Is Hemophagocytic Lymphohistiocytosis (HLH) underdiagnosed in critical care setting?

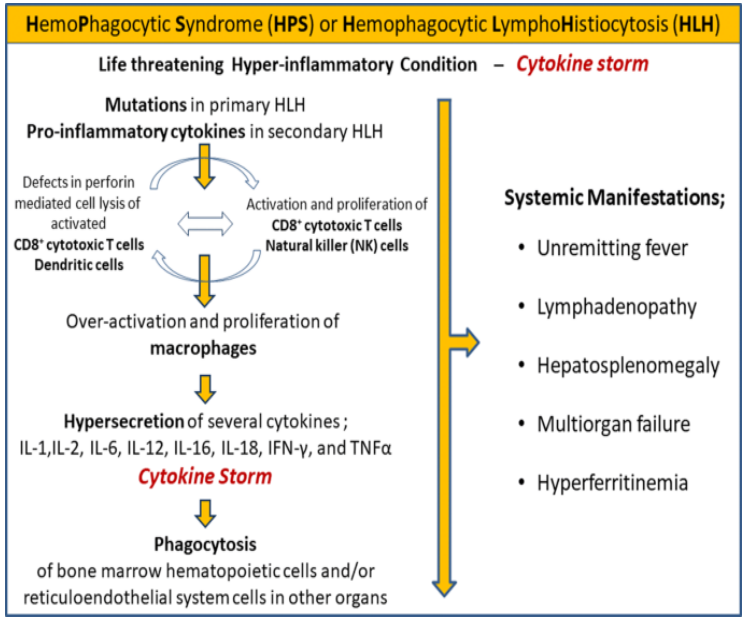
Asna Shahab, MD[1]. Rahul Rane, MD[2]. Hasan Awais, MD[3]. Ashish Jain, MD[4]. Ibrahim Sbeitan, MD[5].*
Department of Internal Medicine, Conemaugh Memorial Medical Center, Johnstown, PA• www.conemaugh.org

INTRODUCTION

- Hemophagocytic lymphohistiocytosis (HLH) is characterized by an abnormal excessive immune activation leading to a possibly life-threatening syndrome, more commonly seen in the pediatric population. HLH is an under-recognized entity in the critical care unit and often remains undiagnosed. Therefore, timely diagnosis and intervention are vital. We present a case of HLH in the setting of the Ebstein Barr virus (EBV) infection.

CASE

- A 59-year-old man was found at his home unresponsive, covered with feces. His vitals were significant for hypotension and a fever of 101F. The patient was immediately transferred to the critical care unit and was intubated to protect the airway. Initial lab workup was significant for hemoglobin 8.5 g/dL, platelets 42,000/microL, white blood cell count 3,000 /uL, ferritin 5835ng/ml, new-onset transaminitis, and acute kidney injury. CT head revealed a 6mm subdural hematoma with a 2mm midline shift to the right. Neurosurgery advised no acute surgical intervention. The blood culture was positive for methicillin-sensitive staph aureus (MSSA), and the patient was started on an appropriate antibiotic. However, the patient's clinical condition continued to deteriorate. In the setting of persistent pancytopenia despite multiple transfusions of blood products, elevated ferritin, and fever, hematology-oncology was consulted for concerns of HLH. A peripheral blood smear showed pancytopenia with normal morphology. An extensive lab workup was ordered, along with a bone marrow aspirate. Based on the diagnostic criteria used in the HLH-2004 trial, our patient fulfilled five diagnostic criteria, i.e., anemia (8.5 g/dL) and thrombocytopenia (42000/microL), hypertriglyceridemia (435 mg/dl), ferritin at 5835 ng/ml, fever 101.1F, IL-2 4155 sufficient to diagnose HLH. However, flow cytometry showed a reversal of CD4/CD8 ratio with no evidence of low NK cells, and bone marrow aspirate was negative for hemophagocytosis. The patient was tested for a possible viral infection and subsequently tested positive for EBV, which could be an infectious trigger for the patient's HLH. The patient was then started on dexamethasone for the treatment of HLH, which led to significant improvement in his clinical condition.



DISCUSSION

- HLH syndrome has two major subsets; primary/familial or secondary. Secondary HLH (sHLH) is more frequently seen in adults and can be triggered by various infections in particular Ebstein-Barr virus (EBV), malignancy, rheumatological conditions or drugs.
- SHLH has no universally agreed diagnostic criteria. In 1994, Histiocyte society proposed a diagnostic criteria which was revised in 2004 and 2009. Fardet et al proposed H-score with a cut off value of 169, yielding 93% sensitivity and 86% specificity in non-ICU patients.
- HLH and sepsis have significant overlap, hence critical care patients who lack clear infectious etiology, unexplained fever, and multi-organ dysfunction, should be worked up for HLH.
- Ferritin levels should be closely monitored. Levels >10,000ug/L in the setting of sepsis increase the tendency of concomitant sHLH.
- SHLH is associated with high mortality if advanced. HLH criteria and H score can aid in diagnosis but should not delay time sensitive management.
- Steroid is the mainstay of the initial treatment. If stress dose steroid is being administered, it can be switched to high dose pulsed methylprednisone. In HLH secondary to lymphoma, there is concern regarding steroid use as some lymphoma be steroid sensitive and can hinder diagnosis.
- Anakinra (Recombinant IL-1 receptor antagonist), is being considered as the emerging first line treatment, as it has low side effects and is well tolerated.
- Intravenous immunoglobulins can be considered with repeat dose in two weeks, due to limited half-life. Plasmapheresis can also be considered.
- Etoposide (cytotoxic agent) can be used in refractory cases, particularly in those associated with EBV or malignancy.

CONCLUSION

- HLH is a clinical syndrome of hyperinflammation, triggered by infections, malignancy, connective tissue disease or drugs.
- HLH should be considered in patients with undifferentiated rapidly progressive organ failure with failure to respond to sepsis management.
- Serum ferritin levels correlate with mortality associated with HLH.
- Hospital mortality associated with HLH in critical care settings is between 52-68%.
- HLH is associated with high mortality, hence the risk of misdiagnosis should be balanced against side effect associated with immunotherapy for timely intervention.

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