

# Haemophagocytosis in Typhoid Fever

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## Summary

This report deals with a young man who developed features of haemophagocytosis during the course of typhoid fever. The pertinent clinical and laboratory features of typhoid-associated haemophagocytosis are discussed. The need for blood component replacement therapy in addition to specific anti-microbials to treat haemophagocytosis complicating typhoid fever is stressed.

**Key words:** Bone marrow failure, pancytopenia, haemophagocytic syndrome.

## Introduction

Typhoid fever is noted for its protean manifestations. We describe a young farmer with typhoid fever whose presentation was primarily haematological in nature.

## Case Report

A 27 year old farmer was admitted to the hospital because of fever. He was well till 2 weeks earlier, when he developed fever with chills and rigors. He also experienced headache, myalgia and loss of appetite. A week later, he developed diffuse abdominal pain with vomiting and diarrhoea. He had approximately 6 to 8 stools per day. The stools were watery initially, but became melaenic on the day of admission. His wife noted bleeding gums a day prior to entry.

His condition deteriorated during this period and he soon became restless and confused, which forced his relatives to bring him to hospital.

Physical examination revealed an ill-looking, toxic and confused young man. He was awake but not alert. He kept muttering to himself. The history was given by his wife.

His temperature was 39.5°C, pulse was 130/minute and blood pressure was 100/90 mm of Hg. He was pale but not jaundiced. There were no ecchymoses or purpuric spots.

The chest was normal. The abdomen was tumid with sluggish bowel sounds. The liver and spleen were not palpable. On rectal examination, the finger glove was stained with melaenic stools and spots of fresh blood.

The laboratory values on admission were as follows:

Haemoglobin (Hb) 9.4 g/dl

Reticulocyte count 0.2%

Total white cells count  $3.8 \times 10^9/l$

Differential count:

Polymorphs 8%

Lymphocytes 19%

Eosinophils 3%

Platelet count  $26 \times 10^9/l$

The red cell indices were consistent with normochromic normocytic anaemia. The peripheral blood film showed pancytopenia. The neutrophils had toxic granulations. There were several target cells, fragmented red cells as well as schistocytes. The platelets were reduced in number.

Bone marrow aspirate was hypo- to normocellular. There were 24% neutrophils, 20% lymphocytes, 6% metamyelocytes, 12% histiocytes and 12% myelocytes. Erythropoiesis, granulopoiesis and thrombopoiesis were normal. The histiocytes showed marked phagocytic activity, engulfing the haemopoietic cellular component viz: erythroid cells, platelets and granulocytes. The bone marrow findings were consistent with haemophagocytic syndrome.

The patient also had abnormal coagulation profile: the prothrombin time was 29.0 seconds (control 10.7 to 13.7 seconds) and the partial thromboplastin time was 57 seconds (control 30 to 44 seconds).

His alkaline phosphatase level was raised at 328 units/litre (normal 40-122 u/l) and the alanine transferase was elevated at 242 units/litre (normal up to 37 u/l). The serum bilirubin was mildly raised at 22  $\mu\text{mol/l}$  (normal 1.7-13.7  $\mu\text{mol/l}$ ). The other liver function tests were normal.

The renal profile was as follows: Blood urea 2.0 mmol/l (2.5-8.2); serum sodium 120 mmol/l (135-152); serum potassium 3.0 mmol/l (3.6-5.4); serum chloride 90 mmol/l (96-108); serum creatinine 0.4 mg% (up to 1.4 mg%).

Urinalysis showed mild proteinuria with numerous red blood cells with occasional pus cells. There were no casts. The culture was negative.

A lumbar puncture was done. The cerebrospinal fluid (CSF) was clear and colourless. The CSF biochemistry including sugar, protein and chloride was normal. Routine Grams stain, Ziehl-Nielsen and Indian Ink stains were negative. The CSF culture too was negative.

The blood culture grew *Salmonella typhi*, which was sensitive to chloramphenicol. The Widal agglutination test was strongly positive, with the titres for T(H) and T(O) being 1:3200 and 1:800 respectively.

The stool and bone marrow aspirate cultures were negative.

The plain abdominal X-ray, as well as the ultrasound examination of the abdomen, was essentially normal.

The patient was treated with intravenous chloramphenicol at 4 gm/day.

## CASE REPORT

The patient, however, had a stormy course in the ward over the following 3 weeks. He had persistent melaenic stools with occasional episodes of frank bleeding per rectum. This resulted in a continuous drop in his haemoglobin level. His platelet and leukocyte counts too remained low on regular monitoring.

He needed continuous blood component replacement therapy to tide over this crisis. He was given a total of 9 units of packed cells, 12 units of fresh frozen plasma, 12 units of cryoprecipitates and 15 units of platelet concentrates over 2 weeks.

He became afebrile after 2 weeks of chloramphenicol. His bleeding tendencies too stopped with normalisation of the coagulation profile and platelet counts around the same time. However, it took another week for the patient to become fully alert and conscious.

He was discharged home after 5 weeks of hospitalisation. He remains well a year later.

### Discussion

The patient, on admission, was thought to suffer from typhoid fever. This was later confirmed by the positive blood culture and markedly raised Widal agglutination titres.

The patient's bleeding tendencies, however, puzzled us. Leucopaenia and thrombocytopenia are recognised features of typhoid fever<sup>1</sup>. Although the fibrinogen degradation product (FDP) level was not done in this patient, his peripheral blood film and coagulation profile suggested disseminated intravascular coagulation (DIVC). The phenomenon of DIVC with its profound clinical expression as seen in our patient appears to be rare in typhoid fever.

Haemophagocytosis was then suspected, as the patient had most of the known features of the syndrome viz: pancytopenia, coagulopathy, DIVC, elevated liver enzymes and hyperbilirubinemia<sup>2-5</sup>. This was subsequently confirmed by the findings of his bone marrow aspirate.

Reactive haemophagocytic syndrome is a distinct clinicopathologic entity. The hallmark of the syndrome is the systemic proliferation of histiocytes showing phagocytosis of haemopoietic cells, resulting in blood cytopenia<sup>2</sup>.

Haemophagocytosis came into prominence when Risdall et al pointed out its association with viruses<sup>3</sup>. Subsequently, the condition was also described in association with bacterial infections<sup>6</sup>.

However, the occurrence of haemophagocytosis in typhoid fever appears to be rare or underreported. A computer-assisted search of the literature (Medline, Biosis Previews, Life Sciences Collection and Excerpta Medica) for the past 15 years revealed only isolated case reports<sup>4-6</sup>. Interestingly, most of these reports seem to come from areas where typhoid fever is non-endemic.

The pathogenesis of marrow failure in typhoid fever is not known. The postulates include the possibility of *Salmonella typhi* being directly toxic to the marrow<sup>4</sup>.

The treatment of bacteria-associated haemophagocytosis consists of supportive therapy in addition to specific anti-microbials. Unlike in malignant histiocytosis, immunosuppressives and chemotherapy are contraindicated in reactive histiocytosis<sup>3</sup>.

Although virus and bacteria-associated haemophagocytosis are thought to be benign, it must be borne in mind that they still carry a 30% to 40% mortality rate<sup>2,5</sup>. But, as shown by our patient, with continuous supportive therapy one should be able to tide over the crisis till the infection is cleared by specific antimicrobials and the process terminates itself spontaneously.

Typhoid fever is an endemic problem in our region, particularly in the rural settings. Haemophagocytosis should be entertained in these patients when they have an unexplained pancytopenia, abnormal coagulation profile and/or bleeding tendencies. We believe our patient illustrates the need to treat such patients in centres with adequate blood bank facilities if one wishes to deal with this rare but fatal event in typhoid fever successfully.

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