Case Report

Hemophagocytosis and miliary tuberculosis in a patient in the intensive care unit

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Abstract

We report a 60-year-old woman who was admitted to our hospital with high-grade fever and dyspnea. Laboratory findings showed pancytopenia and examination of aspirated bone marrow showed mature histiocytes with marked hemophagocytosis. The patient's condition continued to deteriorate despite adequate antibiotic coverage. Her respiratory condition worsened, so she was transferred to the ICU and ventilated. Transbroncheal biopsy was performed, which showed caseating granuloma suggesting pulmonary TB. Eight weeks later, bone marrow culture in Lowenstein media confirmed the presence of mycobacterium tuberculosis susceptible to INH, Rifampcine, pyrasinamide, ethambutol and streptomycin. Though anti-tuberculous therapy was started, she died after 28 days of hospitalization.

Key words: Hemophagocytosis, critically ill patient, miliary tuberculosis

In 1979, Risdall *et al*[1] first introduced the term, "virus associated hemophagocytic syndrome" (HPS) and laid down the criteria for its separation from malignant histiocytosis. The syndrome is characterized by high fever, constitutional symptoms, lymphadenopathy, hepatosplenomegaly, skin rashes, pancytopenia and liver function and coagulation abnormalities. The pathologic hallmark of this condition is benign histiocytic proliferation and striking hemophagocytosis in the bone marrow and lymph nodes. Among infection-associated HPS, *Mycobacterium tuberculosis* infection has been described as a severe but infrequent cause.[2]

Case Report

A 60-year-old woman with a history of diabetes mellitus type II and hypertension on regular treatment, was admitted to the hospital with symptoms of fever and productive cough. Her symptoms started about two weeks before admission, with fever for three days followed by productive cough. Other medical history was unremarkable. On examination, the patient was in distress with respiratory rate of 28/minute. The pulse was 120/min; BP 90/60 mmHg; Lung examination showed bilateral crepitation. The remainder of her examination was unremarkable. Initial arterial blood gas (ABG) analysis while receiving oxygen at 3 L/min via nasal cannulas, showed pH of 7.46, PaO_2 of 70 mm Hg, $PaCO_2$ of 30 mm Hg and HCO_3^- of 20 mEq/L. The leukocyte count was 2970/μL with 90% neutrophils; platelet count, 95,000/μL; hemoglobin, 9.5 g/dL;_Blood chemistry, liver profile and coagulations studies were within normal limits; C-reactive protein was elevated**.** PPD test was negative with a negative anergic panel. Legionella, brucella, mycoplasm titers were negative, as well as HIV ELISA test was negative, while CD4 cell count was not carried out in this patient.

Malaria parasite smear was negative, as well as two sets of blood cultures and urine culture were negative. Chest radiograph and computed tomography scan showed diffuse reticulonodular shadow [Figure 1].

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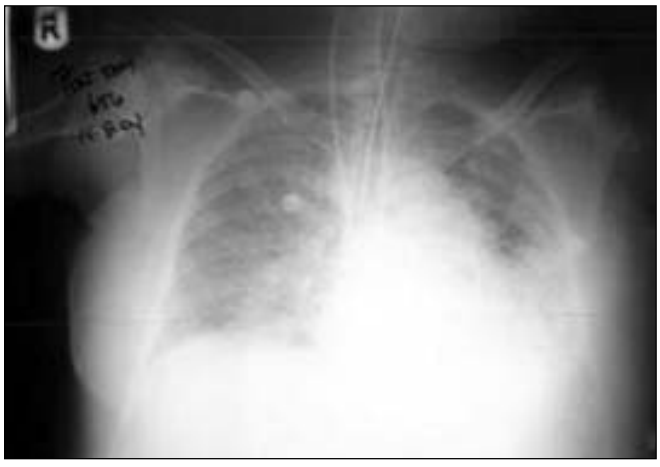

Figure 1: Chest X-ray shows bilateral infiltration

Abdomen ultrasound and CT abdomen showed normal study; she was treated as having atypical pneumonia with ceftrixone and azithromycin with no improvement.

The patient was transferred to the medical intensive care unit with shock (BP, 60/40) and high fever, not responding to multiple drugs. She was intubated and ventilated with assist control, central line was inserted and inotropes was started. Bone marrow aspiration and biopsy were done and amikacine, teicoplanin, fluconazole and meropenum were initiated empirically. Bone marrow aspiration and biopsy showed hemophagocytosis [Figure 2]. Broncheoalveolar lavage (BAL) was negative for malignancy, AFB, gram staining and culture; Echocardiography revealed normal study; Transbroncheal biopsy showed caseating granuloma suggesting pulmonary TB. Consequently, antituberculous was initiated with four drugs. Eight weeks later, sputum, BAL and bone marrow cultures in Lowenstein media confirmed the presence of mycobactrium tuberculosis.

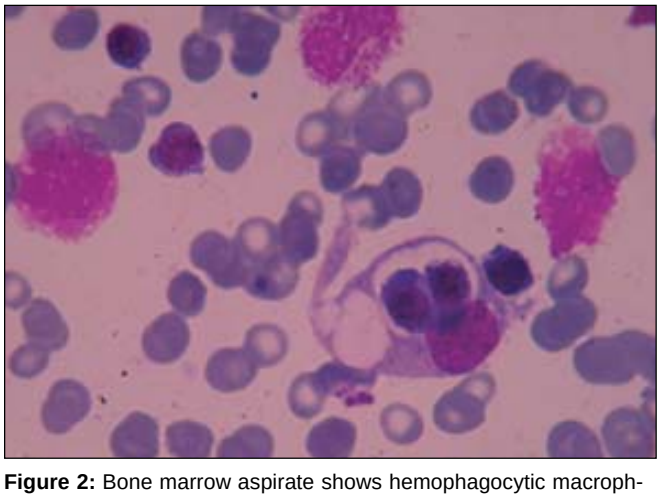

Figure 2: Bone marrow aspirate shows hemophagocytic macrophage engulfing a neutrophil and platelets. (MG Giemsa stain 1000x)

On the following days, the patient's condition deteriorated and she expired soon thereafter.

Discussion

Two main forms of hemophagocytic syndrome are recognized - primary (familial) and secondary - the latter associated with either infection or malignancy.[3-5] Both forms are associated with proliferation of benign macrophages that demonstrate avid phagocytosis of hematolymphoid cells in reticuloendothelial organs and bone marrow (BM).

Familial hemophagocytic syndrome is an autosomal recessive disorder, usually presenting in infancy, associated with constitutional defects in the cytotoxic function of T cells and NK-cells.[4] The defect in cytotoxicity results in uncontrolled T-cell and monocyte activation and hypercytokinemia.

Secondary hemophagocytic syndrome has been associated with a variety of viral, bacterial (including tuberculosis), fungal and parasitic infections, as well as collagen-vascular diseases[6-11] and malignancies, particularly T-cell lymphomas.[12-14]

Infection-associated hemophagocytic syndrome occurs predominantly in immunocompromised patients and is usually fatal. The disorder is rare in apparently immunocompetent patients with variable outcome.[1-14] Patients with infection-associated hemophagocytic syndrome also have defective cytotoxic function, T-cell and macrophage activation and hypercytokinemia, but the cytotoxic defect is transient in these patients.

The clinical presentation of miliary TB is highly variable. Subacute or chronic presentations are more common than acute presentations[15] (the median duration of illness 2 month). The nonspecific nature of the presentation may account for the fact that this diagnosis is often missed.[16-18] Our patient presented with fever, pancytopenia and weight loss. There was no skin rash or organomegaly and the liver function test and coagulation profile were normal. The diagnosis of disseminated tuberculosis in this patient was delayed, because the sputum and broncheoalveolar lavage (BAL)

stain for AFB were negative. Consequently early initiation of antituberculous treatment was delayed, which lead to deterioration of patient's condition and death.

Secondary HPS associated with pathogens other than EBV, including sepsis, typhoid fever, tuberculosis and leishmaniasis, may resolve with treatment of the underlying infection in 60-70% of cases.[19,20] Among adults with HPS, age > 30 years appears to be associated with an increased risk for death.[21] In general, tuberculosis-associated HPS carries a poor prognosis both in HIV and non-HIV-infected patients.[2] The poor prognosis is due to delayed diagnosis and compromised immunity.

Although the prominent bone marrow hemophagocytosis, fever and pancytopenia may lead to diagnostic confusion, patients in the intensive care unit with hemophagocytic syndrome should be vigorously screened for tuberculosis, to initiate antituberculous therapy early to improve the outcome.

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