes, HIV and was not suffering from active tuberculosis or any other chronic disease affecting the liver or kidney. There was no current or past use of any immunosuppressant drugs.

Oral ulcers are the most common mucocutaneous presentation in patients with DH.[6] Cutaneous lesions of DH are most commonly seen on the face, arms, and legs. The rarer sites of involvement, which have been reported include hands, feet, chest, back, penis, and perianal region.[7] The various cutaneous manifestations which can occur in a case of DH include papules (including molluscum contagiosum-like lesions, acneiform eruptions), plaques, pustules, and nodules along with hyperpigmentation of skin.

The most important feature, which differentiates a case of subacute DH from the chronic DH, is the absence of involvement of other organ systems in the chronic type; since in this case, the fungus was demonstrated from more than one organ system, i.e., bone marrow and skin we treated this case as subacute DH.

Subacute DH is distinguished from the acute form primarily by the more prolonged nature of symptoms before the patient comes under medical attention. Fever is the presenting symptom in about 50% cases; physical findings include hepatosplenomegaly and oral ulcers. Anemia and leukopenia are noted in up to 40% and thrombocytopenia in 20% cases. Platelet count is rarely less than 20,000/µL.[8]

In some cases, endocarditis and infection of other vascular structures may also be a manifestation of subacute DH.[9] The aortic and mitral valves are affected more commonly than right-sided valves. Apart from liver and spleen, gastrointestinal tract is one of the most common sites affected by subacute DH manifesting as macroscopic ulcers of the large and small bowel but with symptoms of diarrhea and abdominal pain are only occasionally seen.[10] Central nervous system infection manifests most commonly as chronic meningitis.[10,11]

Although symptoms arising from involvement of adrenal glands are not common, autopsy series have shown organ involvement by the fungus in approximately 80% of cases.[12] Overt Addison's disease is uncommon occurring in less than 10% of cases.

Many patients diagnosed with acute histoplasmosis do not require specific treatment and will recover spontaneously. However, treatment is recommended for all cases of progressive DH.[13] Among severe cases,

mortality rate can be as high as 50%, even when Amphotericin B therapy has been administered. However, 98% of milder cases respond to this treatment.[14] A 6- to 12-month course of oral itraconazole is recommended as the treatment of choice.[15] Those who require hospitalization, who do not respond to Toitraconazole, or those patients who are immunosuppressed are treated with Amphotericin B till infection is controlled and then switched to Itraconazole to complete a total 12 months of therapy.

DH is not an uncommon etiology of fever of prolonged duration even in immunocompetent individuals and should be kept as a differential diagnosis of prolonged fever presenting with mucocutanous lesions, organomegaly, lymphadenopathy with pancytopenia because delayed diagnosis and treatment increases mortality.

Conflict of Interest: None

References

1. George S. Deepe Jr. Histoplasma capsulatum Mandell, Douglas & Bennett's Principles & Practice of Infectious disease 7th edition. 2010 : 3305-18.
2. Randhawa HS, Khan ZU. Histoplasma in India: Current status. *Indian J Chest Disease Allied Sci* 1994; 36: 193-213.
3. Subramanian S, Abraham OC, Rupali P et al. Disseminated Histoplasmosis . *JAPI* 2005; 53: 185-89.
4. Gopalakrishnan R, Senthur Nambi P, Ramasubramanian V et al. Histoplasmosis in India: Truly uncommon or uncommonly recognized? *JAPI* 2012; 60: 25-28.
5. Diybendu De, Nath UK. Disseminated histoplasmosis in immunocompetent individuals-not a so rare entity in India. *Mediterranean Journal of Hematology & Infectious Disease* 2015; 7(1): e2015028.
6. Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. 3rd edition. New York: *Elsevier: Saunders* 2012.
7. Paul AY, Aldrich S, Scott RS et al. Disseminated histoplasmosis in a patient with AIDS: Case report and review of literature. *Cutis* 2007; 80: 309-12.
8. Goodwin RA Jr, Shapiro JL, Thurman GH et al. Disseminated histoplasmosis: Clinical and pathological correlations. *Medicine (Baltimore*) 1980; 59: 1-31.
9. Blair TP, Waugh RA, Pollack M et al. Histoplasma Capsulatum endocarditis. *Am Heart J* 1980; 99: 783-88.
10. Sturium HS, Kouchoukos NT, Ahluvin RC. Gastrointestinal manifestations of disseminated histoplasmosis. *Am J Surg* 1965; 110: 435-40.
11. Wheat LJ, Batteiger BE, Sathapatayavongs B. Histoplasma capsulatum infections of the central nervous system: A clinical review. *Medicine (Baltimore)* 1990; 69: 244-60.
12. Wilson DA, Muchmore HG, Tisdal RG et al. Histoplasmosis of the adrenal glands studied by CT. *Radiology* 1984; 150: 779-83.
13. Wheat J, Sarosi G, McKinsey D et al. Practice guidelines for management of patients with histoplasmosis. *Clinical Infectious Diseases* 2000; 30: 688-95.
14. Klein NC, Cunha BA. New antifungal drugs for pulmonary mycoses. *Chest* 1996; 110: 525-32.
15. Dismukes WE, Brdsher RW Jr., Cloud GC et al. Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycosis study Group. *Am J Med* 1992; 93: 489-97.

Date of Submission: 10th Jun. 2017

Date of Acceptance: 12th Jun. 2017