Typhoid fever with severe pancytopenia

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Summary
A patient suffering from typhoid fever with severe pancytopenia is presented. Bone marrow examination revealed extensive haemophagocytosis which possibly contributed to the pancytopenia.

Keywords: pancytopenia, haemophagocytosis, typhoid fever

Typhoid fever, which continues to be a major public health problem in India, has shown changing modes of presentation and complications over the last few years.[1] Though leukopenia with neutropenia are characteristic findings, pancytopenia with severe thrombocytopenia is uncommon.

Haemophagocytosis in the bone marrow is characteristic of malignant histiocytosis and is commonly associated with several infections.[2-4] We draw attention to this finding, which is possibly the reason for the severe symptomatic pancytopenia seen in our patient.

Case report

A 26-year-old woman presented with a 15-day history of moderate grade, intermittent fever. There was a history of melaena for 10 days and bleeding from the oral cavity for three days. There were no associated abdominal symptoms. There was no history of bleeding from any site or menorrhagia in the past.

At presentation, the patient was conscious, febrile and toxic. There was marked pallor, minimal icterus and oozing of blood from the buccal mucous membrane. She was haemodynamically stable and there was no petechiae or ecchymosis on the skin. Fundus examination and examination of heart and chest was unremarkable. Abdomen was soft with mild diffuse tenderness. The spleen tip was palpable and there was 2 cm soft, nontender, hepatomegaly. There was no sternal tenderness. An examination of the neurological system was unremarkable. A provisional diagnosis of typhoid fever with gastrointestinal bleed was made and the patient was hospitalised. In view of the spontaneous bleeding from the buccal mucous membrane and hepatosplenomegaly, a differential diagnosis of acute leukaemia was also entertained.

Investigations at admission revealed a haemoglobin of 9.9 g/dl, total leucocyte count of 1.6×10^9/l (neutrophils 64%) and a platelet count of 17×10^9/l. Peripheral smear showed normocytic, normochromic red blood cells with mild anisocytosis and severe leukopenia and thrombocytopenia. There were no blast cells. Urinalysis was unremarkable. Blood sugar, urea, creatinine and electrolytes were normal. Liver function tests revealed a serum bilirubin of 37.4 μmol/l and serum alkaline phosphatase of 212 IU/l. Aspartate transaminase and alanine transaminase were 300 IU/l and 226 IU/l, respectively. Bleeding time was eight minutes. A coagulation profile was within normal limits. Chest X-ray was normal. Blood samples were sent for culture and Widal testing. In view of severe pancytopenia and sponatenous bleeding, a bone marrow aspiration was done and sent for cytology and culture examinations. The patient was started on parenteral ciprofloxacin (200 mg intravenously every 12 hours).

On the second day, the patient became drowsy, poorly responsive and incontinent. There was an increase in bleeding from the gums. She continued to be febrile but was haemodynamically stable. A clinical possibility of an intracranial bleed (due to severe thrombocytopenia) was entertained. Meningeal signs were absent, there was no focal neurological deficit and fundus was normal. A repeat haemogram revealed a haemoglobin of 7.2 g/dl, leucocytes of 1.7×10^9/l and platelets of 15×10^9/l. A repeat coagulogram showed no coagulation abnormalities. Computed tomography of the head and examination of cerebrospinal fluid were normal. The patient was transfused four units of platelet-rich plasma and one unit of fresh blood.

Blood culture after 48 hours had grown *Salmonella typhi*, sensitive to ciprofloxacin but resistant to chloramphenicol. A more than four-fold rise of antibody titres to 'O' and 'H' antigens of *S typhi* was found in the serum. Bone marrow examination revealed a cellular marrow with normal haematopoietic elements and a large number of phagocytes showing leukoerythrophagocytosis (figure). Bone mar-

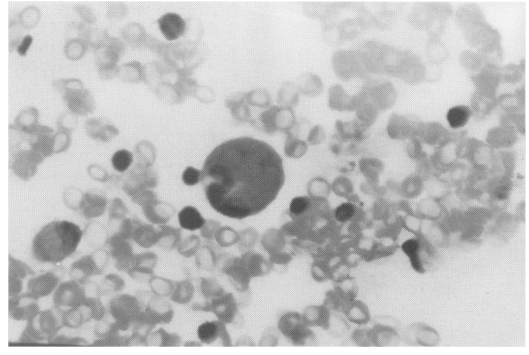

Figure Macrophage engulfing leukocytes, erythrocytes and platelets (leukoerythrophagocytosis)

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Learning points

- typhoid fever must be included in the differential diagnosis of pancytopenia secondary to systemic diseases
- reactive haemophagocytosis syndrome can occur due to infection with *S typhi*
- haemophagocytosis may contribute to the pancytopenia that occurs in some patients with typhoid fever
- haemophagocytosis due to typhoid fever carries a favourable prognosis with institution of specific therapy

Causes of fever and pancytopenia

Primary bone marrow disorders
- acute leukaemias
- bone marrow lymphomas
- myelodysplastic syndromes
- hairy cell leukaemia
- multiple myeloma
- megaloblastic anaemia
- paroxysmal nocturnal haemoglobinuria (rare)

Systemic diseases
- systemic lupus erythematosus
- sarcoidosis
- rheumatoid arthritis
- haemophagocytic lymphohistiocytosis
- cytophagic histiocytic panniculitis
- post-transfusion graft-versus-host disease
- disseminated metastatic carcinoma
- paraneoplastic syndrome
- malignant histiocytosis (histiocytic medullary reticulosis)

Systemic infections
- viral: Epstein – Barr virus, cytomegalovirus, human immunodeficiency virus, H simplex, varicella zoster, hepatitis B and C, adenovirus
- ricketssial: Q fever, human Ehrlichiosis, mediterranean spotted fever
- protozoal: malaria, visceral leishmaniasis, systemic toxoplasmosis, human babesiosis
- bacterial: enteric infections, brucellosis, overwhelming bacterial sepsis
- disseminated tuberculosis
- disseminated *Mycobacterium avium/ intracellulare* infection
- disseminated fungal infections (histoplasmosis)

row culture also grew *S typhi*. Serology for viral hepatitis was negative.

A definitive diagnosis of typhoid fever with severe pancytopenia, gastrointestinal bleed, encephalopathy and typhoid hepatitis was made. Ciprofloxacin was continued, along with supportive care. The patient showed defervescence of fever on the fifth day. Sensorium improved, melaena cleared and bleeding from the buccal mucous membrane stopped. Oral ciprofloxacin (500 mg 12 hourly) was started on the sixth day and continued for a total period of two weeks. Serial haematological examinations revealed an increase in haemoglobin, leucocytes and platelet counts to 9.8 g/dl, 5.9×10^9/l and 182×10^9/l, respectively, on the twelfth day. Liver function tests returned to normal. The patient recovered fully and was discharged from the hospital on the fourteenth day.

Discussion

The clinical profile of typhoid fever and its complications have been changing over the past few years. Leukopenia with or without neutropenia are the characteristic haematological features; its association with severe pancytopenia has been reported infrequently in English literature.[2,5] This case was remarkable for the degree of thrombocytopenia causing bleeding, thus raising the suspicion of leukaemia and leading us to do an urgent bone marrow examination. 'Erythrophagocytosis' was described as the classical morphological feature in the lymphoid tissue and bone marrow of patients with typhoid fever as early as 1960.[6] This is not seen so frequently now, probably because bone marrow examinations are not done routinely in most cases of typhoid fever, as often the treatment is started empirically or based on microbiological evidence. Extensive haemophagocytosis is a possible explanation for the severe pancytopenia in this patient. Such patients, with an unusual exaggerated histiocytic inflammatory reaction to infection, though severely ill, are known to recover with the institution of specific therapy.

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