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CASE REPORT

Histoplasmosis on bone marrow aspirate cytological examination associated with hemophagocytosis and pancytopenia in an AIDS patient

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A 38-year-old woman who presented with unexplained fever and pancytopenia was subjected to a bone marrow examination. Her bone marrow aspirate smear showed no obvious pathological finding except for the presence of hemophagocytosis and mild plasmacytosis. In view of hemophagocytosis, a thorough examination of the smear was conducted and revealed the presence of histoplasmosis. She was advised to undergo evaluation of her immunological status, and she tested positive for human immunodeficiency virus (HIV) infection. This case highlights that hemophagocytosis in the marrow may be an early sign of underlying disease, and that careful examination of bone marrow smears may reveal subtle infections. In addition, histoplasmosis with hemophagocytosis may be associated with pancytopenia, and hence, the HIV status of the patient should always be investigated.

Key Words Hemophagocytosis, Histoplasmosis, Bone marrow examination, Pancytopenia

INTRODUCTION

Although hemophagocytosis is an interesting phenomenon, it is commonly overlooked during bone marrow examination. Hemophagocytosis may be associated with infections, ineffective hemopoiesis, leukemia, granulocyte-macrophage colony stimulating factor therapy, or hemophagocytic lymphohistiocytosis (HLH) [1]. Hemophagocytosis is the phenomenon of engulfment and phagocytosis of hemopoietic cells, neutrophils, erythrocytes, or cellular debris by macrophages or histiocytes. We present this case because it emphasizes the fact that hemophagocytosis observed on bone marrow examination may provide an early hint for a thorough examination of the marrow for any latent infection. In addition, patients with histoplasmosis on bone marrow examination may present with pancytopenia, and hence, their human immunodeficiency virus (HIV) status should always be investigated.

CASE REPORT

The patient was a 38-year-old woman residing in Uttarakhand state, which is situated in the Northern Himalayan region of India. She had no significant travel history and presented with unexplained fever associated with chills, rigors, cough, and loss of appetite for the past 2 months. Clinical examination showed that the patient had anemia and bilateral cervical lymphadenopathy with right-sided pleural effusion. Hematological investigations showed that she had progressive pancytopenia (hemoglobin, 4.7 g/dL; total leukocyte count, 1.6×10^9/L; and platelet count, 30×10^9/L). Her blood culture examination tested negative for tuberculosis and typhoid, and her rapid malarial test (QDx Malaria Pv/Pf; Piramal Healthcare, India) for *Plasmodium vivax* and *Plasmodium falciparum* also tested negative. A careful examination of the peripheral blood smear showed no evidence of malarial parasites or any other organism. In view of pancytopenia and unexplained pyrexia, we performed a bone marrow examination. The bone marrow aspirate smears were normocellular for age and showed normoblastic erythroid

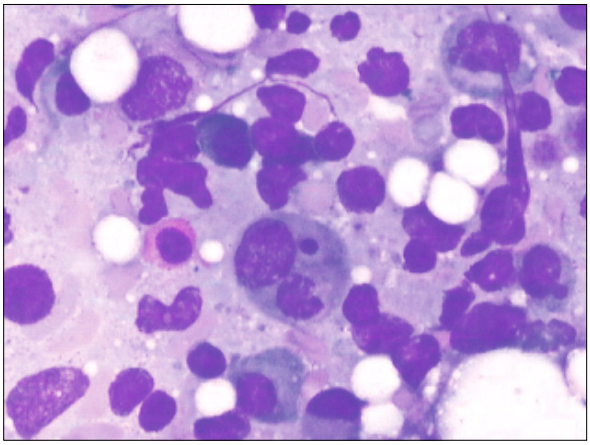

Fig. 1. Bone marrow aspirate showing hemophagocytosis (Jenner-Giemsa stain; 400×).

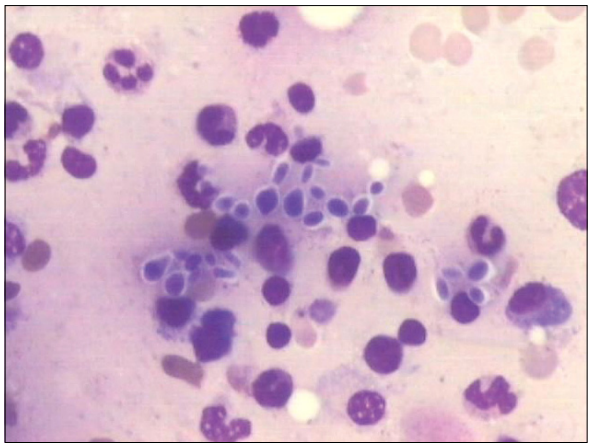

Fig. 2. Bone marrow aspirate showing yeast-like cells of histoplasmosis with a clear halo around them (Jenner-Giemsa stain; 400×).

hyperplasia with increased plasma cells (12%), but showed no obvious pathological finding. Interestingly, however, the bone marrow smear showed hemophagocytosis (Fig. 1). In view of hemophagocytosis and increased number of plasma cells, we conducted a thorough examination of the smear for signs of infection. The bone marrow aspirate smear showed negative staining for acid-fast bacilli (Ziehl-Neelsen stain). A detailed examination of the smears revealed very few fungal hyphae and oval, budding yeast-like cells that were morphologically identified as *Histoplasma*. The yeast-like cells were spherical to oval, measured 2-4 μm in diameter, and had a clear space or halo around them (Fig. 2). Staining with Gomori's methenamine silver also revealed pseudohyphae showing segmental constrictions (Fig. 3). The patient was advised to undergo an evaluation of her immunological status and was found to be positive for HIV infection. She responded effectively to ketoconazole.

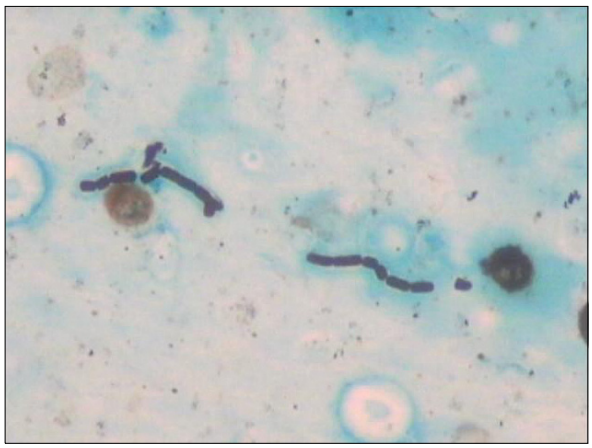

Fig. 3. Bone marrow aspirate showing pseudohyphae budding from yeast-like cells (Gomori's methenamine silver stain; 400×).

DISCUSSION

Hemophagocytosis results from immunological activation that may be triggered in response to various conditions such as infection, lymphoma, or HLH. In lymphomas, the enhanced macrophage proliferation and phagocytosis may be in response to the lymphokines secreted by lymphoma cells; whereas, in HLH, the highly stimulated but ineffective immune response may be a result of defective cytotoxic function of natural killer cells and cytotoxic T-lymphocytes [1, 2]. During an infection, phagocytosis involves binding of the Fc and C3b receptors followed by engulfment and destruction of the antigen [3]. Hemophagocytosis may be an important feature observed during marrow examination in cases of infections [4]. These infections may include tuberculosis, typhoid, leishmaniasis, malaria, and fungal infections, such as histoplasmosis and candidiasis. In the present case, the possibility of tuberculosis, typhoid, leishmaniasis, and malaria were excluded by blood culture and careful examination of the peripheral blood and bone marrow aspirate smear.

Histoplasmosis is a rare fungal infection observed in the bone marrow, and compromised immunity due to malignancies, chemotherapy, organ transplantation, and AIDS are considered important predisposing factors for disseminated histoplasmosis [5, 6]. Pancytopenia may be associated with histoplasmosis, particularly in patients showing hemophagocytosis [7, 8]. Our patient presented with pancytopenia and showed the presence of hemophagocytosis in the marrow; this was an early indicator of infection. This was followed by a thorough examination of the smears, revealing the presence of mild histoplasmosis, in which *Histoplasma* manifested in the form of fungal hyphae and oval budding yeast-like cells. A previous report has documented the case of a newborn, who was diagnosed with histoplasmosis on the basis of peripheral blood smear analysis [9]. Although *Cryptococcus* and *Blastomyces dermatitidis* may resemble

the yeast forms of *Histoplasma*, they can be differentiated on the basis of the feature that cryptococci are usually carminophilic, and *B. dermatitidis* cells are multinucleated, thick-walled, and bud from a broad base [10]. Viral infections such as those caused by the Epstein-Barr virus (EBV) may also be associated with hemophagocytosis, but our patient was not investigated for EBV infection, because she refused to undergo further tests. Because immunodeficiency is an important predisposing factor for disseminated histoplasmosis, we advised our patient to undergo testing for histoplasmosis; she then tested positive for HIV infection. Jeong *et al.* have also reported a case of disseminated histoplasmosis in a patient with HIV infection, where the bone marrow smear examination revealed numerous *Histoplasma capsulatum* cells [11]. In contrast to our case, the aforementioned case was associated with tuberculosis, and the authors suggested that histoplasmosis should be considered along with tuberculosis in immunocompromised patients, because disseminated histoplasmosis and tuberculosis have similar clinical manifestations. However, cases of histoplasmosis in immunocompetent individuals have also been reported [12, 13].

Thus, if hemophagocytosis is observed on a bone marrow examination, clinicians should immediately consider the associated conditions, and this should be followed by a thorough examination of the marrow for any subtle pathological finding, including infections. In addition, histoplasmosis with hemophagocytosis may be associated with pancytopenia, and the HIV status of the patient should always be examined.

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