

Hemophagocytic Syndrome – Should We Consider it More Often?

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ABSTRACT

Hemophagocytic syndrome (HPS) is a rare condition characterized by overactive histiocytes, hepatosplenomegaly, fever and cytopenia, with two major types: familial, autosomal recessive genetic disease and acquired that can occur during systemic infections, immunodeficiency or malignancy. Inappropriate activation of macrophages by cytokines is the major mechanism of the disease. We report a case of an adult patient with HPS. After thorough clinical investigation, we have not been able to establish the underlying disease, and corticosteroids therapy was initiated empirically. After 8 months follow-up the patient is well with normal laboratory findings.

Key words: hemophagocytic syndrome, hemophagocytic lymphohistiocytosis, secondary

Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH) or erythrophagocytic lymphohistiocytosis (EL) is a rare condition characterized by overactive (otherwise normal) histiocytes, hepatosplenomegaly, fever and cytopenia¹.

There are two major types of HPS². Primary (i.e. familial – FHL) is the inherited form, autosomal recessive genetic disease with onset in the first year of childhood. Secondary (i.e. acquired HPS) occurs after strong immunologic stimulation that can be a part of systemic infections, autoimmune diseases, immunodeficiency or malignancy.

Accepted theory for pathophysiology involves inappropriate activation of macrophages by activated T cells³. Large quantities of cytokines, primarily tumor necrosis factor- α (TNF- α), interferon gamma (INF- γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) cause macrophage proliferation and activation with further release of interleukin-1 (IL-1) and IL-6⁴. Interleukin-18 seems to have an important role in the activation also⁵. Activated macrophages phagocytose blood cells throughout reticuloendothelial system which is the main site of involvement.

The triggering mechanisms that lead to inappropriate immune activation are different in familial and acquired HPS. Perforin, a membrane protein of cytotoxic cells such as NK cells has an important role in the genesis of

at least one type of FLH^{6,7}. It is a part of cytoplasm granules of NK cells and cytotoxic T-cells that are released after stimulation to form pores in target cells thus damaging and ultimately destroying it by osmotic lysis. Patients with perforin deficiency have impaired NK activity that could lead to activation of T-cells in an inappropriate manner. Other NK cell disorders have been associated with FLH⁸. Secondary HPS can be initiated by a number of pathogens, of which the best understood is the pathogenesis of Epstein-Barr virus (EBV) associated HPS^{9,10}. Any kind of tumor, but more frequently lymphomas can lead to production of cytokines whether by direct production or immune system stimulation. Overproduction of TNF- α , INF- γ and other cytokines can lead to the cascade of reaction leading to macrophage over-stimulation.

Clinical presentation always includes fever, cytopenia and splenomegaly. Skin rash, hepatomegaly, lymphadenopathy, CNS disorders, jaundice and coagulopathy may also be present. Laboratory findings in addition to cytopenia include hyperfibrinogenemia, hypertriglyceridemia, high ferritine and low haptoglobine concentrations, liver damage and hyponatremia. Characteristic finding is cytological or histological confirmation of hemophagocytosis in an aspirate or biopsy of bone marrow, liver, spleen, lymph node or skin. Diagnostic criteria for HPS have been established^{1,2}. NK cell activity can be determined as an aid in determining between HPS types, since

reactive disease has normal NK activity, unlike familial FLH. NK cell is also impaired in secondary HPS especially in systemic onset as juvenile rheumatoid arthritis. Perforin expression can also be determined, as well as PRF-1 gene mutations and other gene mutations.

Familial types of HPS are treated with different approaches that include corticosteroids, immunosuppressive and antineoplastic drugs¹¹. The main goal is to achieve clinical stability. In cases of disease refractory to such treatment, bone marrow transplantation (BMT) should be considered¹². In the case of reactive HPS, underlying disease must be sought and treated appropriately if present. The same treatment as for FHL can be applied and for non-reactive patients a BMT must be considered.

Case Report

A 59-year-old male was admitted because of a fever that lasted for 6 weeks, anemia, leucopenia and weight loss of 8 kg over several months. Fever occurred usually in the afternoons, without chills and there were no other symptoms.

Patient's history was scarce: he had suffered a brainstem infarction 4 years before, and had his gallbladder removed due to gallstones. Initial examination revealed fever (37.8 °C), pale skin, hepatomegaly and splenomegaly (4 cm and 5 cm below costal margin respectively). Blood count showed neutropenia and anemia, whereas thrombocytes were only slightly reduced. Hyponatremia, hypertriglyceridemia, elevated liver enzymes and lactate dehydrogenase activity, elevated ferritine and low haptoglobine concentrations were present. Other electrolytes were normal, no alterations in coagulation tests were present and electrophoresis of serum proteins was normal as well as the values for available tumor markers (PSA, CEA, AFP, Ca-19-9, Ca-125).

Imaging methods (chest radiogram, abdominal ultrasound and CT) revealed no pathology in the thorax, enlarged spleen and liver with homogenous structure and several enlarged retroperitoneal lymph nodes.

Clinical presentation and laboratory findings were suggestive for hematological or infectious disease, but numerous microbiological tests performed during the course of hospitalization were negative. Several blood and urine cultures, also pharyngeal and nasal swabs were taken and all were negative. Serology for B and C hepatitis viruses and HIV virus was negative. IgG antibodies for Cytomegalo and Epstein-Barr virus were positive, but IgM were negative. Available tests for leishmaniasis, shistosomiasis and malaria were negative.

Cytology of sternal aspirate was done early, and showed normal hematopoiesis, but histiocytes that phagocyte mostly erythrocytes and rarely granulocytes were present, as well as some multinuclear cells. Following that finding, spleen biopsy and bone marrow biopsy were done and phagocytosis of erythrocytes was found in both. The diagnosis of hemophagocytic syndrome was set.

In the following patient evaluation possible causes for secondary HPS were considered. No proof for malignant disease was found after examination of gastrointestinal, respiratory and urinary systems. No criteria for systemic autoimmune disease were met. Besides the positive anti-EBV and anti-CMV IgG, no infection could have been connected with the patient's condition.

Without any known condition that could have been treated, corticosteroid treatment was chosen. A daily dose of 40 mg (0.5 mg per kg) methylprednisolone was administered orally and clinical condition improved rapidly. Fever disappeared three days after initiating treatment and blood count normalized on 7th day of treatment, patient was discharged three days after that. The dose of methylprednisolone was reduced gradually over eight weeks to 12 mg per day, but that led to a fall in blood count, primarily thrombocytes (110,000/ml) and leucocytes (3,000/mL). The values normalized with increase of steroid dose. During the eight-month follow up, our patient developed steroid diabetes, but other laboratory findings remained normal even after another reduction of drug dose to 16 mg daily, with well general condition of the patient. Repeated abdominal ultrasounds showed gradual reduction of spleen size which normalized six months after initiation of treatment.

Discussion

In the presented case of an adult male patient with HPS, no underlying condition that could be »accused« for the condition could be proven. Malignant disease, bacterial and parasitic infection, as well as autoimmune or other immunology disorder has been ruled out. The patient was serologically positive for a past EBV and CMV infection (positive IgG and negative IgM). Clinical course of the disease is not in concordance with known course of EBV associated HPS which is mainly much more severe. Any infection in theory could trigger the disease, and since there has been at least six weeks from the onset of symptoms to first examination, it is possible that an unknown infectious agent other than CMV or EBV was involved. No actual infection however was present during the hospitalization.

HPS is usually described as severe even in the case of secondary type. We have managed to achieve complete remission after several weeks of low dose corticosteroids treatment, but maintenance therapy is still required for our patient.

Although clinical presentation of the condition is anything but characteristic, and laboratory findings are also not specific, histology or cytology finding of hemophagocytosis is very characteristic, and necessary for the diagnosis. In cases of unexplained fever with hepato and splenomegaly it should be considered, especially if the laboratory findings are suggestive. There are reports that up to 60% of initial bone marrow aspirates can be negative for hemophagocytosis, so the examination should be repeated at least once if there is clinical suspicion of HPS.

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HEMOFAGOCITARNI SINDROM – TREBAMO LI ČEŠĆE MISLITI NA NJEGA?

SAŽETAK

Hemofagocitarni sindrom (HFS) je rijetko stanje karakterizirano hiperaktivnošću histiocita, hepatosplenomegalijom, vrućicom i citopenijom. Postoje dva osnovna oblika sindroma: obiteljni, autosomno recesivna nasljedna bolest te stečeni oblik koji može nastati za vrijeme sistemskih infekcija, imunodeficijencije ili uz maligne bolesti. Neodgovarajuća aktivacija makrofaga citokinima osnovna je u mehanizmu nastanka ove bolesti. Opisujemo odraslog bolesnika s HFS kod kojega nakon temeljite kliničke obrade nije otkriven primarni uzrok bolesti, a sistemska terapija kortikosteroidima empirijski uključena. Nakon osam mjeseci kontrole bolesnik je klinički dobro s urednim laboratorijskim nalazima.