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CASE REPORT

Hemophagocytic Lymphohistiocytosis: A Rare Case

K B Vijay[1], H T Tejasvi[2]*, S B Vijeth[3], S R Vagesh Kumar[4]

1 Post-Graduate, Department of General Medicine, Basaveshwara Medical College and Hospital, Chitradurga, 577502, Karnataka
2 Associate Professor, Department of General Medicine, Basaveshwara Medical College and Hospital, Chitradurga, 577502, Karnataka
3 Professor, Department of General Medicine, Basaveshwara Medical College and Hospital, Chitradurga, 577502, Karnataka
4 Professor and Head of Department, Department of General Medicine, Basaveshwara Medical College and Hospital, Chitradurga, 577502, Karnataka

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* **Corresponding author**.

tejasviht@gmail.com

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an autoimmune phenomenon characterized by reactive hyperactivity of cytotoxic T cells and histiocytes, leading to hypercytokinemic injury to cells and organ system, which leads to multiorgan dysfunction and ultimate failure. Epstein-Barr virus (EBV) is most commonly associated with secondary HLH with high mortality, but increasing evidence suggests the association of the dengue virus. When associated with dengue infection, it carries a grave prognosis and correlates with the disease severity. Furthermore, it overlaps with dengue sepsis, so it can often be misdiagnosed as sepsis. Typically, the patients have hyperferritinemia, hypertriglyceridemia, transaminitis, and marrow features suggestive of hemophagocytosis. The treatment is usually systemic corticosteroids, intravenous immunoglobulin, and chemotherapy with etoposide. 30 years old male presented to our OPD with complaints of fever for 4-5 months on and off type and generalised weakness. Clinical suspicion alerted us to look for other evidence of HLH on the fourth day of admission, and appropriate investigations were done. Diagnosis of HLH was confirmed by HLH-2004, HScore criteria, and bone marrow aspirate examination. Treatment was given in the form of corticosteroids and chemotherapy along with other supportive measures (dexamethasone). The patient had cardiac arrest and succumbed inspite of necessary measures taken to rescussitate. HLH is life threatening complication. The treatment of this condition requires aggressive immunosuppression with either the cytotoxic agents or anti T cell antibodies.

Keywords: Hemophagocytosis; HLH2004; H Score Criteria; ETOPOSIDE; Cytokine Storm

Introduction

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 not a single disease and it can be encountered in association with a variety of underlying disease that leads to highly stimulated but inactive immune responses. There are two forms of the disease: primary (that includes familiar forms) and secondary or acquired, usually due to infections, malignancy, and autoimmune/autoinflammatory diseases, both forms have similar clinical characteristics[1]. Despite the etiology, HLH is an important cause of fever of unknown origin and extreme elevation of ferritin, associated with multiple organ involvement. Initial signs and symptoms of HLH can mimic common diseases, like infections.

Case Report

A 30-years old male presented to our OPD with complaints of fever for 4-5 months on and off type and generalised weakness. On examination patient had pallor. B/L lower limb edema and splenomegaly were present, no evidence of generalised lymphadenopathy. Work up for tuberculosis, retroviral disease and connective tissue disorder and ANA profile came to be negative. Investigations revealed pancytopenia, hypertrigleceridemia, hyperfibrinogenemia, increased serum ferritin levels, hyponatremia, and liver enzymes were elevated. Bone marrow biopsy shows evidence of Hemophagocytosis. Diagnosis of HLH was confirmed by HLH-2004, HScore criteria. Treated with intravenous steroids (dexamethasone) and other supportive therapy and haematologist opinion was taken, for which ETOPOSIDE therapy was advised, before starting ETOPOSIDE therapy patient had cardiac arrest and succumbed within a month due to sepsis- inspite of necessary measures taken to rescuscitate.

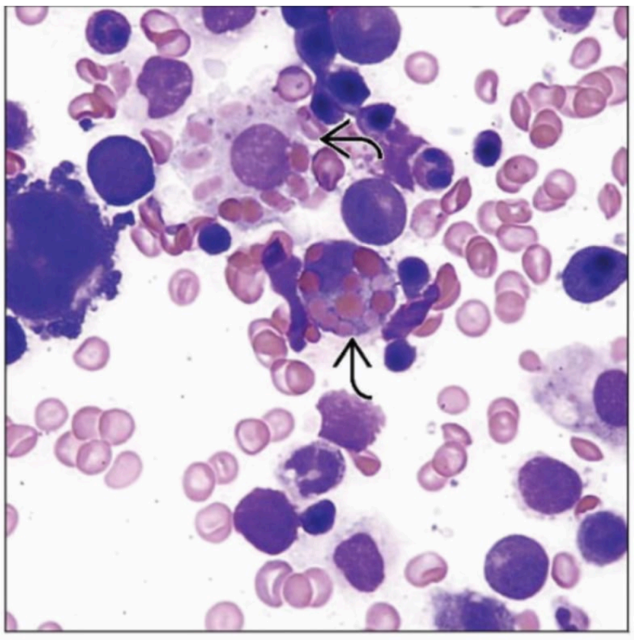

Fig 1. HLH in bone marrow aspirate smear (Wright-Giemsa stain). Histiocytes show erythrophagocytosis. This patient presented with fever and pancytopenia prompting bone marrow examination

Discussion

Hemophagocytic lymphohistiocytosis is an immunologically mediated inflammatory response to viral infections, immune disorders, and malignancy. HLH induces cytokine storms, and the bone marrow shows lymphohistiocytic reaction and macrophagic hemophagocytosis. Though EBV is the most common viral infection known to cause HLH, dengue-indued HLH is being largely reported. Association of HLH with dengue fever is an indicator of severe disease. The overlap between HLH and sepsis syndrome has been known. Most of the patients with HLH have features like fever, hypotension, distributive shock and multisystem organ failure which are also common in severe sepsis and septic shock. As mentioned earlier, a variety of secondary causes, including infections, malignancies, and autoimmune causes, can trigger the disease and imbalance in the immune system. A systematic review reported that infectious causes were the most common cause of HLH. The treatment approach of HLH is targeted first toward the inciting event, which may be a viral infection, autoimmune disorder, or malignancy. The HLH-94 protocol states that induction therapy with etoposide is indicated in malignancy-associated HLH or where there is evidence of clinical deterioration. Other therapies are corticosteroids, intravenous immunoglobulin, and cyclosporin. Allogenic stem cell transplantation is reserved for refractory cases. Hyperferritinemia is strongly associated with HLH, and a cutoff value of >10,000mcg/L is 90% sensitive and 96% specific for its diagnosis. It also correlates with disease activity. This emphasizes the need for closer monitoring in dengue virus-infected patients with hyperferritinemia. In many cases, the underlying etiology of HLH is unclear, making it very difficult to diagnose. The diagnosis of HLH is very challenging; it is indeed based on a set of clinical, laboratory, and histopathological findings. In summary, HLH is a fatal disease particularly challenging to be diagnosed due to its rarity. Highly variable clinical presentations, laboratory findings, and associated diseases make diagnosis more difficult. On the other hand, the identification of the FUO etiology as one of the HLH manifestations and the etiology similarity between FUO and HLH itself makes the diagnosis even more difficult. Often the main problem in starting treatment is delayed diagnosis. Treatment should be

based on the patient's underlying health conditions, clinical manifestations, and suspected underlying causes.

Conclusion

HLH is life threatening complication. HLH is diagnosed using the HLH-2004 and HScore criteria. Treatment focuses on targeting the primary pathology. Drugs used in the treatment of HLH are corticosteroids, intravenous immunoglobulin, and etoposide. A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment options; however, much work remains to raise awareness and improve the effectiveness of treatment regimens.

References

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