CASE REPORTS

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A CASE SERIES

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ABSTRACT

A case series of three children with hemophagocytic lymphohistiocytosis is presented here. While all three had diverse clinical presentations and outcomes, marked hyperferritinemia was common to all. The presence of high serum ferritin levels in an appropriate clinical setting should prompt clinicians to consider the possibility of this rare but very serious disease.

Keywords: Familial, Hemophagocytic, Hyperferritinemia, Lymphohistiocytosis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH), characterized by widespread accumulation of T-lymphocytes and macrophages in various organs, is without treatment, a uniformly fatal disease of infancy and early childhood. The disease is caused by uninhibited lymphocyte-mediated cytotoxicity leading to pro-inflammatory hypercytokinemia[1]. Symptoms are not specific and the disease can mimic many acute childhood illnesses. In recent years the diagnosis and consequently the survival of HLH has markedly improved due to better understanding of the disease and development of clinically helpful diagnostic criteria.

A case series of three patients is presented with diverse clinical presentations and outcomes. These cases highlight the importance of keeping a high index of suspicion for uncommon disorders like HLH in appropriate clinical settings[2].

CASE REPORTS

Case 1

A 5 month old girl was brought for evaluation of worsening anemia of 2 months duration. Parental concerns were based on infection related deaths of 2 siblings at 8 and 11 months of age due to an unidentified illness. Clinical examination revealed marked pallor, a hemic flow murmur and no visceromegaly. Investigations revealed normocytic, normochromic anemia (Hb 6.1 g/dl), with normal TLC ($6.7x10^3$ cmm) and platelet count (196,000/cmm). She had normal Hb electrophoresis and immunoglobulin levels. Liver function tests, renal profile, plasma glucose and coagulation profile (PT 12 seconds, APTT 36 seconds) were normal. Serum ferritin level was 2500 mg /dl in the face of a single blood transfusion given five weeks ago. While being investigated she developed a sepsis like picture with fever, petechial hemorrhages and hepatosplenomegaly. Repeat CBC showed pancytopenia (Hb 4.2 gm/dl, TLC $2.4x10^3$ cmm, platelets 23,000/cmm). An urgent bone marrow examination revealed marked hemophagocytosis. Serum fibrinogen levels were low. She rapidly became hemodynamically unstable, developed end organ dysfunction and died six days after admission. She fulfilled HLH diagnostic criteria. The familial variety of the disease was strongly considered due to suggestive family history and parental consanguinity.

Case 2

A 14 year old boy was booked for bone marrow examination. He had been suffering from acute viral hepatitis for the last two weeks with moderately severe anorexia initially requiring intravenous rehydration for a few days. After a symptom free interval of 1 week and some biochemical improvement he developed easy fatigability, minor nose bleeds and a generalized petechial rash. On examination he had no neurological deficit or lymphadenopathy but appeared pale and jaundiced. There was mild hepatosplenomegaly (liver 3 cm below costal

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margin, spleen 2.5 cm below costal margin) without ascites. Complete blood count revealed pancytopenia (Hb 7.2 gm/dl, TLC 3.9x10^3 mm, platelet 56,000/cmm) with a normal reticulocyte response. The prothrombin and partial thromboplastin times (PT 13 seconds, APTT 35 seconds) were within normal limits. Liver function tests showed mild elevation of liver enzymes (ALT 176 U/l, ALP 767 U/l). Bone marrow examination revealed hemophagocytosis which was reconfirmed on a second bone marrow examination. He had normal triglyceride levels but a high serum ferritin of 1975 mg/dl. Serum fibrinogen levels were low. Monospot test was negative.

Hepatitis A IgM antibodies were positive with negative HbsAg and anti HCV antibodies. He was diagnosed as hepatitis A related acquired HLH. Interestingly before chemotherapy was initiated, his petechial rash began to clear and his blood counts improved spontaneously. Four weeks later he was asymptomatic, had normal blood counts and a repeat bone marrow examination revealed no hemophagocytosis. Eight months after the initial presentation he remains symptom free with normal blood counts and positive hepatitis A IgG.

Case 3

A 2 year old girl, the second child of consanguineous parents, was admitted with pyrexia of unknown origin. There was no hepatosplenomegaly or rash. Physical examination showed no localizing sign. Her lab workup including CBC, ESR, MP slides, urine microscopy, CXR, CSF examination, blood and urine C/S and ANA did not reveal any pathology. Empirical broad spectrum antibiotics and anti-malarials were started but her fever persisted. Over a period of 10 days she developed thrombocytopenia (CBC: Hb 9.7 gm/dl, TLC 5.2x10^3 mm, platelet 21,000/cmm) and edema. Her renal and liver function tests and serum albumin were normal. Serum fibrinogen levels were low, serum triglycerides were high and serum ferritin was 25,000 mg/dl which was rechecked. Bone marrow examination showed marked hemophagocytosis in a reactive marrow with normal megakaryocyte precursors. She fulfilled HLH diagnostic criteria and HLH-2004 protocol was started. After the first two weeks of chemotherapy her fever settled and her blood

Table-1: Diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH 2004 protocol).

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (five or more out of the eight criteria below)
   - Fever
   - Splenomegaly
   - Cytopenias (affecting two of three lineages in the peripheral blood: hemoglobin < 90 g/l , platelets <100×109/l, neutrophils <1.0×109/l)
   - Hypertriglyceridemia or hypofibrinogenemia: fasting triglycerides >3.0 mmol/L, fibrinogen <1.5 g/l
   - Hemophagocytosis in bone marrow, spleen, lymph nodes, or cerebrospinal fluid: no evidence of malignancy
   - Low or absent NK cell activity (according to local laboratory reference)
   - Elevated ferritin (>500 mg/l)
   - Soluble CD25 (i.e. soluble interleukin-2 receptor) above normal limits for age

Either the molecular or the clinical/lab criteria can be used to establish the diagnosis of HLH.

Treatment is justified if a patient meets only four clinical/lab criteria and the clinical suspicion for HLH is high.

counts showed improvement (Hb 10.4 gm/dl, TLC 8.3x10^3 mm, platelets 92,000/cmm).

DISCUSSION

Hemophagocytic lympho histiocytosis (HLH) is a potentially fatal illness with familial and acquired subtypes. Familial HLH affects infants from birth to 18 months of age while acquired cases occur throughout childhood. The reported incidence of HLH is 1.2 children per million per year. This may not reflect the true incidence as several children with HLH remain undiagnosed. The male to female ratio is 1:1. As many as 25% cases of HLH may be familial while 75% occur with a number of infections, autoimmune disorders and malignancies. Distinction between familial and acquired categories cannot be reliably made in some cases; however the management and prognosis for both types of HLH are essentially similar. Familial HLH is often associated with parental consanguinity and inherited in an autosomal recessive fashion[3].

Infections implicated in the acquired form of HLH are Epstein-Barr virus, CMV, parvovirus, hepatitis A, herpes simplex, varicella-zoster, measles, HHV-8 and HIV infection. Bacterial infections like brucellosis, tuberculosis and gram negative sepsis are occasionally responsible[4]. Autoimmune disorders including systemic lupus eryhematosus, juvenile idiopathic arthritis, polyarteritis nodosa and mixed connective tissue disease may be complicated by HLH especially in adults. Secondary HLH may also occur in patients with primary and secondary immune deficiencies as well as in association with NK cell leukemias and various lymphomas[5].

The basic pathophysiologic defect in HLH is cytokine dysfunction. An unrestrained inflammatory response leads to an uninhibited accumulation of activated T-lymphocytes and activated histiocytes in several organs resulting in extremely high levels of cytokines e.g. interferon gamma, tumor necrosis factor (TNF)-alpha, interleukins (IL)-6, IL-10, IL-12, and soluble IL-2 receptor (CD25) . Defective apoptosis of activated T-lymphocytes further contributes to this uncontrolled accumulation[6].

Mutations in the perforin gene appear to be central to the pathogenesis of familial HLH. Perforin is secreted by cytotoxic T-lymphocytes and natural killer (NK) cells and creates a "cell death-inducing pore" through which toxic enzymes enter the target cell and trigger apoptosis. Defective apoptosis resulting from a defective perforin protein leads to accumulation of large numbers of inflammatory cells and cytokine oversecretion. In addition to hypercytokinemia, HLH is associated with low or absent natural killer (NK)-cell and cytotoxic T cell activity[7].

Early clinical features of HLH may include fever, hepatomegaly, splenomegaly, lymphadenopathy, skin rash and neurologic symptoms[8]. The nonspecific nature of these symptoms leads to suspicion of sepsis, hepatitis, encephalitis and even child abuse. The diagnostic difficulty is exemplified by the Swedish study in which 21 out of 32 patients were diagnosed postmortem[9].

A panel of screening tests including complete blood picture, liver function tests, serum ferritin, serum fibrinogen and serum triglycerides helps identify HLH[10]. Cytopenias and a high serum ferritin are vital early markers for HLH and should trigger further investigation. Results from the HLH-94 study indicated that a ferritin level > 500 mg/l was 80% specific for the diagnosis of HLH[6]. The International Histiocyte Society has laid down a set of diagnostic criteria to help clinicians in the timely recognition of this disorder (Table-1). These criteria take into account several key clinical features and laboratory characteristics in combination with tissue examination to detect hemophagocytosis[11].

The management of suspected or confirmed HLH begins with aggressive supportive therapy with blood product transfusions, antibiotics, and nutritional support. Many fatalities are attributable to overwhelming infection and prophylaxis with trimethoprim-

sulphamethoxazole and fluconazole is routinely given. A search for a potential hematopoietic cell transplant donor is initiated at the time of diagnosis so that subsequent management decisions can be made in a timely fashion[12].

Prior to the introduction of HLH-94 protocol, the mortality rate for HLH was > 90%. Three year survival has improved to more than 55% since the advent of this protocol. Induction therapy with dexamethasone, etoposide, cyclosporine (started at week 9), and intrathecal methotrexate is followed by pulses of dexamethasone and etoposide for up to one year. This therapy may be adequate for children whose HLH is secondary to an infection and without NK cell defects. On the basis of the immunologic pathophysiology of familial HLH, a combination of antithymocyte globulins with corticosteroids, cyclosporin A, and intrathecal injections of methotrexate is indicated[7]. HLH 2004 protocol was introduced as an alternative approach to treatment, but has not yet completely replaced the HLH-94 protocol. Patients who do not respond to initial eight weeks of therapy require allogenic hematopoietic cell transplantation[13].

Without therapy familial HLH is a rapidly fatal illness with an average survival of about two months from presentation. The fatality rate of acquired HLH was 90% before the advent of HLH-94 protocol. During the last decade the overall prognosis with regard to survival has improved dramatically. Good remission rates afforded by the HLH-94 and HLH 2004 protocols usually buy sufficient time for the patient during which a BMT donor can often be identified and processed[14].

All our patients fulfilled HLH clinical/lab diagnostic criteria. Our first case was clearly familial. The second case had HLH secondary to Hepatitis A infection. Familial or acquired nature of HLH was not apparent in the third patient since there was no family history of confirmed or suspected HLH and genetic studies were not available. All three patients had very high serum ferritin levels. In a similar case series from Mumbai, hyperferritinemia was found in nine out of ten patients with HLH[15]. In fact hyperferritinemia may be the single most useful indicator for HLH in developing countries where molecular diagnosis and advanced laboratory studies are not often available. It is recommended that serum ferritin levels be measured in all children with pancytopenia.

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