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HEMOPHAGOCYTIC SYNDROME IN TYPHOID FEVER AND BRUCELLOSIS

MOJTABA TABARESTANI

From the Department of Clinical Pathology, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.

ABSTRACT

Hemophagocytic syndrome is a non-malignant process that is characterized clinically by fever, hepatomegaly, splenomegaly, pancytopenia in peripheral blood, and reactive histiocytes in the bone marrow. Bacterial infectious diseases like typhoid fever and brucellosis; and viral infections including CMV, herpes viruses, and Epstein-Barr virus are diagnosed as the cause of this syndrome. In this paper we present six patients with hemophagocytic syndrome who had blood culture or bone marrow culture, and or serology positive for typhoid fever or brucellosis. This is the first report of hemophagocytic syndrome in Iran.

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INTRODUCTION

The hemophagocytic syndrome is a reactive disorder of mononuclear phagocytic system first described by Risdall et al, in 1979.[1] This is a benign histiocytic proliferation usually seen in association with bacterial and viral infections.[1,2] It has been also shown in protozoal and fungal infections, drugs, and several types of malignant neoplasms.

In the hemophagocytic syndrome histiocytosis and hemophagocytosis are non-malignant processes in which reactive histiocytes proliferate in the bone marrow and other organs.[5]

This report describes six patients with typhoid fever and brucellosis who developed a hemophagocytic syndrome (pancytopenia, histiocytosis with hemophagocytosis). This is the first report from Iran.

CASE REPORTS

We have diagnosed six patients with typhoid fever and brucellosis in a teaching hospital. All patients were aged between 12 and 34 years and had clinical symptoms of hepatomegaly, splenomegaly, fever, and pancytopenia in peripheral blood, and hemophagocytosis in the bone marrow. Peripheral blood and bone marrow findings, blood culture, and bone marrow culture results are summarised in Tables I and II.

Case 1. A 34-year-old male gas company worker was admitted to the Imam Reza Hospital with a 15-day history of fever, chills, perspiration, and fatigue and anorexia. Anemia, leukopenia, thrombocytopenia and hepatosplenomegaly was present. An agglutination test for brucella was positive at a titer of 1/1280. Blood culture was also positive for brucella. Widal test was negative. Bone marrow aspiration showed normocellular marrow with hemophagocytosis.

Case 2. A 29-year-old male farmer was admitted to the Imam Reza Hospital with a two week history of fever, chills, and abdominal pain. No enlarged spleen, liver and lymph nodes were observed. Peripheral examination showed leukopenia, thrombocytopenia, anemia, and 4% NRBC. In blood and stool culture *Salmonella typhi* was isolated. Widal agglutination test was positive at a titer of 1/40, but Wright and 2-ME were negative. Bone marrow aspiration showed normocellular marrow with mild plasma cell reaction and hemophagocytosis.

Case 3. A 12-year-old girl was referred to our hospital with a 3-day history of fever, weakness, and anorexia. The patient was pale, but no hepatosplenomegaly was observed. Peripheral blood showed leukopenia and anemia. Blood and stool cultures showed *Salmonella*

Table I. The results of blood culture, bone marrow culture, and serologic reactions in six patients with hemophagocytic syndrome

Patient	Blood Culture	Bone Marrow Culture	Widal test	Wright , Coombs Wright	Hemophagocytosis
1	Brucella	NP*	Neg	1/1280	Present
2	*S. typhi*	NP	1/40	Neg	Present
3	*S. typhi*	NP	1/640	Neg	Present
4	Sterile	*S. typhi*	1/1280	Neg	Present
5	*S. typhi*	NP	1/80	Neg	Present
6	NP	NP	Neg	1/640	Present

*NP=Not performed

typhi. Widal test was positive at the titerof 1/640. Bone marrow aspiration showed hypercellular marrow with lymphoid reaction and hemophagocytosis.

Case 4. A 25-year-old male was admitted to the Imam Reza Hospital with a one month history of fever and weakness. Anemia and hepatosplenomegaly were observed. Peripheral blood studies showed Hb 4.8 gm/dl, Hct 14.4% platelet count 152,000, urea 143 gm/dl, creatinine 5.7 mg/dl. Blood culture was negative but bone marrow culture showed *Salmonella typhi*-. Widal agglutination test was positive at the titer of 1/1280. Bone marrow aspiration showed hypercellular marrow with hemophagocytosis.

Case 5. A 10-year-old girl was referred to the Imam Reza Hospital with two week history of fever, malaise, anorexia, perspiration, weakness, headache, and abdominal pain. No enlarged spleen, liver or lymph nodes were seen. Peripheral blood showed leukopenia, moderate anemia and abnormal liver function test (SGOT 86, SGPT 72), with high LDH 1433. Blood culture was positive for *Salmonella typhi*. Widal agglutination test was positive at 1/80, Wright and Coombs Wright were negative. Bone marrow aspiration showed normocellular marrow with hemophagocytosis.

Case 6. A 50-year-old male was admitted to Imam Reza Hospital with a longstanding fever, back pain, painful extremities, epistaxis, vertigo, and weakness. Splenomegaly was present. Peripheral blood findings include leukopenia, thrombocytopenia, and anemia. Wright agglutination test was positive at 1/640 and 2-ME at 1/60. Bone marrow aspiration showed hypercellular marrow with increased reticulum cell and hemophagocytosis.

DISCUSSION

The patients reported in this paper presented clinically with fever, hepatomegaly, splenomegaly, weakness, perspiration, pancytopenia in peripheral blood and hemophagocytosis in the bone marrow. All patients had positive blood culture, Wright agglutination tests, Widal tests, and bone marrow culture for typhoid fever or brucellosis. Despite cliical manifestations similar to histiocytic medullary reticulosis (HMR), the laboratory findings mentioned above suggest a bacterial infection (typhoid or brucellosis).

Malignant histiocytosis is a fatal neoplastic disorder first described by Scott and Robb-Smith in 1939 and is clinically characterized by fever, weight loss, hepatosplenomegaly, generalized adenopathy, and pancytopenia.[6] In a recent review by McKenna et al.,[7] the various histiocytic hemophagocytic syndromes were classified into malignant and benign types according to the histologic features of the histiocytes. Cases of hemophagocytic syndrome are characterized by mature histiocytes as an indicator of a reactive process. In most cases an underlying infectious agent is found in association with reactive histiocytosis.[5]

Several infectious diseases caused by intracellular

Table II. The results of peripheral blood examination of six patients with hemophagocytic syndrome

Patients	cells×10⁹/L		(%)					Hb	Hct	MCV	MCH	MCHC
	WBC	Platelets	PMN	Lymph	Mono	Eos	band					
1	1.2	60	32	68	-	-	-	13.3	0.350	71	27	37
2	3.6	37	55	43	2	-	-	10.2	0.314	89	29	33
3	1.9	30	70	28	2	-	-	7.6	0.239	81	26	31
4	10.7	152	75	21	-	-	4	4.8	0.144	86	30	33
5	4.5	NP	51	48	1	-	-	10.9	0.300	75	27	36
6	1.46	NP	rare...					6.3	0.250	89	22	25

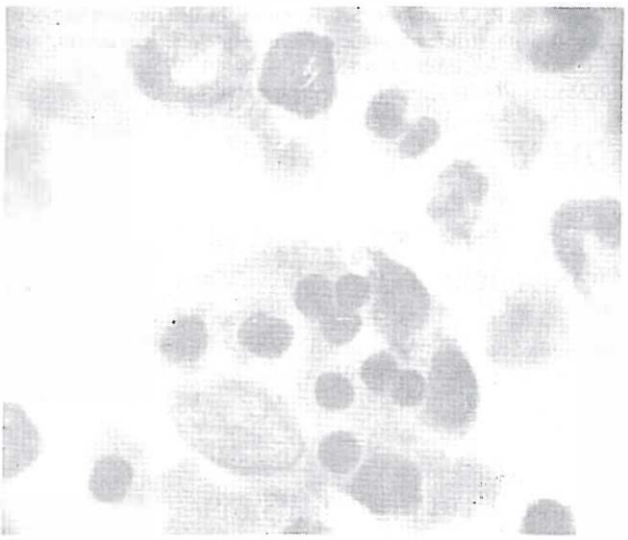

Fig. 1: Bone marrow smear showing histiocyte with hemophagocytosis.

organisms can lead to an activation of the histocytes, the proliferation of which can produce organomegaly and lymphadenopathy.[8] A various number of bacterial, viral, fungal and protozoal agents are associated with hemophagocytic syndrome. The so-called bacterial-associated hemophagocytic syndromes include *Mycobacterium tuberculosis*, brucella, *Escherichia coli*, and salmonella;[2,5,9,10] and the so-called virus-associated hemophagocytic syndrome (VAHS) includes CMV, herpes virus, varicella-zoster virus, Epstein-Barr virus, and adenovirus.[1,2,5] Other infectious diseases associated with HS include leishmaniasis, histoplasmosis, and several types of malignant neoplasms.

Here we report six patients among 15 cases of hemophagocytosis, four with typhoid fever and two with brucellosis. The significance of this syndrome is the presence of clinical findings similar to those that we have seen in histiocytic medullary reticulosis, but the benign cytologic features of the hemophagocytic syndrome are easily recognized and further evaluation is seldom required to make a differential diagnosis from malignant histiocytosis.

So far we have diagnosed 15 patients with hemophagocytic syndrome, but we have chosen six cases for this report, the remaining belong to viral and protozoal diseases. Most patients presented with high fever, pancytopenia, adenopathy, hepatosplenomegaly, and sometimes skin rash. All six patients manifested the characteristic bone marrow findings of the hemophagocytic syndrome. Most patients had bone marrow activity with normo-to-hypercellularmarrow. Typhoid fever was mentioned as a possible cause of histiocytosis with hemophagocytosis. In patients with typhoid fever, the presence of "typhoidal cells" is an important laboratory finding in bone marrow aspirates.[12] In these patients, histiocytic proliferation and granuloma formation with erythrocytes, leukocytes, platelets, and plasma-cell hyperphagocytosis occurs that is similar to histiocytic medullary reticulosis.

The process of histiocytic proliferation in hemophagocytic syndrome is probably reactive which resolves spontaneously after resolution of the infection. Although this histiocyte is non-malignant, the hemophagocytic syndrome is fatal.[5]

The pathogenesis of the hemophagocytic syndrome is unknown, the association of hemophagocytic syndrome with bacterial and viral infections has been proved, put non-infectious agents may participate in its formation.[1,2,5] Peripheral hemocytopenia (or pancytopenia) is a common finding in typhoid and brucellosis and most of our patients showed pancytopenia and hemophagocytosis. Although the mechanism of induction of hemophagocytosis in this syndrome is not clear, we can suggest that it can be responsible for the hemocytopenia syndrome.[8,10]

According to other studies and reports, typhoid fever and brucellosis cause histiocyte proliferation and hemophagocytosis in the bone marrow and hemocytopenia in the peripheral blood. The importance of recognition of this syndrome is for its distinction from malignant histiocytosis and careful search for bacterial, viral, fungal or protozoal agents before accepting other agents as causative factors in the development of hemophagocytic syndrome.

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