Hemophagocytic Lymphohistocytosis Secondary to Tuberculosis: A case report

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ABSTRACT
We report a case of 32 years old male with severe tuberculosis that presented with hemophagocytic lymphohistisocytosis in Sudan line hospital in Port Sudan, Eastern Sudan, in which TB diagnosis depend on PCR and HLH showed five diagnostic and two supportive criteria.

Keywords: Hemophagocytic, lymphohistocytosis, tuberculosis

1. INTRODUCTION

inflammatory condition that occur as primary or acquired. Primary form denotes genetic abnormalities in various protein, while acquired type occurred secondary to many conditions such as malignancy mainly lymphoma, viral infection like EBV, fungal infection, parasitic infection, granulomatous disease and autoimmune disorders. It is characterized by the proliferation of histocytes with phagocytosis of formed elements of blood. Clinical manifestations include signs and symptoms of immune activation and cytopenias.

Pathophysiology
The pathophysiology of HLH depend on a defect in N.K cell and cytotoxic T. cell either absence of them or loss of their function. When N.K cell fail to kill the target infected cell, over stimulation of immune system occur, and this lead to excess of antigen presentation and T- cell proliferation, which is infiltrate organs such as liver, lymph nodes and CNS and this leads to formation of cytokines which is activate macrophage that result in haemophgocytosis.

Criteria of diagnosis [1]
A. Molecular diagnosis of HLH which is used to diagnose the primary type or
B. Three of the following four criteria:
1. fever
2. splenomegaly
3. hepatitis
4. cytopenias plus
C. one of the following four criteria
1. Haemophagocytosis
2. High ferritin
3. increased soluble IL2
4. Absent or decreased NK cells)
D. Supportive criteria of HLH:
1. Hypertriglyceridemia
2. Hyponatraemia
3. hypofibrinogenemia

Treatment
Steroid which is inhibit expression of cytokines. IVIG which is provide cytokine specific antibodies, etoposide which has activity against macrophage. And treatment of underline cause.

2. CASE PRESENTATION

32 years old male, miner, presented with productive cough of moderate amount purulent sputum, throughout the day for the last three months, his condition associated with persistent fever, that doesn’t associate with rigor nor sweating. He lost 12.5% of his weight during the last three months, this precipitated by poor appetite. Four days before presentation he developed dizziness, palpitation, fatigability and abdominal pain. Physical examination revealed that patient was emaciated, febrile and pale. PR 104 beat /min collapsing, RR 21/min, BP 90/50, Temperature 39c, SO2 96%
Systemic examination revealed palpable spleen 4 cm below costal margin, firm, not tender. The rest of examination was unremarkable. Laboratory studies as follow:
TWBCS 6.1 X 10/µL, RBC 3.26 million/µL, HB 7.6 g/dl , HCT 24.7%, MCV 75.8 fl , MCH 23.3 pg , MCHC 30.8 g/dl , platelets 108 x10/ µL , lymphocytes 2.6 x10/ µL , neutrophils 2.8x10 /µL , monocytes 0.5 x 10/ µL, eosinophil 0.2 x 10/ µL, basophil 0.0 x 10 µL .
Peripheral blood film showed leucoerythroblastic blood picture and no blast nor dysplasia. Blood Urea 23.1 mg/dl, serum creatinine 0.99 mg/dl, s. Albumin 2.8g/dl, s. AST 94.5 IU/L, s. ALB 383 IU/L, s. Na 130 mmol/L, s. k 3.9 mmol/L, s. ferritin 2942 µg/L, triglyceride 280 g/dl, ESR 135 mm/hr, serology for HIV, hepatitis B & C, and brucellosis were negative, blood film and ICT for malaria negative, ANA negative, ds DNA negative, rheumatoid factors negative, TST 21 mm (positive), PCR for mycobacterium tuberculosis positive . Bone marrow aspirate showed hyper cellular marrow for his age, normal hemopoesis depressed, bone marrow infiltrated by collection of histocytes, some of them showed hemophagocytes. Trephine biopsy was hypercellular with normal architectures. Histocyte infiltrate the marrow and some of them showed hemophagocytosis. No infiltration of malignant cell. Small granuloma seen. Z-N stain negative.
CXR was normal. Abdominal CT showed splenomegaly and mild ascites.

Figure 1: abdominal CT

Diagnosis
Hemophagocytic Lymphohistocytosis on top of Disseminated tuberculosis

Treatment
Patient received ceftizoxime, anti- tuberculosis therapy, steroid, ferrous sulphate, B12 and blood was transfused.
3. DISCUSSION

Tuberculosis remain common health problem in Sudan with annual rate 1.80 [2]. In Red sea state, eastern Sudan detection rate is about 97% which represent 1185 cases, and 53% of these cases are extrapulmonary TB [3]. Severe tuberculosis disease may affect all systems and presented in different presentation. In this case TB presented as hemophagocytic lymphohistocytosis, this is the first case of HLH that diagnosed in Sudan, it may be really rare, but more probably in such endemic area it may be under diagnosed, because of lack of diagnostic facilities and low awareness about such condition. Actually, during hospital course bone marrow aspirate was investigated for anemia, and when it showed infiltration by collection of histocytes, and some of them showed haemophagocytosis, we start to think in HLH, so this followed by trephine biopsy which is confirm feature of HLH, and then other laboratories parameters was detected. Our case had five of diagnostic criteria of HLH, these are fever, splenomegaly, cytopenia, haemophagocytosis, and hyperferritinaemia, in addition to two supportive criteria which are hypertriglyceridemia and hyponatremia. We didn’t investigate for N.K cell because of lack of facilities. In severe TB disease, such as miliary blood dyscrasias take place [5], and even myelofibrosis occurs [4] and this explain cytopenia. Again, iron metabolism impaired in severe tuberculosis [4], also severity may be complicated by macrophage activity syndrome which is explain haemophagocytosis. While involvement of liver in severe tuberculosis [5] may explain jaundice, hypoalbuminaemia, impaired liver enzymes and hypertriglyceridemia. Hyponatremia may occur in severe TB due to syndrome of inappropriate antidiuretic hormone or reset osmostat [4].

Trephine biopsy showed small granuloma, which is support the diagnosis of tuberculosis, that confirmed by PCR. So, although HLH commonly occur in children, it can occur in adult secondary to granulomatous disease such as tuberculosis, and it represent a severe tuberculosis disease that need introduction of steroid in addition to antituberculous therapy, Early introduction of steroid may improve the outcome, therefore HLH should be consider in severe tuberculosis.

4. CONCLUSION

Hemophagocytic Lymphohistocytosis, although it is a rare condition, it may complicate tuberculosis, increasing both morbidity and mortality of the disease, and it need special consideration in treatment.

ABBREVIATION

ALB: albumin
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
CT: Computed tomography
CXR: Chest x-ray
ESR: Erythrocyte sedimentation rate
HIV: Human immunodeficiency virus
HLH: Hemophagocytic Lymphohistocytosis
PCR: Polymerase chain reaction
TB: Tuberculosis
TST: Tuberculin skin test
TWBC: Total white blood cell count
ZN: Ziehel Nielsen

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