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Disseminated Histoplasmosis in Immunocompetent Patients Presented with Fever of Unknown Origin (FUO)

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Abstract

Histoplasmosis is underreported although in Southeast Asia including Bangladesh is thought to be endemic considering the favorable geo-climatic conditions for the organism. Non-recognition of histoplasmosis is particularly attributed to possible misdiagnosis as tuberculosis (which is endemic here and common in Bangladesh) because histoplasmosis mimics tuberculosis in clinical presentation, imaging and histopathology. Disseminated histoplasmosis mainly occur in immunocompromised patients and rare in immunocompetent subjects. Here we are reporting two cases of disseminated histoplasmosis where both were immunocompetent and presented with FUO. Both patients visited several health centers before coming to us with no definite diagnosis and we got them in a progressive stage. Both were confirmed through bone marrow study. Unfortunately, one of them died from disease progression, sepsis and other complications and another patient gradually improved with treatment (amphotericin B and itraconazole). We are reporting these cases to highlight the fact that disseminated histoplasmosis does occur in immunocompetent patient and may occur with or without pulmonary symptoms.A high index of suspicion is required for diagnosis and delay can often be fatal.

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Introduction

Histoplasmosis is a systemic fungal infection caused by soil based thermally dimorphic fungus *Histoplasma Capsulatum* which exist in a warm and humid environment and thrives in soils enriched with nitrogenous compounds and phosphates derived from avian excreta and bat guano.[1] Infection is typically acquired by inhalation of infectious microconidia during activities like cleaning of chicken coops, visiting bat-infested caves, excavation, demolition of old buildings, and cutting of dead trees which lead to disruption of soil containing the organism and aerosolization of microconidia.[2] The typical incubation period is 7-21 days.[3] Clinically it manifests as three main types- acute pulmonary, chronic pulmonary/cavitary and progressive disseminated histoplasmosis.[4] In most cases, the infection is asymptomatic unless the patient is immunocompromised with impaired cellular immunity.[5] However symptomatic histoplasmosis has also been described in immunocompetent individuals, particularly those at the extremes of age, with underlying pulmonary disease or those who inhale an unusually large inoculum.[6,7] If symptomatic, it most commonly presents as

a self-limiting lung disease as lungs are the main portal of entry for the organism. However, if there is a failure or delay to activate macrophage fungicidal activity to confine and kill the organism, organism continues to grow intracellularly and from portal of entry it disseminates throughout the body via lymphatic and hematogenous circulation i.e., disseminated progressive disease can occur.[8,9] The mortality from untreated disseminated histoplasmosis is nearly 100%, and the disease itself can progress rapidly, causing a fulminant decline within days to weeks.[10] Hence, early diagnosis and prompt initiation of treatment is of paramount importance.

Description of the Cases

Case 1:

A previously known healthy 60-years-old Bangladeshi male from Gazipur was complaining (October 2021) of intermittent fever for 3 months' duration. Initially, for one & half month, the patient had low-grade fever and he did not seek any medical consultation. Later the fever became high grade and he took multiple consultations. His initial baseline laboratory investigations were normal. He was prescribed antipyretics and several empirical antibiotics including ceftriaxone, cefixime and moxifloxacin without any improvement.

At one point, he developed generalized purpuric rash and confusion. He was then referred to Bangabandhu Sheikh Mujib Medical University for further evaluation. On examination, patient was found confused with a high temperature (103°F) although vitals were normal. He had multiple purpuric rash (Figure: 1a) all over the body but more on lower limbs and hepatosplenomegaly (4 cms and 6 cms below costal margin respectively). There was no peripheral lymphadenopathy. Rest of the accessible systemic examination including respiratory, neurological and fundoscopic examination was normal.

He had no medical history suggesting immunosuppression e.g., no history of diabetes mellitus, hypertension, liver disease, kidney disease, rheumatic disease, tuberculosis (TB) & contact with any smear positive TB patient. He did not give any history of recent travel, unsafe sexual exposure, intravenous drug abuse or any blood transfusion in the past. The rest of his family members are in good health and there was no history of similar illness in his family members. His detailed history revealed he was a supervisor by occupation at a garments factory and resided in a damp area located near a forest. There was also a poultry farm near his residence. Of note, he used to walk on bare foot from time to time around his home & a fish bone pricked in his left sole of foot which resulted in a non-healing punctured wound (Figure:1b). His attendant claimed that all his symptoms started gradually after he had this wound.

Subsequent Laboratory investigations revealed progressive thrombocytopenia (20-$\times 10^3/\mu l$), later pancytopenia and worsening renal impairment (serum creatinine: 3mg/dl). Other hematological and biochemical profile are given in table I. Chest Xray P/A view showed nothing significant. USG of whole abdomen revealed hepatosplenomegaly with abdominal lymphadenopathy in left para-aortic region measuring about 3.0×2.4 cm. Infection screening for TB, HIV, Malaria, Kala-azar, Brucella, *Salmonella*, Rickettsia, HBV and HCV were negative. CSF study was normal including normal ADA (6.7 U/L) and Gram staining & AFB staining were negative. Ferritin (10,765ng/ml), and CRP (170.4mg/L) were high. Direct Coomb's test was positive. Due to severe pancytopenia and bleeding manifestation (gross hematuria) he was then transfused one unit of whole blood & three units of platelet concentrates with other supportive treatments including steroid. On bone marrow aspiration multiple intracellular (within histocyte) and extracellular boat shaped organism with surrounding halo were seen suggesting *Histoplasma Capsulatum* (Figure-2). Special stain (PAS + Giemsa) in trephine biopsy also confirmed *Histoplasma Capsulatum* within histiocytes and giant cells. Intravenous (IV) Amphotericin B (0.5mg/kg once a day) and itraconazole (200 mg twice daily) was started. However, unfortunately, 2 days later patient died probably due to disease progression and sepsis.

Case 2:

A previously healthy 40- year- old Bangladeshi male from Noakhali was admitted (February 2022) with complaints of fever for 2 months and significant weight loss. Fever was high grade (highest temperature was 104°F), came daily with evening rise, associated with night sweats and subsided by taking antipyretics. Initially for few days, he had dry cough but that disappeared during rest of his course of his illness. He consulted multiple physicians and received several empirical antibiotics like the previous patient without any significant clinical improvement. He had experienced massive weight loss during his course of illness (approximately 35 kg over 2 month). He also had severe nausea and anorexia for last 15 days without other GI symptoms. He also complained of hematuria and black stool for last 15 days, which resulted

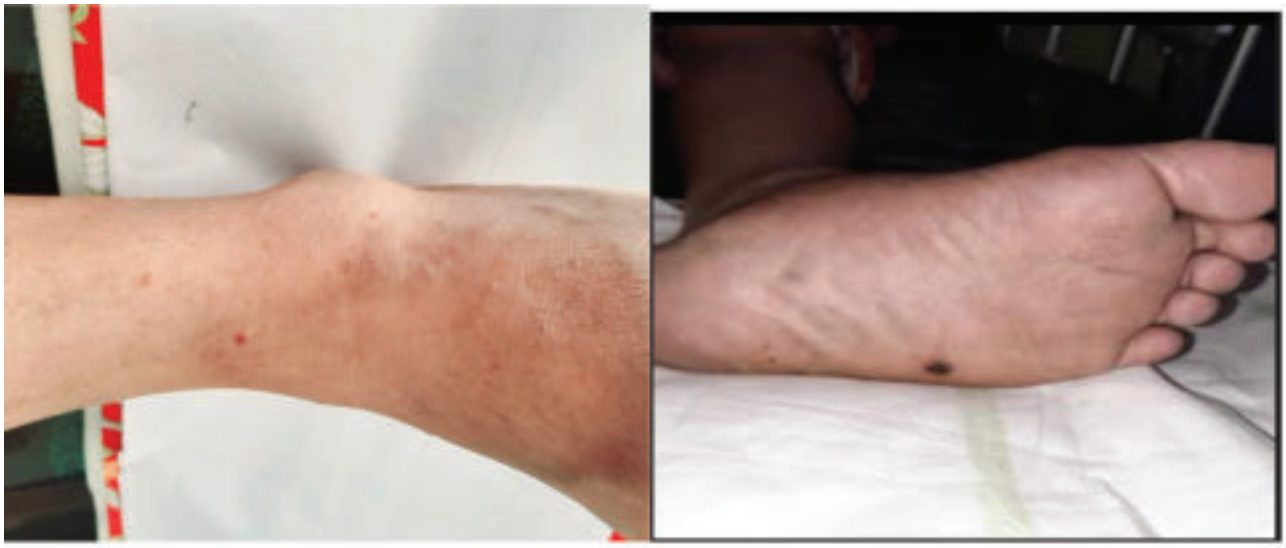

Figure 1. *(a) showing purpuric rash over left ankle and (b) showing a blackish non-healing punctured wound over left sole of the foot*

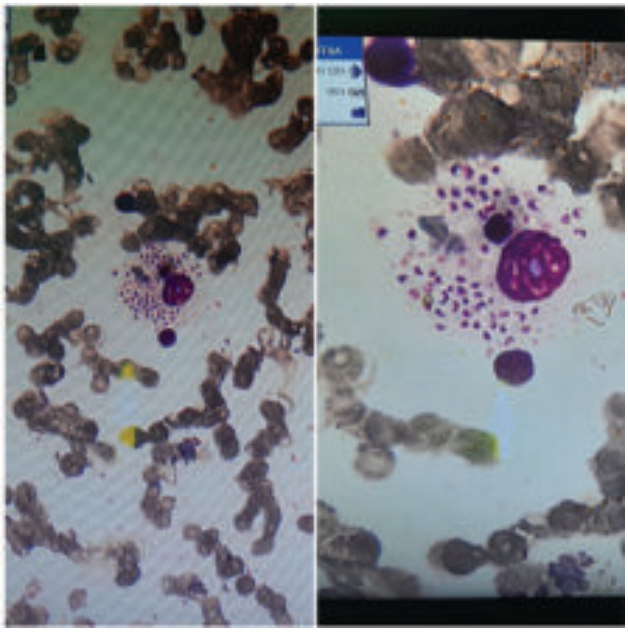

Figure 2. *showing multiple intracellular (within histocyte) and extracellular boat shaped organism with surrounding halo suggesting histoplasma capsulatum*

from severe pancytopenia, and he received four unit of blood transfusion on multiple settings before admitted to our hospital.

He was completely healthy before his illness. He is nonsmoker and did not have any chronic medical conditions suggesting immunosuppression. He did not give any history of contact with any smear positive TB patient, any unprotected sexual exposure, injecting drug abuse, blood transfusion or any recent travel history. His younger brother is diabetic and rest of his family members are in good health. He is a madrasa teacher by occupation who looks after his own property including agricultural fields and fishery. There is a poultry farm near his residence.

On examination the patient was cachectic, moderately anemic and vitals within normal except temperature (103°F). He had whitish patches over his tongue. There was cervical lymphadenopathy (left anterior cervical chain), hepatomegaly and multiple purpuric rashes on his lower limbs. Full laboratory profiles are mentioned in Table 1. Ultrasonography of whole abdomen showed hepatomegaly with deranged liver function tests, which all possibly resulted from granulomatous hepatitis. Chest X ray, Tuberculin skin test, anti HIV1 and 2 antibodies, HBsAg, Anti HCV antibody, blood and urine culture, CEA, S. CA 19.9, S.TSH all were normal. Upper GI endoscopy revealed esophageal and duodenal candidiasis. Bone marrow biopsy showed sheets of histiocyte with granuloma formation where histocyte revealed abundant intra-cytoplasmic yeast bodies of *Histoplasma capsulatum* (positive for PAS and GMS stain). He was immediately put on IV amphotericin B (1mg/kg once daily) and itraconazol (200mg 12 hourly). He was given IV amphotericin B every alternate day for 14 days to avoid renal impairment and electrolyte imbalance (after having 4 daily dose renal impairment and hypokalemia developed). He is also on itraconazol 200 mg 12 hourly for one year. His all symptoms subsided within a week and later discharged. On six and nine months follow-up, he is doing completely well with 16 kg weight gain. We have plan to follow up him for at least one year.

Table 1. *Detailed laboratory (haematological, biochemical and radiological) profile of both the patients*

Tests	Case 1	Case 2	Normal range
Hemoglobin	7.8mg/dl	6.6gm/dl	Male 12-16g/dl
Total WBC count	2300/cumm	1500 /cumm	4000-11000/cumm
Total Platelet count	20000/cumm	30000/cumm	150000-450000/cumm
ALT	50u/l	51u/l	Male up to 42 u/l
AST		80u/l	Male up to 42 u/l
ALP		892u/l	Male 53-128u/l
S. Bilirubin	0.9mg/dl	1.5mg/dl	Up to 1mg/dl
S. Creatinine	3mg/dl	2.09 mg/dl	Up to 1.2mg/dl
Random blood sugar	5.7mmol/l	5.68mmol/l	Up to 7.8 mmol/l
Direct Coomb's test	Positive	Negative	
CRP	170.4mg/l	73.2mg/l	Up to 3mg/l
S. Ferritin	10765ng/ml	>3000ng/ml	25-350ng/ml
Carcinoembryonic antigen (CEA)		0.73ng/ml	<5ng/ml
S. CA 19.9		28.41U/ml	0-35U/ml
S.TSH	2.9 mlU/L	1.3 mlU/L	0.5-5 mlU/L
Mantoux test (MT)		5mm	Up to 10mm
ICT for Malaria	Negative	Negative	
ICT for Kala-Azar	Negative	Negative	
Hepatitis B surface antigen	Negative	Negative	
Hepatitis C antibody screen	Negative	Negative	
HIV 1 and 2 antibodies	Negative	Negative	
Blood and Urine culture	No growth	No growth	
Wound swab from foot wound	Klebsiella growth	N/A	
Chest Xray	Normal	Normal	
Ultrasonography of whole abdomen	Hepatosplenomegaly with abdominal lymphadenopathy	Mild Hepatomegaly	
Upper GI endoscopy	N/A	Esophageal and duodenal candidiasis	
Bone marrow study	Granulomatous inflammation withHistoplasma Capsulatum within histiocyte which stained positive for PAS and GMS stain	Granulomatous inflammation with Histoplasma Capsulatum within histiocyte which stained positive for PAS and GMS stain	

Discussion

Globally, about half a million people are infected with Histoplasma infection every year. However, approximately 100,000 people develop disseminated histoplasmosis.[11] The first histoplasmosis case in Bangladesh was reported in 1982 and the second case in 2005. A retrospective data review from 1962 to 2017, containing information on histoplasmosis in and/or from Bangladesh showed a total of 26 patient with a diagnosis of histoplasmosis.[12] Although Bangladesh is thought to be endemic, few cases been reported to date. In TB endemic area like in Bangladesh, disseminated histoplasmosis is

frequently misdiagnosed as disseminated tuberculosis because it mimics TB.

Disseminated histoplasmosis most commonly occurs in immunocompromised patient. It is thought to be uncommon in immunocompetent patient. Cases in immunocompetent patient have been described in different case series (12) (6). In most of the cases, from contaminated soil with avian excreta and bat guano where organism thrives, infection is acquired through activities that disrupt soil and leads to inhalation of organism and rarely by direct inoculation. In both of our cases, patient's residences were near the poultry farm. Moreover, in first case where patient walks with bare foot from time to time, the onset of signs and symptoms immediately after his foot wound and absence of pulmonary symptoms over the whole course of illness leads to the speculation that he acquired the infection by direct inoculation in his foot wound. Although it is plausible that he may have developed infection from reactivation of latent histoplasmosis but reactivation is most common in immunocompromised patient(13). Disseminated disease can involve any organ including lungs, bone marrow, lymph node, liver, spleen, skin, brain, adrenal glands, and the gastrointestinal tract (6). Renal impairment and Coomb's positive hemolytic anemia is rarely reported elsewhere as in our case (4)(14). There were no features suggesting adrenal involvement in both of our patients although adrenal involvement is common in disseminated histoplasmosis.

Definitive diagnosis of histoplasmosis is made by a combination of histopathologic visualization of organism, culture, or antigen and antibody detection. Initially presumed diagnosis of disseminated TB as well as malignancy was made in our patient, which delayed the diagnosis. Finally, during evaluating pancytopenia bone marrow aspiration and biopsy was done which confirmed the case. The 2007 update by Infectious Diseases Society of America recommends initial amphotericin B treatment followed by itraconazole in moderately severe to severe cases and in less severe cases oral itraconazole only(15). Steroid can be used in progressive disseminated cases and both of our patients received so.

Early diagnosis is crucial as disseminated histoplasmosis is associated with high mortality ranging between 30–50% if treated and 100% if not (11). Disseminated Histoplasmosis does occur in immunocompetent patient and in the appropriate clinical context (especially in FUO in tuberculosis endemic area), it should be considered in both immunocompetent and immunocompromised patients, regardless of pulmonary symptoms.

Declarations

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Informed consent: Written informed consents were obtained in both cases for their anonymized information to be published in this article.

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