Cytodiagnosis of disseminated histoplasmosis in an immunocompetent individual with molluscum contagiosum-like skin lesions and lymphadenopathy

ABSTRACT
Disseminated histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* (*H. capsulatum*). The early clinical manifestations are nonspecific, often lead to diagnostic difficulty, and is misdiagnosed as tuberculosis and seen usually in immunosuppressed states. Fine needle aspiration cytology (FNAC) is a simple, safe, and quick technique to establish the initial diagnosis of *H. capsulatum*, thereby prompting early treatment. The skin involvement is rare in disseminated disease and we describe a case of disseminated histoplasmosis in an immunocompetent patient with unusual molluscum contagiosum like umbilicated skin lesions and FNAC of the cervical lymph node was the only tool for rapid and early confirmatory diagnosis.

Key words: Fine needle aspiration cytology (FNAC); *Histoplasma capsulatum* (*H. capsulatum*); immunocompetent; molluscum contagiosum

Introduction
Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* (*H. capsulatum*), the clinical spectrum of which ranges from transient pulmonary infections to disseminated disease. The infection is acquired with the inhalation of spores of *H. capsulatum* found in soils contaminated by bird and bat excreta.[1] The disseminated histoplasmosis is uncommon and can present as acute, subacute, or chronic illness. The acute form is a rapidly fatal infection, seen in immunocompromised individuals. The chronic form is characterized by an indolent course with an intact cell mediated immune response. The disseminated disease commonly involves lungs, lymph node, spleen, liver, bone marrow, gastrointestinal tract, adrenal gland, and mucous membrane of the oral cavity.[1,2] The present case reveals the importance of fine needle aspiration (FNA) being a simple technique for early diagnosis of infection with *H. capsulatum*. It highlights the occurrence of unusual skin lesions associated with histoplasmosis in an immunocompetent individual and asserts as well that the early clinical course of the same mimics tuberculosis causing a delay in diagnosis.

Case Report
A 26-year-old male presented to the FNA clinic with complaints of episodic fever, dull abdominal pain, and weight loss for the past 1 year. The patient was previously...
investigated for tuberculosis and typhoid with no laboratory evidence of infection and was empirically started on antitubercular therapy (ATT). After 4 months of ATT, he developed multiple skin lesions all over the face with no relief in initial symptoms. He had no significant occupational, past medical, and surgical history.

On examination, the general condition of the patient was poor with the presence of pallor, pedal edema, bilateral cervical lymphadenopathy, and multiple molluscum contagiosum like skin lesions revealing umbilicated papules present all over the face [Figure 1a]. Per abdomen examination revealed mild splenomegaly. Blood and biochemical investigations revealed hemoglobin of 7.2 gm/dL, total leucocyte count −11, 000 cells/mm³, differential counts were −N78 L8 M12 E2, platelet count 78,000/mm³, and serum glutamate-pyruvate transaminase (SGPT) was 78.91 U/L. Other biochemical parameters were within normal range. Test for malaria antigen and rapid test for typhoid immunoglobulin M (IgM) Ab was negative. Antibodies for human immunodeficiency virus (HIV) 1 and 2 were not detected. FNA from bilateral cervical lymph nodes showed similar morphology. Smears revealed acute and chronic inflammatory cells along with many intracellular and extracellular small organisms surrounded by a clear halo in a hemorrhagic background. Few showed biphasic-staining pattern with lighter and darker poles [Figure 1b]. Multinucleated histiocytes with the intracellular yeast forms were seen as well. Periodic acid–Schiff (PAS) stain showed positive staining of the organism [Figure 1c]. The cytological impression was of infection with H. capsulatum and culture study was advised for confirmation.

Subsequent skin biopsy showed the presence of many histiocytes with intracellular H. capsulatum [Figure 1d]. These organisms revealed positive staining with the PAS stain. Bone marrow examination revealed an increase in the number of histiocytes, the presence of toxic granules and cytoplasmic vacuoles in myeloid cells, and an occasional macrophage showing the H. capsulatum. The culture study for isolation of H. capsulatum was not successful.

Computed tomography (CT) thorax and abdomen revealed multiple cavitatary nodules with feeding vessel sign in bilateral lungs, mediastinal, mesenteric and retroperitoneal lymphadenopathy, hepatomegaly with multiple granulomas, and splenomegaly with upper pole abscess. The patient had no laboratory evidence of immunodeficiency.

The patient was started on intravenous amphotericin B. On the 5th day of the treatment, the clinical condition of the patient worsened due to deranged coagulation profile leading to disseminated intravascular coagulation. In the following 48 h, the patient developed respiratory arrest, followed by cardiac arrest, and expired.

**Discussion**

Disseminated histoplasmosis is an uncommon airborne disease caused by dimorphic fungus H. capsulatum from the soil infected with bird and bat excreta. The course of the illness may be acute, which is seen primarily in infants and immunocompromised patients with high-grade fever with anemia, leukocytopenia, thrombocytopenia, and hepatosplenomegaly. Chronic disseminated histoplasmosis is associated with destructive lesions in the number of organs and occurs almost exclusively in adults. The early clinical manifestation are nonspecific, often leads to diagnostic difficulty, and is misdiagnosed as tuberculosis due to the high prevalence of tuberculosis in India. Similar diagnostic dilemma in our case must have led to the early start of ATT and delay in diagnosis. The predisposing factors for histoplasmosis are extremes of age, immunosuppressed patients, acquired immunodeficiency disease syndrome, cancer, solid organ or bone marrow transplant, and corticosteroid therapy. However, the patient in this case was immunocompetent and did not show any clinical improvement. The sites most commonly involved in disseminated histoplasmosis are lungs, lymph nodes, spleen, liver, bone marrow, gastrointestinal tract, adrenal, and the mucus membrane of the oral cavity. The skin involvement is rare in disseminated disease and
occurs in only 6% of patients in the form of hyperpigmented, erythematous nodule, papule, or ulcerative lesions. In our case, the patient had unusual molluscum contagiosum-like umbilicated lesions all over the face. Such lesions have been described in cutaneous histoplasmosis in HIV-positive patients. Contrary to which, the index case describes these lesions in an immunocompetent individual and as a part of disseminated disease process.

The common cytological differential diagnosis includes, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis and Leishmania donovani. The size of the organism, localization (intracellular or extracellular), and cytomorphology helps differentiate from *H. capsulatum* [Table 1].

The development of specific nucleic acid probes has facilitated the identification of *H. capsulatum* in cultures with atypical morphology. Intravenous amphotericin B is the recommended treatment to reduce mortality in patients with disseminated histoplasmosis. In our case, amphotericin treatment could not limit the disease progression and the patient succumbed to shock due to respiratory failure and coagulopathy.

In the index case, the patient’s initial symptoms mimicked tuberculosis with nondiagnostic laboratory investigations. The unusual finding that needs to be emphasized is the disseminated disease with uncommon skin lesions in an immunocompetent patient. Fine needle aspiration cytology (FNAC) of the lymph node was the only tool for rapid and early confirmatory diagnosis. FNAC is a simple, safe, and quick technique to establish the initial diagnosis of *H. capsulatum*, thereby prompting early treatment.

Although, hyperpigmentation and erythematous papules and nodules are common skin manifestations, histoplasmosis may be suspected as well in cases with molluscum contagiosum-like skin lesions in association with lymphadenopathy, fever, and weight loss.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Jaiswal S, Viz M, Chand G, Misra R, Pandey R. Diagnosis of adrenal histoplasmosis by fine needle aspiration cytology: An analysis based on five cases. Cytopathology 2011;22:323-8.
2. Gupta N, Arora SK, Rajwanshi A, Nijhawan R, Srinivasan R. Histoplasmosis: Cytodiagnosis and review of literature with special emphasis on differential diagnosis on cytomorphology. Cytopathology 2010;21:240-4.
3. Seema S, Kumari N, Ghosh P, Aggarwal A. Disseminated histoplasmosis in an immunocompetent individual — A case report. Indian J Pathol Microbiol 2005;48:204-6.
4. Mukherjee A, Tangri R, Verma N, Gautam D. Chronic disseminated histoplasmosis bone marrow involvement in an immunocompetent patient. Indian J Hematol Blood Transfus 2010;26:65-7.
5. Hinshaw M, Longley BJ. Fungal diseases. In: Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, Xu X, editors. Lever’s Histopathology of the Skin. 10th ed. New Delhi: Lippincott Williams & Wilkins; 2010. p. 611.
6. Arghya B, Kaushik M, Mimi G, Subrata C. Cytodiagnosis of cutaneous histoplasmosis in HIV positive patient initially presenting with multiple umbilicated disseminated skin nodules. Diagn Cytopathol 2013;41:459-62.
7. Rana C, Krishnani N, Kumari N. Bilateral adrenal histoplasmosis in immunocompetent patients. Diagn Cytopathol 2011;39:294-6.