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Abstract

Five patients of acquired Hemophagocytic Lymphohistiocytosis (HLH) were seen in a tertiary care hospital over a period of 25 years. Three of the patients had a culture proved Salmonella typhi infection and one had evidence of Epstein Barr virus infection. The three patients with Enteric fever were managed with antibiotic therapy and the one with EBV associated HLH received etoposide, cyclosporine and steroids. The other patient was treated with pulsed steroid therapy. One patient died of sepsis during his relapse. HLH must be considered in patients with fever with prolonged cytopenias.

Introduction

Hemophagocytosis is the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells (1), and constitutes an important finding in patients with hemophagocytic syndrome, more properly referred to as hemophagocytic lymphohistiocytosis (HLH) (2). HLH is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver, or lymph nodes. Initially the syndrome was thought of a sporadic disease resultant on neoplastic proliferation of histiocytes but subsequently, a familial form of the disease (3) (now referred to as familial hemophagocytic lymphohistiocytosis [4]) was described and the nearly simultaneous development of fatal HLH by a father and son in 1965 indicated that infection might play a role (5). HLH has since been associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as collagen-vascular diseases (6-10) and malignancies, particularly T-cell lymphomas (11). There is, however, a paucity of literature, especially from our part of the world. The present case series describes five patients seen over a 19-year period who presented with prolonged cytopenias and subsequently were proved to have hemophagocytosis on bone marrow examination.

Case Report(s)

In the present case series, we describe five patients who presented with prolonged cytopenias. Table 1 depicts the clinical features of these patients. Three out of the four patients had a diagnosis of salmonellosis confirmed by isolation of Salmonella typhi. All the patients presented with fever of varying duration with evidence of clinical bleeding (n=2). Clinical features included splenomegaly. Pancytopenia of varying severity was evidenced upon hematological investigation. Serum lactic dehydrogenase was elevated in all the patients whereas elevated ferritin and triglyceride in 2 of the five in whom it was available. Cultures form blood, urine and bone marrow aspirate were sterile. Serologies for EBV, CMV HAV, HAB and HIV were negative in 4 of the cases and was positive in patient no 5. Bone marrow aspiration revealed evidence of hemophagocytosis (Fig 1,2). NK cell activity was normal in 2 of the patients in whom it was done. Patients with a diagnosis of enteric fever were treated with antibiotics as per culture sensitivity reports. They responded to antibiotics and their blood counts returned to normal values. Patient no 4 was treated with intravenous pulses of methyl prednisolone following which her fever subsided and counts returned to normal. Serum ferritin and LDH levels also normalized. She continues to have normal counts and is asymptomatic over a followup of 12 months. Patient no 5 was put on steroids, etoposide and cyclosporine. The patient responded with response of fever, counts, ferritin and LDH. However he was readmitted after 4 months of his initial illness with a sepsis syndrome with recurrence of the pancytopenia. He was planned for a bone marrow transplantation but he succumbed to his sepsis.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life threatening condition characterized by uncontrolled activation of macrophages and lymphocytes. The syndrome, which affects mainly the pediatric population but can involve any age, has also been referred to as histiocytic medullary reticulosis and was first described in 1939. (12) The disorder was initially belived to exist in sporadic form only but
subsequently a familial form has been reported which is referred to as familial hemophagocytic lymphohistiocytosis (FHLH) (4). Familial HLH is an autosomal recessive disorder first described by Farquhar and Claireaux in 1952, (3) and is also termed variously as familial hemophagocytic reticulosis. Farquhar’s disease, familial erythrophagocytic lymphohistiocytosis, lymphohistiocytic reticulosis with phagocytosis, or lymphohistiocytosis. Its incidence is 1.2 cases per million children under 15 years as reported in Sweden (13). Most cases are no older than three years. Evolution is similar to a septic picture but with no detectable etiologic agent. The diagnosis of FHLH is made based on the presence of clinical criteria and is confirmed by molecular genetic testing. Four disease subtypes (FHL1, FHL2, FHL3, and FHL4) are described and three genes have been identified and characterized: PRF1 (FHL2), UNC13D (FHL3), and STX11 (FHL4) (14).

Secondary HLH (acquired HLH) occurs after strong immunologic activation such as that occurs with a variety of viral, bacterial, fungal, and parasitic infections, as well as collagen-vascular diseases (7-10) and malignancies, particularly T-cell lymphomas. (11-15) Virus-associated hemophagocytic syndrome was first described in immunodeficient patients receiving organ transplantation.(16). Subsequently, it was shown to be present even in immunocompetent patients. The main viruses involved are Epstein-Barr virus, cytomegalovirus, adenovirus and parvovirus B19. The hemophagocytic syndrome, described in HIV positive patients, is generally associated with other viruses, especially the Epstein-Barr virus, or to other infections (1,16,17). The reactive forms of HLH are difficult to distinguish from the hereditary forms especially as patients with familial HLH may have hemophagocytic syndrome after a documented viral infection (18). HLH has also been described in Weber-Christian’s disease (as a histiocytic cytophagic panniculitis) (16); in the advanced phase of Chediak-Higashi’s syndrome (1); in systemic lupus erythematosus (7) and in patients receiving parenteral feeding with high lipid content (1, 19).

The pathological hallmark of the syndrome is aggressive proliferation of macrophages and histiocytes which phagocyte other blood cells leading to the clinical symptoms. This uncontrolled growth is nonmalignant and in contrast to the lineage of cells in Langerhans cells Histiocytosis does not appear clonal. The preferential sites of involvement include spleen, lymph nodes, bone marrow, liver, skin and membranes that surround the spinal cord. (20)

Although the processes underlying the pathophysiology of HLH are not entirely understood, a current accepted theory involves an inappropriate immune reaction caused by activated T cells associated with macrophage activation and inadequate apoptosis of immunogenic cells. (21). Perforins and NK cells have been proposed to play crucial roles in the causation of HLH even as the exact mechanisms are unclear (22-24).

Upon activation, NK cells release granules containing granzymes and perforins which form pores in the target cell membrane and causes osmotic lysis and protein degradation respectively. An impairment of the cytotoxic function of NK cells and cytotoxic T lymphocytes has been demonstrated which in turn results in increased T cell activation and expansion resulting in production of large quantities of inflammatory cytokines, including interferon α (IFN α), tumor necrosis factor α (TNF α) and granulocyte macrophage colony stimulating factor (GM-CSF). A sustained macrophage activation and tissue infiltration as well as production of interleukins, IL-1 and IL-6, results and causes extensive damage with associated clinical and biochemical features including cytopenias, coagulopathy and high triglycerides (20). Factors leading to cytolytic defects in acquired HLH are less clear. Viruses have been reported to interfere with T cell activity by specific proteins or cytokines (25,26).

The diagnosis of HLH is based upon finding typical clinical and biochemical features (27,28). Five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis) were proposed to be satisfied for a definite diagnosis of HLH in the HLH-94 study (28). In HLH-2004 three additional criteria were introduced; low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. Altogether five of these eight criteria must be fulfilled, unless family history or molecular diagnosis is consistent with HLH (29). Measurement of natural killer (NK) cell activity has been shown to be useful in distinguishing primary from secondary HLH. Children with confirmed familial disease have been reported to have persistently low or absent NK cell activity. Those with secondary HLH may have low NK cell activity at presentation, but this typically normalizes with remission of illness (20, 30, 31).

Untreated, familial disease is fatal in all cases. Stem cell transplantation (SCT) is the only curative treatment. Since many patients do not have a family history or a proven genetic defect a surrogate marker for genetic disease is persistent disease activity or
relapses on or off treatment. In patients without family history and complete resolution of all symptoms, elective cessation of therapy is recommended to prevent an unnecessary SCT for transient, acquired HLH. This, however, is not without risk since a relapse may be accompanied by severe symptoms. Thus these patients have to be closely monitored to restart therapy in time.

Also, acquired infection associated HLH has a high fatality rate of 50% in children. (32). If a treatable organism is found, appropriate therapy may be given but anti-infectious therapy may not sufficient to control HLH. The immediate aim of treatment is to suppress hypercytokinemia that is responsible for the life-threatening symptoms. Three of our cases had a antibiotics associated response of the biochemical and clinical features of HLH. There are only few reports of Salmonella infection induced HLH and has been reported to result in varied clinical and hematological features like jaundice and pancytopenia (33-41). All of our patients with typhoid fever had pancytopenia at presentation and thus hemophagocytosis could be contributory to the development of pancytopenia in patients with typhoid fever.

Standard treatment for HLH is a combination of corticosteroids, cyclosporin A and etoposide. All patients with known familial disease, suspected genetic disease, age below 1 year and patients with life-threatening symptoms such as coagulopathy, profound cytopenia or neurological disease should receive therapy according to the present HLH 2004 protocol. Etoposide may be life-saving especially in patients with EBV-associated HLH (42) and the benefit outweighs the possible side effects of etoposide.

Conclusion

We conclude that physicians must possess a high index of suspicion for diagnosing HLH amongst patients presenting with fever and cytopenias as appropriately administered therapy can be life saving in this potentially fatal disease.

References

Illustrations

Illustration 1

Figure 1. Evidence of hemophagocytosis (Patient 5)

Illustration 2

Hemophagocytosis (Patient no 5)
Illustration 3

Depicting the pertinent clinical and biochemical features of the patients. TLC=Total leukocyte count, DLC= Differential leukocyte count, P=Polymorphs, L=Lymphocytes, LDH=Lactic dehydrogenase, HS=Hemophagocytosis.

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