Hemophagocytosis: A Complication of Acute Q Fever in a Child

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We describe an 11-year-old boy with acute Q fever complicated by hemophagocytosis. In addition to pancytopenia, the boy presented with hyponatremia, hypofibrinogenemia, and changes in lipid metabolism. Examination of a bone marrow aspirate revealed striking hemophagocytosis. All of the pathological changes were caused by an activated macrophage system. We also discuss the possible role that pathogenetic mechanisms play in these changes.

Pancytopenia can be due to bone marrow failure or increased consumption of mature blood cells. Hemophagocytosis by activated tissue macrophages in the bone marrow is a rather uncommon cause of increased consumption. The proliferation of these cells is caused by either neoplastic transformation or increased activation of macrophages. Many different stimuli, most often infections, may lead to the activation of macrophages. It has been suggested that each infectious agent may give rise to macrophage activation with a subsequent hemophagocytic syndrome [1]. We describe an 11-year-old child with acute Q fever complicated by hemophagocytosis. To our knowledge, this association has not been previously described in children.

An 11-year-old boy was admitted to our hospital because of a high fever. Three weeks before admission, he became acutely ill with fever while on holiday in Spain. In addition to a severe nonlocalizing headache, he had a dry cough. The patient was treated with oral penicillin without clinical improvement. During the 3 weeks of his illness, he lost 3 kg of body weight. The patient did not report any contact with cows, sheep, goats, or cats.

At the time of physical examination, the boy was markedly distressed. The rectal temperature was 40°C, and he was shaking. The liver span was 14 cm, and the spleen tip was just palpable. The remainder of the physical examination was unremarkable. The hallmark of the laboratory investigations was pancytopenia. The erythrocyte sedimentation rate was normal. Other pathological findings included diminished levels of serum sodium and fibrinogen and elevated levels of liver enzymes and triglycerides. All relevant results of laboratory tests are summarized in table 1. Repeated blood cultures and cultures of urine, stool, throat specimens, and nasopharyngeal secretions yielded no pathogens. Examination of thick blood films revealed no *Plasmodium* organisms. A tuberculin test was negative. Chest roentgenography did not reveal any abnormalities. Ultrasonography of the abdomen confirmed hepatosplenomegaly. Results of repeated transthoracic echocardiographic examinations were normal. Examination of a bone marrow aspirate showed normocellular marrow with an increase in the number of megakaryocytes and myeloid elements. There was hemophagocytosis of granulocytes and erythrocytes by macrophages (figure 1).

The fever and most of the other clinical features resolved spontaneously during the 3-week stay in the hospital. The hemoglobin level, platelet count, and leukocyte count returned to normal by the end of the second week. At that time, a mild maculopapular rash appeared on the trunk and arms; this rash lasted 2 weeks. Two weeks later, the patient complained of transient arthralgia. His wrists, ankles, and left middle finger were swollen and tender for 5 days.

The diagnosis of Q fever was made by serology. An initial CF test for *Coxiella burnetii* was negative. Eighteen days after admission, antibodies to *C. burnetii* could be detected. The diagnosis of acute Q fever was confirmed by immunofluorescence, which revealed the higher titers of antibody to phase II antigen (table 2). After the positive serology was obtained, therapy with a 2-week course of doxycycline was started. The patient's convalescence was protracted, lasting almost 1 year.

Our patient presented with an acute, severe illness. The main signs were fever and pancytopenia. Examination of a bone marrow aspirate excluded the presence of a hematologic malignancy but revealed evidence of striking hemophagocytosis. The finding of hemophagocytosis initiated an investigation for an infectious agent, including serology for Q fever. Q fever is a worldwide zoonosis [2] that is caused by the rickettsial organism *C. burnetii.* Primary reservoirs for human infections are domestic animals like cattle, sheep, and goats. Exposure to parturient animals is a special risk factor because the organisms are shed in increased numbers during pregnancy. Humans become infected by inhalation of contaminated dust.

The incidence of Q fever among humans is unknown because 30% to 70% of patients may have subclinical infection [3]. The clinical picture that the remainder of patients present with is rather nonspecific; it is most often a flulike syndrome. The lung is the organ most affected by Q fever. Clinical signs of pneumonia may initially lead to the presumptive diagnosis of

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Table 1. Results of laboratory tests for a child with Q fever complicated by hemophagocytosis.

Test	Value
Erythrocyte sedimentation rate	2 mm/h
C-Reactive protein level	2.1 mg/100 mL
Hematocrit	30%
Hemoglobin level	9.9 g/dL
Mean corpuscular volume	77 fL
Reticulocyte count	0.2%
Platelet count	54,000/μL
WBC count	1,600/μL
Band forms	41%
Segmented neutrophils	13%
Monocytes	12%
Lymphocytes	34%
Alanine aminotransferase level	62 U/L
Aspartate aminotransferase level	72 U/L
γ-Glutamyltransferase level	58 U/L
Cholinesterase level	2,580 U/L
Bilirubin level	0.5 mg/100 mL
Lactate dehydrogenase level	1,089 U/L
Sodium level	126 mmol/L
Fibrinogen level	130 mg/100 mL (normal, 200–350 mg/100 mL)
Triglyceride level	300 mg/100 mL
Cholesterol level	142 mg/100 mL
α-Lipoprotein level	2 mg/100 mL (normal, 22–89 mg/100 mL)
β-Lipoprotein level	131 mg/100 mL (normal, 63–120 mg/100 mL)

this infection. Radiologically evident changes may be observed for up to 79% of symptomatic patients [2]. The second most affected organ is the liver. As in our case, results of liver function tests are abnormal for up to 85% of patients with Q fever [2].

Hematologic complications of Q fever occur infrequently. Occasionally, hemolytic anemia [4] due to cold agglutinins and thrombocytopenia [5], especially that associated with endocarditis, are noted. There have been a number of reports of bone marrow granulomas [6]. Examination of a bone marrow aspirate from our patient did not show any granulomas. Unfortunately, a bone marrow biopsy was not performed. There have been two reports of bone marrow hypoplasia [1, 7]. To our knowledge, only one other case of Q fever associated with hemophagocytosis has been reported. Estrov et al. [8] described a 51-year-old man with Q fever who presented with mild pancytopenia due to hemophagocytosis; the pancytopenia was less marked than that in our patient, the serum concentration of sodium was normal, and the levels of cholesterol and fibrinogen were not mentioned. Examination of bone marrow from our patient revealed an increased histiocyte count, with phagocytosis mainly of RBCs. Tetracycline therapy with doxycycline was commenced. Results of the blood film examination and the bone marrow examination returned to normal after 3 weeks

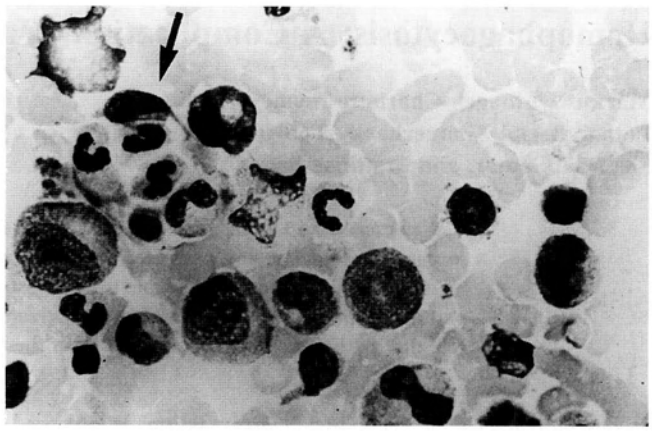

Figure 1. Photomicrograph of a bone marrow aspirate from a boy with Q fever complicated by hemophagocytosis that shows phagocytosed granulocytes and a nucleated RBC within the cytoplasm of a macrophage (*arrow*) (Pappenheim's stain; original magnification, × 1,000).

and 3 months, respectively. The exact pathogenesis of hemophagocytosis is not yet known. Bacterial lipopolysaccharides and some cytokines, such as IL-6, TNF, IFNs, and granulocyte-macrophage colony-stimulating factor, cause the proliferation or activation of macrophages [9]. These "hyperactivated" macrophages in the bone marrow can cause phagocytosis of precursor and mature cells.

In addition, the activated macrophage system is responsible for changes in hemostasis and lipid metabolism. Macrophages secrete plasminogen activator [9], thus leading to the consumption of fibrinogen. The impaired function of liver cells may have contributed to our patient's low level of fibrinogen; the hypofibrinogenemia explains his unusually low erythrocyte sedimentation rate. The low levels of high-density lipoprotein are presumably the result of a deficiency of lecithin-cholesterol acyltransferase in the liver. Lecithin-cholesterol acyltransferase is the key enzyme in the production of high-density lipoproteins. Besides the low levels of high-density lipoprotein, high

Table 2. Results of serological tests for *Coxiella burnetii* for a child with Q fever complicated by hemophagocytosis.

	Result per days after admission			
Test	2	18	40	204
CF	Negative	1:40	1:160	1:80
IF				
Phase I IgM			1:32	
Phase I IgG			1:8	
IF				
Phase II IgM			1:128	
Phase II IgG			1:1,024	

NOTE. CF = complement fixation; IF = immunofluorescence.

levels of triglycerides were noted. These levels could be the result of the decrease in lipoprotein-lipase secretion [9]. Decreased activity of lipoprotein-lipase leads to an increased level of chylomicrons and consequently triglycerides. High levels of TNF inhibit the enzyme lipoprotein-lipase and stimulate hepatic lipogenesis [10].

Acute Q fever is usually a self-limited disease; the mortality rate associated with Q fever is $<1\%$ and the convalescence of a patient with Q fever usually lasts months [2]. In 5% of cases of acute Q fever, the course can become chronic (particularly when there is preexisting valvular disease), with a mortality rate as high as 30% to 60% [2]. To avoid chronic disease, the patient should be treated accordingly following the diagnosis of Q fever. After a follow-up of nearly 1 year, our patient has recovered slowly and has no evidence of chronic disease.

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