

Hemophagocytosis with disseminated histoplasmosis detected through bone marrow analysis - a case report

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Abstract

Background: Histoplasmosis is caused by *Histoplasma capsulatum* which can lead to a broad spectrum of disease. Culture remains the gold standard till date; however, this is a slow-growing fungus that may take a considerable time before a conclusion can be made. This case highlights the importance of careful bone marrow evaluation to identify the fungal bodies, especially in the presence of increased hemophagocytic activity.

Case Presentation: We present a 36-year-old man with newly diagnosed retroviral disease, presented with fever, pancytopenia, and hepatosplenomegaly. Bone marrow aspirate smear showed increased hemophagocytic activity with the presence of intracellular organisms. Trephine biopsy showed similar features with the presence of fungal bodies detected via Periodic acid-Schiff stain.

Conclusion: In conclusion, bone marrow examination plays a crucial role in the diagnosis of some fungal infections, especially in centers where culture or serological tests are not readily available.

Keywords: *Histoplasma capsulatum*, histoplasmosis, HLH, hemophagocytosis, pancytopenia, case report.

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Background

Histoplasmosis is a widespread infection resulting from *Histoplasma capsulatum*, manifesting across a range of conditions from asymptomatic to severe disseminated disease. While most patients only show mild symptoms and a self-limiting infection, immunocompromised patients can become severely ill and this can lead to mortality. Diagnosis of this infection has been through culture which has remained as the gold standard. Unfortunately, they are a slow-growing fungal organism which can delay the identification and treatment. Thus, other means of detection such as bone marrow examination may play a pivotal role in the detection of these organisms.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition where the immune system becomes overactive. It can be triggered by various forms of infections; however, it is easy to be overlooked during bone marrow examination, especially in subtle cases. We emphasize the importance of careful bone marrow examination to detect the presence of hemophagocytosis and intracellular organisms to assist in the prompt treatment of the patients.

Case Presentation

The patient was a 36-year-old male who was diagnosed with retroviral disease 1 month before presenting to our hospital with persistent fever of 38°C–39°C and pancytopenia. He was initially started on HAART treatment; however, they were with-held due to derangements in renal profile and liver functions. Clinical examination showed the presence of hepatosplenomegaly. Hematological investigations showed persistent pancytopenia with hemoglobin of 6.5g/dl, WBC of $1.2 \times 10^9/l$ with ANC of $0.8 \times 10^9/l$, and platelet of $68 \times 10^9/l$. There was no any absolute lymphocytosis. His full blood picture did not show any abnormal lymphoid cells. Ferritin was markedly raised with >2,9511.20 ng/ml. Triglyceride level was 45 mg/dl which is considered optimal. Serum fibrinogen was 170 mg/dl which is slightly reduced. His peripheral blood culture did not yield any significant growth. Considering the presence of pancytopenia and fever without an obvious cause, we conducted a bone marrow examination. The bone marrow smear shows normocellularity with left-shifted maturation of granulocytes. No increase in blasts or lymphopoiesis was noted. There were presence of histiocytes with some hemophagocytic activity. Interestingly,

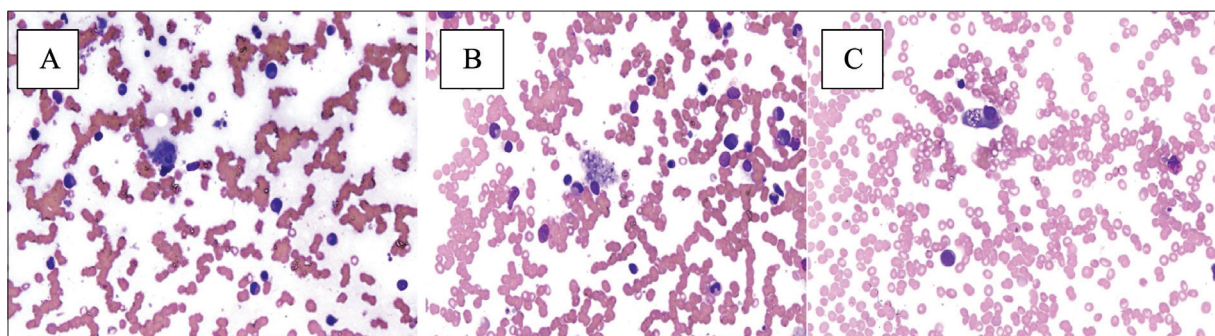


Figure 1. Bone marrow aspirate showing (A) Increase in haemophagocytic activity (X400), (B & C) Presence of intracellular organisms which were encapsulated found within the macrophages (X400).

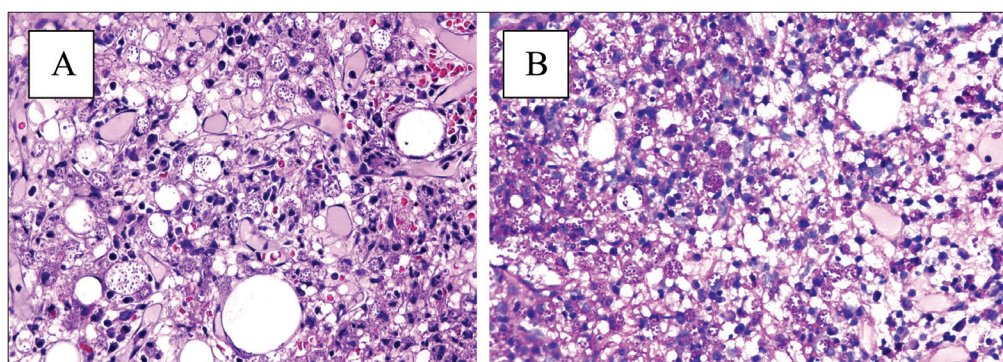


Figure 2. Trephine biopsy (A) Presence of encapsulated intracellular organism in H&E (X400). (B) PAS stain highlighting the encapsulated fungal bodies (X400).

there were presence of intracellular organism seen within the histiocytes which were spherical to oval with the presence of surrounding halo. These organisms were also seen extracellularly. Trephine biopsy showed the presence of fungal bodies which were encapsulated, highlighted by Periodic acid-Schiff (PAS) stain, morphologically likely to be *H. capsulatum*. No increase in blasts or any lymphoid clusters were seen. Fungal culture from the bone marrow aspirate showed a slow-growing mold which was white brown with a cottony appearance. Lactophenol cotton blue (LPCB) stain of the isolated mold was done, and it showed an abundant spherical-shaped macroconidia and microconidia with long septate hyphae. There was an occasional presence of a knobby appearance of tuberculate macroconidia. Therefore, the isolate was sent to the referral lab for confirmation using polymerase chain reaction (PCR) which identified the fungal as *H. capsulatum*, further confirming our findings.

Unfortunately, the patient succumbed to his illness due to severe sepsis before any further intervention could be done.

Discussion

Hemophagocytosis is a serious condition characterized by the excessive activation of the immune system, causing the destruction of blood cells by macrophages. They can be triggered by various conditions such as infection, lymphoma, or HLH. While lymphokines secreted by lymphoma cells may cause increased macrophage proliferation

and phagocytosis in lymphomas, impaired cytotoxic function of natural killer cells and cytotoxic T-lymphocytes potentially be the cause of the overactive but ineffective immune response in HLH [1,2]. Following the binding of Fc and C3b receptors during an infection, the antigen undergoes engulfment and subsequent destruction through phagocytosis [3]. A frequent observation in AIDS cases is the connection between HLH and *H. capsulatum* [4,5]. In our case, the possibility of other infections has been ruled out through blood culture and thorough examination of peripheral blood and bone marrow.

Patients with HIV/AIDS are most commonly affected with histoplasmosis globally [6,7]. Other immunocompromised individuals who are susceptible to histoplasmosis include those who have had transplants, are using immunosuppressive medications (such as steroids), or have hematological malignancies [7,8]. Histoplasmosis symptoms can vary based on the patient's characteristics, the site of infection, and the severity of the illness. Common symptoms include fever, coughing, exhaustion, and weight loss [7,9].

Histoplasmosis is induced by a dimorphic fungus, *H. capsulatum* which can appear as a yeast form within the body's temperature and as a hyaline mold form in the natural surroundings [7,10]. The yeasts are round to ellipsoidal, have a purple nucleus, and are surrounded by a clear halo. The majority of them are found inside cells, while some may be located outside macrophages [7,10].

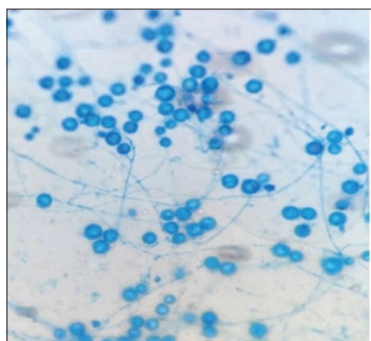


Figure 3. LPCB mount showing spherical-shaped macroconidia and microconidia with long septate hyphae highly suggestive of *H. capsulatum*.

Table 1. HLH 2004 criteria (at least 5/8 parameters need to be fulfilled).

Fever	≥ 38.5°C
Hypertriglyceridemia/hypofibrinogenemia	Fasting Triglycerides ≥300 mg/dl or Fibrinogen <150 mg/dl
Cytopenias	Two or more cell lines
Hyperferritinemia	≥500 ug/l
Hemophagocytosis	Evidence of hemophagocytosis in bone marrow, lymph nodes, spleen
Splenomegaly	-
Low/absent NK cell activity	-
sCD25	≥2,400 U/ml

The laboratory diagnosis of Histoplasmosis still relies primarily on culture, which is considered the gold standard, however, these organisms are slow-growing and typically require 2-3 weeks, but sometimes up to 8 weeks [7,10]. For quicker detection, other techniques such as serology or direct examination can be used. Although serology is helpful for diagnosis, not all laboratory facilities have access to it as in our center. Direct examination under a microscope can provide imaging evidence of *Histoplasma* [7,10]. In a limited resource setting as in our center, we had to rely on a referral laboratory for the definite diagnosis of the organism which surely would consume time and eventually delay treatment for the patient.

Our patient presented with pancytopenia and showed evidence of hemophagocytosis in the bone marrow. The diagnostic criteria for HLH in the 2004 guidelines have been previously established [11] (Table 1). Our patient fulfills the criteria of HLH (fever, elevated ferritin, hemophagocytosis in bone marrow, cytopenias affecting 2 of 3 blood lineages, and splenomegaly). Serum fibrinogen is approaching the HLH criteria. Unfortunately, we do not have the tests for NK-cell activity or CD25. However, it is essential to emphasize that hyperferritinemia by itself is not exclusive to HLH, as this can be seen elevated in acute phase reaction as well [5,10,12] although marked

elevation as in our case could be a strong indicator for HLH provided other criterias are met.

Conclusion

This case illustrates how the bone marrow examination was especially helpful in identifying the patient's infection as some of the corroborative assays take longer to produce the results. In immunosuppressed prospective HLH patients, a high degree of clinical suspicion for infection is required in both pathologic and clinical practice.

What is new?

There were case reports published previously regarding histoplasmosis; however, this case report highlights the importance of bone marrow examination in detecting the organisms in a center with no serological method for confirmation, thus, posing a challenge.

Acknowledgement

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List of Abbreviations

HLH	Hemophagocytic lymphohistiocytosis
LPCB	Lactol-phenol-cotton blue
PAS	Periodic acid-Schiff
PCR	Polymerase chain reaction.

Conflicting interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

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Consent for publication

Written informed consent was obtained from the next of kin.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

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Summary of the case

1	Patient (gender, age)	36 years old, male
2	Final diagnosis	Disseminated histoplasmosis with hemophagocytosis
3	Symptoms	Fever
4	Medications	HAART - with-held
5	Clinical procedure	Bone marrow examination, blood culture, PCR
6	Specialty	Pathology