

DISSEMINATED HISTOPLASMOSIS IN A PATIENT WITH AIDS –**A CASE REPORT AND REVIEW OF LITERATURE**Bhuiyan MNZ¹, Giti S², Islam MS³, Uddin MN⁴**Abstract**

Introduction: Histoplasmosis is a primary systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic fungus. The organism is inhaled in the form of conidia or hyphal fragments and transforms to the yeast phase during infection. Acute disseminated histoplasmosis is seen in association with immunocompromise state, including HIV infection. Disseminated histoplasmosis can simulate other opportunistic infections and should be considered in the AIDS patient presenting with a low CD4+ T cell count.

Case report: A case of disseminated histoplasmosis in a 30 years young male with AIDS, a brick field worker having history of exposure, hailing from a northern division of Bangladesh reported to AFIP, Dhaka on 19 April, 2012 with the complaints of fever for 06 months, cough and weight loss (>10 kg) for 02 months, loss of appetite for 01 month, bleeding from ear, nose, gum and rectum for 12 days and passage of loose stool for 03 days. Physical findings were ill looking appearance, high fever, severe anaemia, mild dehydration, hyperpigmented papular eruptions over both feet, front of chest and left axilla, reduced level of consciousness and hypotension. Systemic examination revealed increased vocal resonance and crepitations on right side of the chest. Diagnosis was confirmed by the presence of histiocytes containing numerous yeast cells of *Histoplasma capsulatum* in bone marrow aspirate. At that time his CD4+T cell count was 42 cells / μ l and HIV – RNA load was 9.6 x10³/ml.

Conclusion: This report emphasizes the points which should raise suspicion of this entity, especially in those critically ill patients where the diagnosis can easily be missed confusing with pulmonary tuberculosis and visceral leishmaniasis and is fatal if not treated.

Key-words: Disseminated histoplasmosis, *Histoplasma capsulatum*, AIDS, CD4+T cell count

Introduction

Histoplasmosis is a systemic fungal disease also known as Darling's disease, caused by the dimorphic fungus *Histoplasma capsulatum*. It was first described by Samuel Darling in 1906 in an adult patient who presumably died of miliary tuberculosis¹. The occurrence of histoplasmosis in patients with AIDS was first described in 1983, is now the most commonly diagnosed endemic mycosis in America, Africa and Asia². This fungus has been isolated from soil containing bird and bat faeces especially in caves and next to chicken houses. It is classified into three varieties, two of which are pathogenic to humans: *H. capsulatum* var. *duboisii*, found mainly in Africa, and *H. capsulatum* var. *capsulatum*, distributed worldwide. Infection results from the inhalation of the fungal microconidia, through which it enters the reticuloendothelial system and resides in macrophages. Most individuals with intact cellular immunity are asymptomatic or have mild pulmonary symptoms. Severe disseminated histoplasmosis develops in people with primary or secondary deficiency of cellular immunity.

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Immunosuppressed conditions due either to infections like HIV or drugs raise the possibility of histoplasmosis. Approximately, 10% cases of histoplasmosis develop progressive disseminated histoplasmosis (PDH). Disseminated histoplasmosis may present as acute PDH with fever, malaise and cough mimicking pulmonary tuberculosis. Chronic PDH manifests as fever, sweats, weight loss, organomegaly and lymphadenopathy³.

In Bangladeshi context, reporting of histoplasmosis in medical literature is very rare⁴. We present a case of histoplasmosis in a young individual with a history of prior sexual exposure in an endemic area who initially had pulmonary involvement and later progressed to develop disseminated histoplasmosis.

Case Report

A 30 years old previously healthy male, a brick field worker was admitted with the complaints of intermittent fever with dry cough of 6 months duration, bleeding from ear, nose, gum, and rectum for 12 days, mild respiratory distress for 7 days, passage of loose stool for 3 days and disorientation for 2 days in Kumudini Medical College hospital on 05 April 2012 for better treatment and discharged as a case of pancytopenia on 12 April 2012. He was advised for bone marrow study from AFIP and referred to Dhaka Medical College Hospital for better treatment. His previous medical history was unremarkable except for the fact that he was given anti-tuberculous drugs for 9 months for a presumed diagnosis of pulmonary tuberculosis in March 2006. The patient had a history of travel and sexual exposure in an endemic zone, Sub-Saharan country. He was not on any drug that might have induced immunosuppression.

On general examination, the patient was emaciated, ill looking, febrile with a recorded temperature of 102° F, level of consciousness on Glasgow Coma Scale 10, tachypnic, hypotensive (blood pressure 90/60 mm Hg) and dehydrated.

Natural orifices was examined and found multiple ulcers with bleeding from nose and mouth. Dermatologic survey revealed erythematous plaques over the chest, left axilla and lower limbs which was non-tender and non-itchy. His systemic examination revealed bronchial breath sound, increased vocal resonance and crepitations on right side of the chest. The patient's laboratory investigations showed anemia with hemoglobin 6.6 g/dL, ESR 100 mm in 1st hour, total WBC count 13000/ cmm, normal platelet count, direct Coomb's test positive, prothombin time 18 seconds, serum creatinine 1.4 mg/dL, serum albumin 25 g/l, serum globulin 60 g/l, serum alkaline phosphatase 527 U/L, serum ALT 103 U/L, serum ferritin 847 ng/ml and serum LDH 1003 U/L . Sputum for Acid-fast bacillus and Mantoux test were negative. Veneral Disease Research Laboratory (VDRL) test was non-reactive. Cultures from blood and sputum yielded the growth of *Esch. coli* at 37°c in aerobic condition and skin scrapping for fungus culture was negative. Serological tests for HIV included Immunochromatography (ICT) test (Figure-1), Enzyme-Linked Immunosorbent Assay (ELISA) and Western blot revealed positive. Chest X-ray showed fairly large ill defined opacity in right upper and middle zone (Figure-2). Computed tomography (CT) of whole abdomen showed poorly excreting kidney (Figure-3). Peripheral blood smear revealed few neutrophils containing phagocytic vacuoles and yeast cells of *Histoplasma capsulatum* (Figure-4). Bone marrow aspirate showed plenty of intracellular round to oval parasites with eccentric crescent shaped nucleus suggestive of *Histoplasma capsulatum* (Figure- 5).

A diagnosis of “ Disseminated histoplasmosis in a patient with AIDS” was made and the patient was planned for treatment as per the Bangladesh national guideline for the management of opportunistic infections in Dhaka Medical College Hospital. Unfortunately, the patient developed aspiration pneumonia and expired on 20 April, 2012.



Fig-1: Immunochromatography test (ICT)- Positive for HIV



Fig-2: Chest X-ray –Fairly large ill defined opacity in right upper and middle zone.

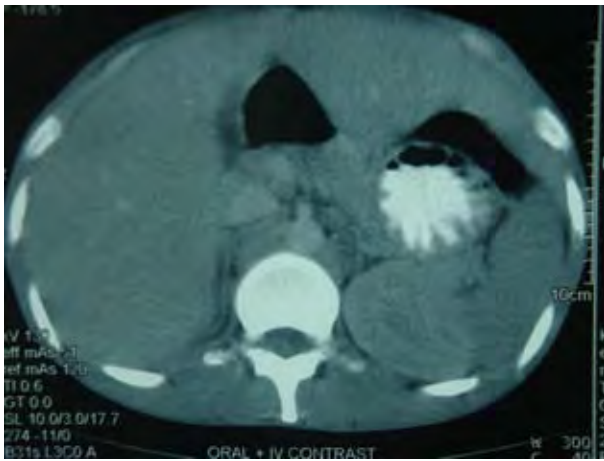


Fig-3: CT Scan- Poorly excreting kidney

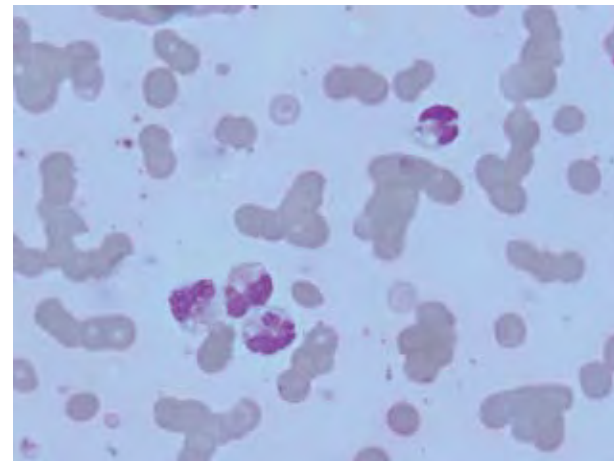
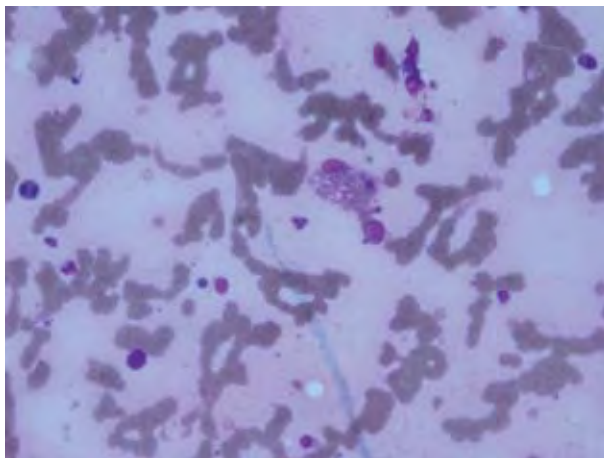
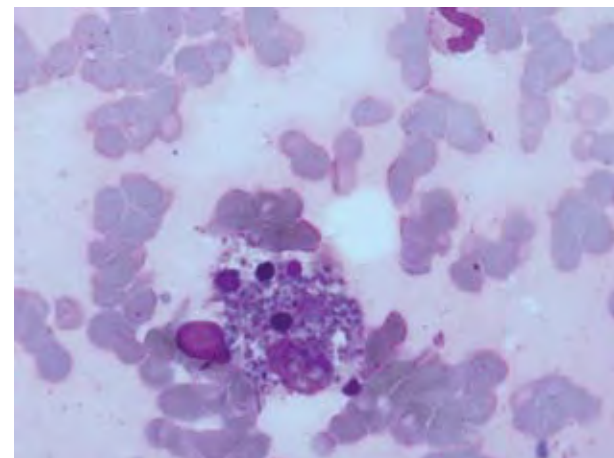


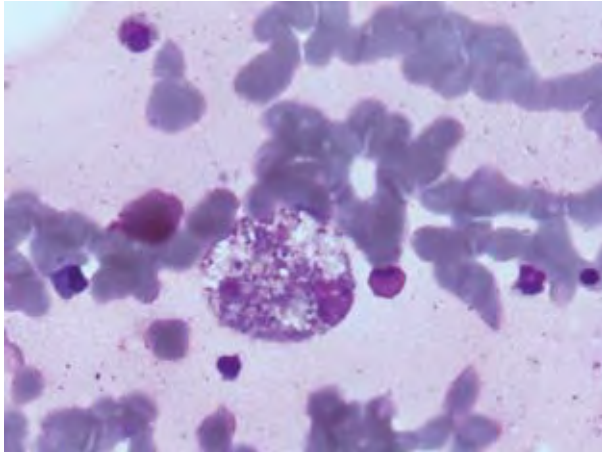
Fig-4: PBF-Few neutrophils contain phagocytic vacuoles and yeast cells of *Histoplasma capsulatum*.



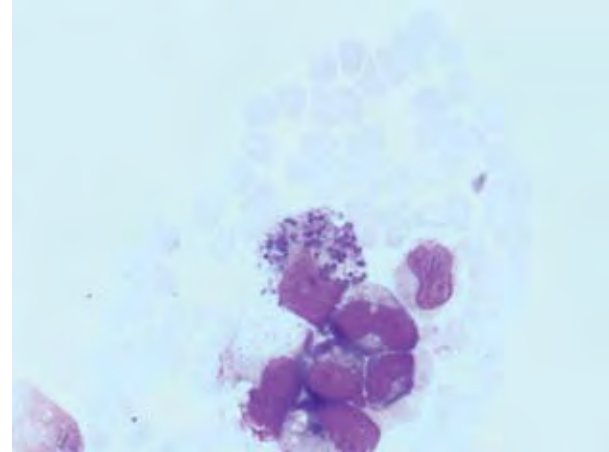
a



b



c



d

Fig-5: (a, b, c,d) Bone marrow- Histiocytes containing numerous yeast cells of *Histoplasma capsulatum*.

Discussion

H. capsulatum is a dimorphic fungus, an intracellular organism, which parasitizes the reticulo-endothelial system in histoplasmosis involving the bone marrow, spleen, liver, kidney, central nervous system, and other organs. The organism exists as a saprophyte in nature and has been isolated from soil, most often when contaminated with chicken-feathers or droppings. Its spores are infectious to humans by the airborne route⁵.

Incidence of histoplasmosis in non-endemic areas is far fewer than endemic areas. Commonly, histoplasmosis occurs in non-endemic areas due to travel or residence in endemic areas. Additionally, it may be found outside endemic areas where microfoci of *Histoplasma* are the source of infection⁶. Incidence of histoplasmosis in Bangladesh is not available. Sporadic cases have been reported in different literature.

The severity of clinical manifestations depend on size of the inoculum, underlying health of the patient and immune status. Majority of patients with AIDS present with disseminated infection while immunocompetent individuals demonstrate clinical features ranging from asymptomatic infection to rapidly fatal pulmonary infections. In between, patients may develop a variety of clinical manifestations including acute or subacute pulmonary diseases,

progressive disseminated diseases, pericarditis, arthritis or less commonly, fibrosing mediastinitis⁷. Disseminated histoplasmosis may present either as self-limited disease or progressive disseminated histoplasmosis⁶. Hepatomegaly, splenomegaly, bone marrow suppression, elevated hepatic enzymes are some of the features. Calcified granuloma in the spleen is a common finding in people living in the endemic zone. Blood culture is rarely positive in acute stage. Specific cell-mediated immunity plays an important role in controlling the infection in lung and extrapulmonary tissues.

Progressive disseminated histoplasmosis usually occurs either in patients at extremes of age or in patients with an underlying immune deficiency state due to AIDS, leukemia, lymphoma, systemic lupus erythematosus, systemic corticosteroids, solid organ transplantation and anti-tumor necrosis factor agents. Not all patients harbour an immunodeficient status⁶. Ongoing research has identified defects in interferon- α /interleukin-12 pathway as a possible explanation in otherwise healthy individuals who develop progressive disseminated histoplasmosis⁷. The clinical features include fever, weight loss, fatigue, respiratory complaints like cough and shortness of breath. Hepatomegaly, splenomegaly, lymphadenopathy and bone marrow involvement are found in less than 50% of cases.

Few patients may present with acute shock-like episodes with hypotension and coagulopathy. In significant number of cases, the only findings are fever and progressive weight loss⁶.

Laboratory diagnosis of histoplasmosis can be made by growth of histoplasma in culture. Bone marrow aspirate, peripheral blood smear, lymph node biopsy, bronchoalveolar lavage fluid, transbronchial biopsy specimen and biopsy from cutaneous lesions can be used for diagnosis⁸. Among all these, bone marrow examination has the highest diagnostic yield⁹. Isolation of *H. capsulatum* has historically provided the strongest evidence of infection, but identification of the organism may take up to 4 weeks. Specimens most likely to yield *H. capsulatum* are blood and bone marrow. However, it is noteworthy that blood or bone marrow culture results were much less likely to be positive (40%–55%). Lysis-centrifugation (Isolator) cultures are more sensitive for fungal pathogens and can detect growth earlier but are more expensive and more labour-intensive than conventional systems¹⁰. Other laboratory abnormalities include anemia, leukopenia, pancytopenia, elevated liver enzymes, increased ferritin and serum lactate dehydrogenase. Antigen detection in urine and serum by radioimmunoassay is highly sensitive in disseminated infection. It can also be used for monitoring response to treatment especially in AIDS patient. The most common finding on chest imaging is diffuse interstitial or reticulonodular and miliary infiltrates⁶. Chest X-ray in chronic pulmonary histoplasmosis may also show upper lobe involvement with cavitation leading to a misdiagnosis of pulmonary tuberculosis.

The recommended treatment regimen for disseminated histoplasmosis is liposomal Amphotericin B for 1-2 weeks followed by oral itraconazole for at least 12 months.¹¹ Suppressing therapy with itraconazole may be required in immunocompromised patients like AIDS or organ transplant patients⁹. Liposomal Amphotericin B is better than conventional Amphotericin B in terms of toxicity and therapeutic efficacy.

Our patient presented with chronic respiratory complaints of cough with fever followed by respiratory distress and disorientation. Before admission, his initial symptoms and imaging findings led to the diagnosis of pulmonary tuberculosis which is widely prevalent in Bangladesh. Indeed, histoplasmosis is under-reported from Bangladesh due to low index of suspicion and lack of diagnostic facility. Another possible explanation of underdiagnosis is that disseminated histoplasmosis resembles visceral leishmaniasis in many aspects with features of fever, weight loss, hepatosplenomegaly. Moreover, both of these are responsive to Amphotericin B. Our patient did not have organomegaly which is found in only one-third of patients. Bone marrow involvement is suggested by anaemia, raised ESR, peripheral blood smear and bone marrow aspirate containing yeast cells of *Histoplasma capsulatum*. These findings along with thrombocytopenia are the most common hematological abnormalities⁵.

Literature review revealed only 5 cases of histoplasmosis from Bangladesh— a 69-year-old male with oral ulcer, hepatosplenomegaly, anemia and leukopenia¹². Another patient was diagnosed in a neighboring country and the third patient, a renal transplant receiver on immunosuppressive therapy, was diagnosed and treated in the United States (US) where he returned from Bangladesh after a visit. This patient did not travel to or was living in histoplasmosis endemic zone of US, namely Ohio and Mississippi River Valleys. The authors concluded that the temporal relationship of his visit to Bangladesh and onset of symptoms suggested that he was infected after he came in contact with chicken houses in Bangladesh.⁸ Reports from India suggest the presence of endemic foci in abandoned houses containing bat guano and in forest soil.¹³ The fourth patient – a 56 years old apparently healthy male without any history of travel to endemic zone who initially had pulmonary involvement and later progressed to develop disseminated histoplasmosis¹⁴.

The latest case – a 36 years old HIV positive male, a storekeeper of a chemical company, manifested with dermatologic, oral and lymph node lesions diagnosed as a case of disseminated histoplasmosis⁴.

Conclusion

AIDS is a global problem. It has now been reported from more than 190 countries around the world, and the pool of HIV-infected persons in Africa and Asia is large and expanding. According to UN AIDS estimate, near about 12,000 HIV cases are present in Bangladesh, which is still < 1% of the total population. The number is likely to be increased further due to transmigration of people around the globe, as in this particular case we discussed. Histoplasmosis is an uncommon cause of Pyrexia of Unknown Origin (PUO) among HIV-infected patients in the Indian subcontinent where tuberculosis, especially extrapulmonary tuberculosis, is the leading cause. Despite a few case reports of histoplasmosis in Bangladesh, the presence of *H. capsulatum* appears common in the East Indian states and nearby the Ganges river. Every clinically suspicious patient should be tested for HIV screening followed by confirmatory test. Early detection of HIV cases can prevent the deadly handshake of opportunistic infection like Histoplasmosis. This report serves as a timely reminder that medical teams caring for HIV-infected and other immunosuppressed patients must remain aware of conditions which may be otherwise uncommon in the environment of their patients and in the team's experience.

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