Infection Associated Hemophagocytic Lymphohistiocytosis: A Case Report

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ABSTRACT

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 syndrome, more properly referred to as hemophagocytic lymphohistiocytosis (HLH). HLH is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly and hemophagocytosis in bone marrow, liver or lymph nodes. It has been associated with a variety of viral, bacterial, fungal and parasitic infections, as well as collagen-vascular diseases and malignancies and is uniformly fatal if left untreated. We report *Staphylococcus aureus*-induced hemophagocytic lymphohistiocytosis in a 3-month-old girl presenting with respiratory distress, sepsis and multiorgan failure. This case report may at least in part guide pediatricians and other physicians to recognize this rare entity of infection triggering fatal HLH and thus proper treatment may be instituted in those affected with this disease at the earliest.

Keywords: Hemophagocyte, infection, histiocyte

The term hemophagocytosis describes the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets and their precursor cells.1 It is a serious and potentially life-threatening histiocytic disorder in children and adults. A hallmark of hemophagocytic lymphohistiocytosis (HLH) is impaired or absent function of natural killer (NK) cells and cytotoxic T-cells (CTL).2,3 In its most severe form, it leads to a sepsis-like picture and multiorgan failure (MOF). We report the case of a 3-month-old female child who presented with very severe pneumonia (due to *Staphylococcus aureus*) resulting in HLH with acute respiratory distress syndrome (ARDS) and multiorgan failure. This case report may at least in part guide pediatricians to recognize this rare entity of infection triggering fatal HLH.

CASE REPORT

A 3-month-old girl child was referred to our institute with the history of fever, rash, abdominal distension and refusal to feed of 3-weeks duration. When she was 2 months old, she started having progressive dyspnea, abdominal distension and low-grade fever. Investigations done in a local hospital were noncontributory and she was put on bronchodilators and antibiotics with the diagnosis of sepsis. She improved marginally with the medications. Three weeks back, her symptoms worsened and she developed fever and rash. She was referred to our institution for further management. On examination, she was conscious, febrile (39°C) and tachypneic. She was having generalized edema, conjunctival congestion, ecchymosis and icterus. She was not cyanosed. Pulse was 162/mt with noninvasive blood pressure of 80/50 mmHg. She had splenomegaly and free fluid in the abdomen. There were fine crepitations involving the base of left lung. Heart sounds were normally heard without any murmur. There was no signs of meningeal irritation, no focal neurological deficit and normal fundus.

On investigating, urine examination showed trace protein and a few pus cells. Blood examination revealed hemoglobin (Hb) of 8.0 g/dl; total count (TC) of 2,500/mm³; differential count (DC) of P35, L60, E5. erythrocyte sedimentation rate (ESR) of 18 mm/1st hour. She had thrombocytopenia, with platelet count 37,000/mm³.

Peripheral smear report showed microcytic hypochromic anemia, anisopoikilocytosis and
polychromatic cells, shift to left with toxic granules, decreased platelet count and no malarial parasite.

ECG showed sinus tachycardia. Chest X-ray revealed alveolar opacities involving left lower zone. ABG showed hypoxemia. Liver function tests revealed bilirubin 7.2 mg%, total protein 4.3 mg%, albumin 2 mg%, serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase (SGOT/SGPT) 324/56, SAP 204. Renal function tests showed blood urea 60 mg% and creatinine1 mg%. RBS was 116 mg%; there was hypocalcemia with calcium of 7 mg% and phosphate 3.8 mg%. Serial monitoring of INR showed values of 1.75, 1.9 and 2.5, respectively. Anti nuclear antibody, viral markers for human immunodeficiency virus (HIV), hepatitis A, B, C and E, serology for Weil’s and Dengue, Widal test, rapid malarial test, Mantoux test, gastric lavage for acid-fast bacilli (AFB) were negative. Thyroid profile was normal. Echo showed no evidence of infective endocarditis and normal systolic function. Blood culture and sensitivity isolated \(S.\) \textit{aureus} species. Urine culture was sterile. Sonogram of abdomen revealed splenomegaly, ascites and right pleural effusion. Serum ferritin was elevated (1,250 ng/ml; [0-150 ng/ml]).

With the diagnosis of \textit{Staphylococcal pneumonia} with multiorgan dysfunction she was shifted to the pediatric intensive care unit (ICU); where she was started on extended spectrum penicillins and ceftazidime along with blood products for coagulopathy. (She already received a course of antibiotics from the local hospital from which she was referred).

With the course of time, there was no clinical improvement. So, a bone marrow study was done which showed increased number of histiocytes with hemophagocytosis. The clinical scenario was very much suggestive of HLH (macrophage activation syndrome secondary to \(S.\) \textit{pneumonia} and sepsis) with fever, rash, splenomegaly, pancytopenia and hemophagocytosis. She was put on ventilatory support and given a course of intravenous immunoglobulin (IVIG), in addition to the antibiotics and steroids. In spite of our efforts she succumbed on the sixth post admission day.

**DISCUSSION**

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy, although it has been seen in all age groups.

It is of two types - primary HLH\(^4\) and secondary HLH (acquired HLH), which occurs after strong immunologic activation by systemic infection (virus, bacteria and protozoa), autoimmune disorders or underlying malignancy.

There occurs overwhelming activation of normal T cells and macrophages, which can cause clinical and hematological alterations. The pathological hallmark of this disease is the aggressive proliferation of activated macrophages and histiocytes, which phagocytose other cells, namely red blood corpuscles (RBCs), white blood corpuscles (WBCs) and platelets, leading to the clinical symptoms.

The uncontrolled growth is nonmalignant and does not appear clonal in contrast to the lineage of cells in Langerhans cell histiocytosis (histiocytosis X). The spleen, lymph nodes, bone marrow, liver, skin and membranes that surround the brain and spinal cord are preferential sites of involvement.\(^5\) A current accepted theory suggests an inappropriate immune reaction caused by proliferating and activated T cells associated with macrophage activation and inadequate apoptosis of immunogenic cells.\(^6\) Although, the precise mechanism remains unclear, many research teams propose convincing pictures for the role of perforin and NK cells in the HLH subtypes.\(^7-9\)

The clinical presentation is in many aspects similar to the so-called systemic inflammation response syndrome (SIRS). And death is inevitable in the absence of treatment. The clinical entity has to be suspected when patients present with fever unresponsive to antibiotics, general fatigue, falling ESR, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

The diagnostic criteria is as follows:\(^2\)

- Familial disease/known genetic defect
Clinical and laboratory criteria (5/8 criteria)
- Fever
- Splenomegaly
- Cytopenia ≥ 2 cell lines
- Hb < 90 g/l (below 4 weeks < 120 g/l)
- Neutrophils < 1 x 10^9/L
- Hypertriglyceridemia and/or hypofibrinogenemia
- Fasting triglycerides ≥3 mmol/l
- Fibrinogen <1.5 g/l
- Ferritin ≥500 μg/l
- sCD25 ≥2400 U/ml
- Decreased and/or absent NK-cell activity
- Hemophagocytosis in bone marrow, cerebrospinal fluid or lymph nodes

Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, lactate dehydrogenase (LDH) >1,000 U/l.

For confirmation tissue diagnosis is needed. Hemophagocytosis must be demonstrated in the bone marrow, spleen or lymph nodes. In our case, almost all criteria are present. The newest treatment protocol, HLH-2004, is based on the Histiocyte Society’s original HLH-94 protocol, with some minor modifications. It represents a consolidation of the various approaches to treatment, with the goals being to first achieve clinical stability and then to cure with bone marrow transplantation (BMT). Antimyocytic prophylaxis is used during the initial doses of dexamethasone. Sulfamethoxazole and trimethoprim (i.e. cotrimoxazole) is used during the initial doses of dexamethasone. Supportive care is needed to ensure clinical stability and then to cure with bone marrow transplantation (BMT). Antimyocytic prophylaxis is used during the initial doses of dexamethasone. Sulfamethoxazole and trimethoprim (i.e. cotrimoxazole) is used during the initial doses of dexamethasone.

One group found that IVIG was effective in suppressing symptoms when administered within hours of disease onset. Serum ferritin was used as a marker for macrophage activation, and treatment was administered accordingly. Patients may be classified into high-risk and low-risk groups, with only the high-risk groups receiving the etoposide (i.e. VP-16) regimens. Patients who are at low-risk may be treated as effectively with only cyclosporine, corticosteroids or IVIG.

In the absence of prospective controlled trials, corticosteroids, cyclosporin A and etoposide are administered with varied success. Recent case reports show promising results with an anti-TNF-α approach and plasmapheresis. Supportive care is needed to ensure that the patient with HLH remains stable until a bone marrow donor can be found. This includes transfusions of RBCs, platelets, and fresh frozen plasma, as well as nutritional support in addition to the treatment protocol.

This case is presented to enlighten pediatricians and other physicians regarding the clinical entity of hemophagocytic lymphohistiocytosis to be suspected, when patients present with fever unresponsive to antibiotics, organomegaly, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

REFERENCES