

CASE REPORT

## Spontaneous recovery of haemophagocytic syndrome in an adolescent girl receiving anti-tuberculosis treatment

Ramesh Bhat Yellanthoor<sup>1</sup>, Annamma Kurien<sup>2</sup>, Shruti Kakkar<sup>1</sup>, MS Padma<sup>1</sup>,  
Vamsi Sivarama Raju<sup>1</sup>, Sherin George<sup>1</sup>

<sup>1</sup> Department of Paediatrics, Kasturba Medical College, Manipal University, Udupi District, Karnataka, India

<sup>2</sup> Department of Pathology, Melaka Manipal Medical College, Manipal, India

### ABSTRACT

Infection associated haemophagocytic syndrome (HPS) is rare and could be potentially fatal. Reactive HPS has been reported with various infections including tuberculosis. Tuberculosis associated HPS is more common in adults than in children. Severe pancytopenia due to HPS complicating tuberculosis and while on therapy has been rarely described. Success of therapy depends on early initiation of treatment. We describe herein a 13-years old girl who developed severe pancytopenia while on anti-tuberculous treatment. Her bone marrow aspirate showed trilineage dyspoiesis, histiocytes with phagocytosed debris and haemophagocytosis confirming a reactive haemophagocytic syndrome. She recovered completely with supportive treatment. *J Microbiol Infect Dis* 2013;3(4): 211-213

**Key words:** tuberculosis, pancytopenia, haemophagocytosis, spontaneous recovery

### Anti-tüberküloz tedavisi alan ergen yaştaki bir kız çocuğunda kendiliğinden iyileşen hemofagositik sendrom

### ÖZET

Enfeksiyon ilişkili hemofagositik sendrom (HPS) nadirdir ve potansiyel olarak ölümcül olabilir. Reaktif HPS, tüberküloz dâhil olmak üzere çeşitli enfeksiyonlarla birlikte bildirilmiştir. Tüberküloz ilişkili HPS erişkinlerde çocuklara göre daha sık görülür. Tüberküloz tedavisi ile birlikte HPS ilişkili şiddetli pansitopeni nadiren bildirilmiştir. Tedavi başarısı tedavinin erken başlamasına bağlıdır. Bu makalede anti-tüberküloz tedavisi sırasında ciddi pansitopeni gelişen 13 yaşında bir kız çocuğu sunulmaktadır. Kemik iliği aspirasyonunda trilineage dispoyez, debris fagosite etmiş histiyositler ve reaktif HPS'yi gösteren hemofagositoz vardı. Hasta destek tedavisi ile tamamen iyileşti.

**Anahtar kelimeler:** Tüberküloz, pansitopeni, hemofagositoz, kendiliğinden iyileşme

### INTRODUCTION

Haemophagocytic syndrome (HPS) has been reported rarely with tuberculosis. Severe pancytopenia due to HPS complicating tuberculosis disease as such, after initiation of treatment for tuberculosis and resulting in mortality has been rarely reported.<sup>1-4</sup> We describe herein a 13-year-old girl patient developing severe pancytopenia during anti-tuberculosis treatment, bone marrow findings suggesting HPS and treatment success.

### CASE REPORT

A 13-year-old girl on anti-tuberculosis therapy for pleural effusion presented with history of easy fa-

tigability of 15 days duration and swelling of lower limbs of one week duration. There was no history of cough, fever, chest pain or rash. Two months earlier she presented with cough, hemoptysis and chest pain along with weight loss. Clinical examination, chest X-Ray, pleural fluid analysis and strongly positive Mantoux test (induration of 20 mm x 20 mm) suggested pleural effusion of tuberculosis etiology. She was put on rifampicin, isoniazid, pyrazinamide and ethambutol. She showed remarkable improvement by 15 days. Her complete blood count (CBC) and liver function tests done a month later were normal. Chest X-Ray showed partial resolution of earlier findings. There was no history of intercurrent illness and she gained weight significantly.

**Correspondence:** Y Ramesh Bhat, Department of Paediatrics, Kasturba Medical College, Manipal University, Manipal 576104, Udupi District, Karnataka, India E-mail: docrameshbhat@yahoo.co.in

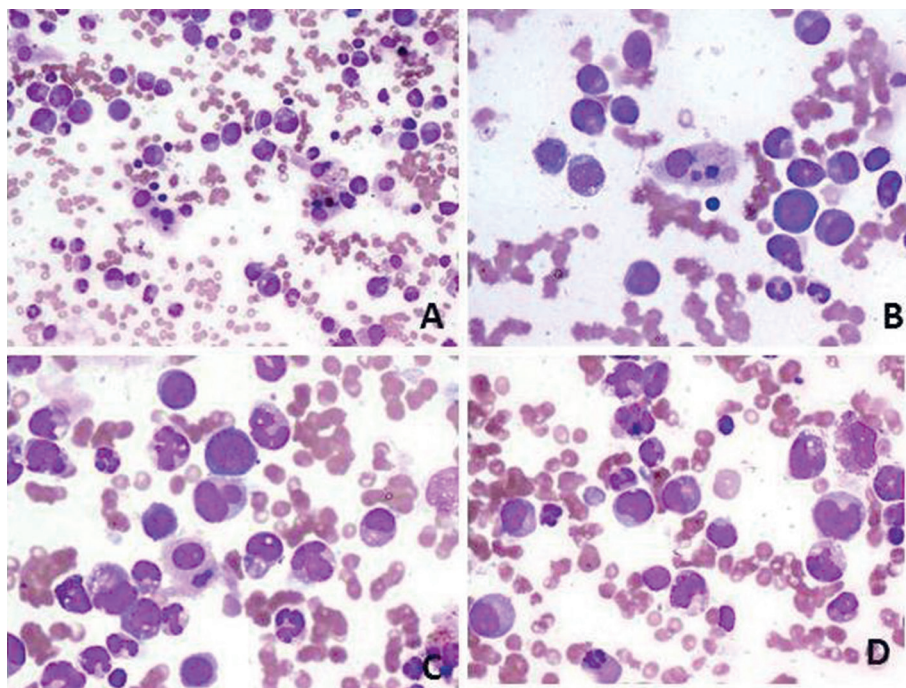
Received: 23.04.2013, Accepted: 13.07.2013

Copyright © Journal of Microbiology and Infectious Diseases 2013, All rights reserved

On the second admission she was afebrile, her pulse rate was 140/min, respiratory rate (RR) 25/min and arterial blood pressure (BP) was 90/60 mmHg. She had severe pallor. Her physical examination revealed bilateral pitting pedal edema. There was no jaundice, cyanosis, clubbing, lymphadenopathy, hepatosplenomegaly, and evidence of pleural effusion or ascites. Cardiovascular and central nervous system (CNS) examinations were normal. Chest x-ray showed resolving of the previous consolidation. Investigations showed marked anemia (hemoglobin, 3.1 g/dL), reduced total leucocyte count ( $3200/\text{mm}^3$ ) and platelet count ( $80,000/\text{mm}^3$ ). Erythrocyte sedimentation rate (ESR) was 81 mm/hours. Red blood cell (RBC) indices were normal with the red blood cell distribution width (RDW) of 11.9%. Peripheral blood smear showed normocytic normochromic red cells with mild anisopoikilocytosis. No abnormal cell was seen. She was transfused with two units of packed RBCs. Over the next two days there was further reduction in leucocyte count ( $2330/\text{mm}^3$ ) and platelets ( $35000/\text{mm}^3$ ) with clinical bleeding. She also developed fever. Her serum electrolytes, cre-

atinine, uric acid, liver function tests, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal. Lactate dehydrogenase (LDH) enzyme level was high (438 U/L).

Bone marrow aspiration was performed to evaluate the cause for pancytopenia. The marrow was hypercellular with trilineage dyspoiesis. Myeloid:Erythroid (M:E) ratio was 5.3:1. Marrow iron stores were increased. Histiocytes with phagocytosed debris, haemophagocytosis and trilineage dyspoiesis were seen (Figure 1A, B, C, and D). Reactive HPS was considered. She was treated with packed RBC and platelet transfusions. Anti-tuberculosis treatment was continued. She responded well to supportive therapy and by day 12 of admission, blood haemoglobin concentration (13.1 g/dL), leucocyte count ( $9500/\text{mm}^3$ ) and platelet ( $153,000/\text{mm}^3$ ) were normalised. Anti-tuberculosis medications were continued and she was discharged. She remained asymptomatic during subsequent follow up at 2 weeks, 4 weeks and 4 months with normal haemoglobin, leucocyte and platelet counts.



**Figure 1.** Leishman stain of bone marrow aspirate smear. **A:** many histiocytes with hemophagocytosis (x100), **B:** histiocyte with hemophagocytosis (x400), **C:** a histiocyte with hemophagocytosis with dyspoietic erythroid precursor (megaloblastoid) and myeloid precursor (abnormal lobations), (x400), **D:** dyspoiesis of erythroid and myeloid elements (x400)

## DISCUSSION

HPS is characterized by dysregulated proliferation of mature histiocytes and uncontrolled phagocytosis of the platelet, erythrocytes, lymphocytes and their hematopoietic precursors in the bone marrow and other reticuloendothelial system (RES).<sup>1-3,5</sup> Systemic manifestations are mainly due to cytopenia

like in our case. Reactive HPS has been reported with various infections including tuberculosis.<sup>1-5</sup> Severe HPS developing after initiation of tuberculosis treatment was reported by Balkis et al.<sup>1</sup> Fulminant course and fatal outcome has also been reported.<sup>3</sup>

The most prominent laboratory abnormalities noted in HPS are cytopenias, which may be pro-

found.<sup>5</sup> In the present case all three cell lines were severely affected. Haemolysis, hyperbilirubinemia and disseminated intravascular coagulation (DIC) may be associated, all of which were absent in our case. The serum level of LDH may be elevated as in our case. Most patients have hypertriglyceridemia, elevated ferritin and low serum fibrinogen. These investigations were not done in our case due to financial constraints. However, bone marrow showed increased iron stores.

Phagocytosis of blood cells and their precursors is a hallmark of haemophagocytic syndromes. Hemophagocytosis in the bone marrow was characteristically demonstrated in our case. In addition, there was trilineage dyspoiesis. Marked dyserythropoiesis is not an uncommon phenomenon in HPS and can even mask the phagocytic process. Haemophagocytosis is achieved mostly by monocytes and macrophages. Excessive activation of monocytes may be due to stimulation by high levels of activating cytokines. High levels of interferon- $\gamma$ , soluble interleukin-2 receptor, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1, interleukin-6 and interleukin-18 have been demonstrated; suggesting that elaboration of activating cytokines by T-helper (TH) cells promotes activation of macrophages in this disease. In tuberculosis, reactive HPS may result from a poorly regulated or inappropriate TH1 response to intracellular pathogens.<sup>5</sup>

Situations with increased physiological haemophagocytosis have to be considered before making the diagnosis of HPS.<sup>6</sup> Haemophagocytosis as a physiological process may be observed in situations such as haemolytic and aplastic anemia, graft versus host (GVHD) disease following transfusions and cytotoxic therapies. But, haemophagocytosis in the context of HPS is normally a systemic event like in our case. Despite the limitations, morphological evidence of haemophagocytosis is still considered the gold standard in the diagnosis of HPS and can be demonstrated in many organs, in particular bone marrow, spleen, liver and lymph nodes. During HPS, haemophagocytosis is found consistently in organs of the RES.<sup>6</sup>

The diagnosis of HPS is based on five of eight criteria namely fever, splenomegaly, bicytopenia,

hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis, low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels unless family history or molecular diagnosis is consistent with HLH. The limitations of diagnosing HPS in this patient include not fulfilling the five criteria. Systemic manifestations and typical bone marrow findings confirmed HPS. Morphological evidence of haemophagocytosis is still considered the gold standard in the diagnosis of HPS.<sup>6</sup>

Supportive treatment and immunomodulatory therapy such as immunoglobulins, steroids and chemotherapy are recommended as therapy.<sup>1-5</sup> Underlying infection also needs to be treated promptly. Success of therapy is likely if initiated early in the course of illness. The present case responded well to supportive therapy.

In conclusion, severe pancytopenia in tuberculosis patients could rarely be due to secondary HPS. Early diagnosis and treatment are essential to avoid a fatal outcome.

**Funding:** None

**Competing interest:** The authors declare that they have no competing interests

## REFERENCES

1. Balkis MM, Bazzi L, Taher A, et al. Severe hemophagocytic syndrome developing after treatment initiation for disseminated *Mycobacterium tuberculosis*: case report and literature review. *Scand J Infect Dis* 2009;41:535-537.
2. Okascharoen C, Nuntnarumit P, Sirinavin S. Neonatal tuberculosis associated with shock, disseminated intravascular coagulation, hemophagocytic syndrome, and hypercalcemia: a case report. *J Perinatol* 2003;23:79-81.
3. Balasubramanian S, Kaarthigeyan K, Aparna V, Srinivas S. Tuberculosis-associated hemophagocytic syndrome in infancy. *Indian Pediatr* 2008;45:593-595.
4. Dilber E, Erduran E, Kalyoncu M, et al. Hemophagocytic syndrome as an initial presentation of miliary tuberculosis without pulmonary findings. *Scand J Infect Dis* 2002;34:689-692.
5. Fisman DN. Hemophagocytic syndromes and infection. *Emerg Infect Dis* 2000;6:601-608.
6. Emmenegger U, Schaer DJ, Larroche C, Neftel KA. Haemophagocytic syndromes in adults: current concepts and challenges ahead. *Swiss Med Wkly* 2005;135:299-314.