Case Report

Sepsis of unknown origin with multiorgan failure syndrome: Think of hemophagocytic lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis is a clinic pathologic entity characterized by increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system. It is a potentially lethal disorder due to an uncontrolled immune response to a triggering agent. HPS may be primary, or secondary to malignancy, infections, auto-immune diseases, and pharmacotherapy. HPS is a rare, but life-threatening complication. Herein, we described a female patient with HPS with secondary sepsis. Our objective was to raise the importance of early diagnosis of HFS by presenting a representative case.

Keywords: Hemophagocytic lymphohistiocytosis, macrophages, multiorgan failure, sepsis

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.160291

Quick Response Code:

Introduction

The term hemophagocytosis describes the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells. This phenomenon is an important finding in patients with hemophagocytic lymphohistiocytosis (HLH). HLH is an unusual syndrome characterized by fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors) in bone marrow and other tissues. We report an adult patient who presented with systemic inflammatory response syndrome and features consistent with severe sepsis and septic shock, who subsequently received a diagnosis of secondary HLH. We reviewed the relationship between HLH and septic shock from the perspective of an intensivist.

Case Report

A 50 years female presented to Intensive Care Unit (ICU) with fever, rash, and loss of appetite. She was admitted in an outside hospital with 24 h of epigastric abdominal pain radiating to her flanks. There was no history of night sweats, weight loss, new medications, or toxin exposure. On admission, she presented with a temperature of 38.5°C, a heart rate of 120/min, and an erythematous scaling rash covering over 50% of her body surface area, with increased scaling over her scalp. Her abdomen was soft and nontender, with splenomegaly palpable 3 cm below the costal margin. There was no peripheral lymphadenopathy, and the rest of her physical exam was unremarkable. Her initial blood work consisted of an elevated ferritin and lactic acid dehydrogenase (LDH) level, pancytopenia, acute kidney injury, hepatitis, and hypofibrinogenemia. Broad-spectrum empirical antibiotics were administered for the presumed diagnosis of sepsis, but without apparent benefit. Over a period of 2–4 days, she developed

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How to cite this article: Maheshwari N, Mandal AK, Sahni N. Sepsis of unknown origin with multiorgan failure syndrome: Think of hemophagocytic lymphohistiocytosis. Indian J Crit Care Med 2015;19:419-21.

pressor-dependent hypotension, acute respiratory distress syndrome (ARDS), acute kidney injury, bicytopenia (anemia and thrombocytopenia), deranged liver functions (transaminitis), and coagulopathy; and increased inflammatory markers C-reactive protein and patent cooperation treaty. The clinical course in this patient met the criteria for severe sepsis and septic shock except in that it was unclear whether associated infections were causative. Persistent fever, severe pancytopenia, hyperferritinemia, hypertriglyceridemia, increased LDH, and splenomegaly eventually prompted bone marrow aspiration (BMA) leading to the diagnosis of HLH. No family history of HLH was found, and a primary familial form was considered unlikely. According to the computed tomography (CT) scan and bone marrow biopsy results, no hematological malignancy was thought to be responsible for a secondary form. Despite an extensive multi-site sampling and serological studies, no bacterial or fungal infection was found. Laboratory tests for viral infection including Epstein-Barr virus, cytomegalovirus, herpes simplex virus, viral hepatitis B and C, HIV were unremarkable.

Prolonged fever, splenomegaly, bicytopenia, hypofibrinogenemia, hyperferritinemia, and hypertriglyceridemia confirmed the diagnosis of HFS. The delay in diagnosis due to its rare incidence leads the patient to secondary sepsis in spite of aggressive and symptomatic treatment. She finally succumbed to severe ARDS, septic shock, and coagulopathy.

Discussion

HLH is a rare disease characterized by uncontrolled proliferation of mature histiocytes, hemophagocytosis, and up-regulation of inflammatory cytokines. The more typical findings are fever, peripheral cytopenia affecting two lineages at least, hepatosplenomegaly, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis. Recently, the histiocyte society updated its guidelines[1] and proposed to add three diagnostic criteria: Hyperferritinemia decreased or absent natural killer (NK) cell activity, and high soluble interleukin-2 receptor serum levels. Five among eight of these criteria should be fulfilled to confirm the diagnosis. They were present in our patient, who developed high persistent fever, severe pancytopenia, splenomegaly on abdominal CT scan, and very high plasma levels of ferritin, triglycerides, and LDH.

The HLH-2004 diagnostic criteria considered the gold standard are largely based on studies of children with familial HLH. Many of the criteria have poor operating characteristics when considered in the differential diagnosis of septic shock in adults. Fever, anemia, thrombocytopenia, hypofibrinogenemia,[2] and hypertriglyceridemia[3] are common features of both syndromes. Several studies show that hyperferritinemia consistent with HLH (>500 μg/L) occurs in the majority of adults with septic shock.[4,5] The sensitivity of diagnostic criteria such as hypertriglyceridemia, hypofibrinogenemia, and splenomegaly may be no better than about 50%.[6,7] The sensitivity of NK cell activity and soluble CD-25 levels approaches 100%,[8] but these tests are not widely available.

A strict requirement to fulfill five HLH-2004 diagnostic criteria in the adult patient in an ICU could delay potentially lifesaving therapy. Other available HLH-2004 criteria should be used in conjunction, with consideration of the limitations in their operating characteristics and logistics in the ICU. In our opinion, HLH treatment should be considered in patients with the clinical syndrome of unremitting severe sepsis and/or septic shock with bicytopenia or pancytopenia, elevated ferritin levels, prompting for a BMA, which will show histiocytic hemophagocytosis. Untreated primary HLH is rapidly fatal within a few weeks.[9] Prompt and adequate treatment are of crucial importance for a positive outcome. Therapy should be started in all cases with high suspicion after diagnostic tests have been initiated, but regardless of whether the results of all examinations have been obtained. Among patients who are acutely ill or deteriorating, we suggest HLH-specific therapy based on the HLH-94 protocol or enrollment in a clinical trial rather than treatment based on the HLH-2004 protocol.[10] HLH-94-based therapy includes etoposide and dexamethasone given at tapering doses over 8 weeks, with intrathecal methotrexate and hydrocortisone for those with central nervous system involvement. We do not use cyclosporin routinely, although some hematologists do. Additional supportive measures include transfusion of blood products as indicated, induction of amenorrhea, and use of prophylactic antibiotics. The response to initial therapy is a major factor in determining the need for additional therapy including hematopoietic cell transplant. A short course of intravenous (IV) methylprednisolone (1–2 mg/kg/d) is often sufficient in treating HS associated with secondary infections. This treatment is given in concert with adequate anti infectious agents, and it must be administered for the shortest time necessary for correction of the most life-threatening symptoms associated with HS because of the added immunosuppression in the context of severe infection. New antiviral drugs such as cidofovir or ribavirin and rituximab (anti-CD20 antibody) may be useful. Consideration should be given to the

use of IV immunoglobulin in infection-associated HS, to minimize the risk of immunosuppression. Importantly, however, the initiation of HLH-specific therapy for severely ill patients should not be delayed while awaiting resolution of a system infection. The ideal therapy for patients with HLH remains unknown. Clinicians are encouraged to enter patients in clinical trials such as the hybrid immunotherapy for HLH trial in the United States (HIT-HLH; NCT01104025) or the EURO-HIT-HLH trial in Europe (EudraCT2011-002052-14). The HLH-2004 trial is closed to accrual.

Further study of HLH, may provide important insights into the optimal treatment of sepsis, perhaps leading to the identification of a subset of patients with sepsis in which tissue damage secondary to a hyper inflammatory state might be ameliorated by immunosuppressive therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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