

Histoplasmosis on bone marrow aspirate smears associated with hemophagocytosis in a patient with Tuberculosis

Sir,

Histoplasmosis infection causes spectrum of illness ranging from transient respiratory infections to disseminated disease. It is caused by a dimorphic fungus *Histoplasma capsulatum* [1-3] and the mode of infection is through inhalation of its spores. The disseminated histoplasmosis is not common and can present as acute, subacute or chronic illness [2-4]. The acute form is fatal and usually seen in immunocompromised individuals while the chronic form has an indolent course.

A 42-year-old male presented to hospital with fever with chill, loss of weight and appetite along with fatigue for last three months. He also had cough with expectoration and shortness of breath for last 1.5 months. On examination few enlarged lymph nodes were found in right posterior triangle of neck and epitrochlear region. Per abdominal examination revealed splenomegaly and enlarged left lobe of liver.

Complete blood count showed haemoglobin of 9 gm/dl, total leukocyte count of 6300/ μ L (with differential count: polymorphs-75%, lymphocyte- 23%, eosinophils-02%, monocyte-01%) and platelet count-1.4 lacs/ μ L. Red blood cells were normocytic normochromic with leukocytes within normal range and adequate platelets on peripheral smear examination. His erythrocyte sedimentation rate was increased with 44mm/hr. His serum electrolytes, liver and kidney function tests were within normal limit. His blood & urine culture did not show any growth while Malaria & Leishmaniasis were ruled out (RK-39 antibody negative).

Ultrasound of abdomen revealed massive splenomegaly (20cms) and cholelithiasis. Contrast enhanced computed tomography (CECT) thorax revealed subtle alveolar opacities in right middle lobe with ground glass opacities in the lateral basal segment of right lower lobe. A provisional diagnosis of Swine flu viral pneumonia was made, however, the real time PCR was also negative. Tuberculosis was confirmed on ELISA and the patient was started on anti-tubercular drugs.

Bone marrow examination showed erythroid series cells with predominantly normoblastic reaction (few megaloblasts) and myeloid cells in all stages of maturation. Megakaryocytes were adequately seen. Many scattered histiocytes were seen containing intracellular yeast forms of *Histoplasma spp.* (Fig. 1a-d). Bone marrow biopsy confirmed the presence of yeast forms which showed Per-iodic Schiff (PAS) stain positivity. Lymph node biopsy also revealed the presence of *Histoplasma organism* (PAS positive). Based on the bone marrow cytomorphology along with clinical, radiological and histological details, a diagnosis of "Disseminated Histoplasmosis" was made.

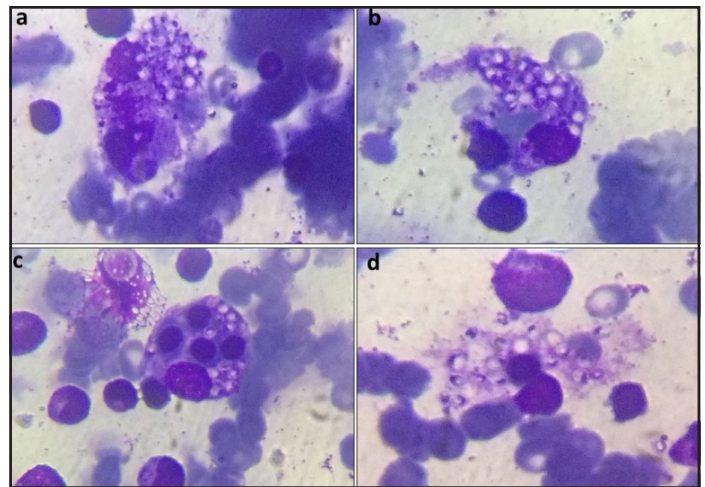


Figure 1(a-d): Bone marrow aspirate smears showing hematopoietic cells along with numerous intra-cellular and extra-cellular spores of *Histoplasma spp.* with a clear halo around them [a-d: Leishman, 400X]

Histoplasma capsulatum is a thermally dimorphic fungus. Majority of infections are asymptomatic in immunocompetent hosts, but clinical disease is common in immunosuppressed patients. Pulmonary disease is most common; however, as a part of disseminated disease gastrointestinal histoplasmosis may cause diarrhea, bleeding, pain, nausea, vomiting, flu-like symptoms or obstruction [3-5].

The predisposing factors for this infection are extremes of age and patients with cancer, solid organ or bone marrow transplant [2-5]. The common sites involved in disseminated histoplasmosis are lungs, lymph node, spleen, liver, bone marrow, gastrointestinal tract, adrenal gland, and mucous membrane of the oral cavity; rarely skin [3-6].

As the early clinical manifestations of such infections are non-specific, it often leads to diagnostic difficulty and is misdiagnosed as tuberculosis due to its high incidence in India. In our case also, TB was a differential and the diagnosis of TB was confirmed on PCR. The patient was started on ATT as well. Hemophagocytosis may be an important feature observed during marrow examination in cases of infections. These infections may include tuberculosis, typhoid, leishmaniasis, malaria, and fungal infections, such as histoplasmosis and candidiasis [4-6]. In the index case, many scattered histiocytes were noted with intracytoplasmic yeast forms of *Histoplasma*. Bone marrow cytomorphology helped in revealing an underlying infection in conjunction with diagnosis of TB in the same patient.

The common cytomorphological differential diagnosis includes various infections like *cryptococcosis*, *blastomycosis*, *Coccidioides infection* and *Leishmaniasis* [4-7]. However, a careful examination of cytomorphology, size, and location

of these organisms helps in differentiating these from *H. capsulatum* [4-7]. The yeast forms of *Histoplasma* are 2-5 µm in size with basophilic crescent shaped nucleus seen within macrophages; even extracellular often with a pericellular halo. It can be easily differentiated from *Leishmania donovani* which is 2-4 µm, small intracellular protozoa and has a kinetoplast.

Cryptococcus is slightly larger in size (4-12 µm) with a tear-drop shaped buds and spores with a distinct mucopolysaccharide rich wide capsule [3-6]. *Blastomyces dermatidis* are 8-15 µm in size and has thick walled spore with a broad-based bud and double contoured wall. Similarly, *Coccidioidomycosis immitis* can be differentiated on cytology because of larger size (10-80 µm) and having thick walled spore with granular cytoplasm. The larger spore would contain endospore as well. So, keeping these cytological findings in mind we can easily differentiate these organisms on basis of morphology [3-7]. Intravenous amphotericin B is the recommended treatment to reduce mortality in patients with disseminated histoplasmosis infection [6-7].

To conclude, the present case highlights that hemophagocytosis in the marrow may be an early sign of underlying secondary infection in a patient of tuberculosis. Careful examination of bone marrow smears may help in correct identification of subtle infections. In our case, correct identification of yeast forms of *Histoplasma capsulatum* helped in initiating the treatment at the earliest thereby preventing the unwanted complications.

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