

# Hemophagocytic Lymphohistiocytosis Secondary to Acute Hepatitis E Infection: A Rare Association

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## Abstract

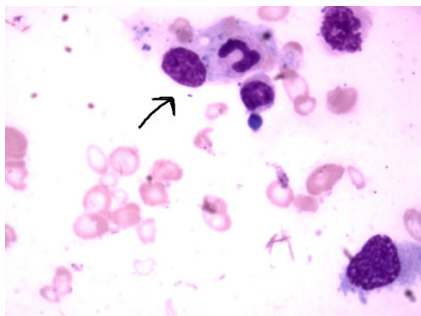
Viral infections are commonest cause of secondary hemophagocytic lymphohistiocytosis (HLH) and Epstein Bar Virus is associated with majority of cases. We report a rare case of HLH associated with acute hepatitis E virus infection.

## Introduction

**H**emophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal condition, in which body's own inappropriate hyperimmune response leads to hypercytokinemia (cytokine storm syndrome) and subsequently the vivid manifestations of syndrome.<sup>1</sup> It may be primary (underlying genetic mutations) or secondary triggered by infections, malignancy or rheumatological disorders, immunosuppressed states. Among viral infections, it is most commonly associated with EBV, CMV and HHV-8 infection.<sup>1,2</sup> Here we report a rare case of HLH associated with acute Hepatitis E virus infection.

## Case Presentation

A 20 year male resident of Jharkhand referred to us during the acute viral hepatitis epidemic in Shimla in December 2015 with yellowish discoloration of eyes for 1month, vomiting for 4 days and fever for 1 day. He had associated pruritus, clay coloured stools, high coloured urine and decreased appetite. He didnot consume



**Fig. 1: Hemophagocytosis in Bone Marrow of the patient**

alcohol. He was being treated for acute viral hepatitis at Zonal hospital on OPD basis for 3 weeks but no records were available. He didnot take any indigenous drugs. On examination he was febrile with 103°F temperature, had icterus, cervical lymphadenopathy, hepatomegaly and moderate splenomegaly. Clinical possibility of acute viral hepatitis with pyrexia under evaluation was kept and investigations ordered. Haematological findings were anaemia (Hb 8.5%), leucopenia with neutropenia (TLC 3700mm<sup>3</sup>, ANC 900mm<sup>3</sup>) and thrombocytosis (5,19,000mm<sup>3</sup>). Peripheral smear showed anisocytosis, macrocytes with schistocytes. Biochemistry report revealed hyponatremia (130meq/l), conjugate hyperbilirubinemia (total bilirubin-29.11mg/dl, direct bilirubin-14.22 dl), SGOT 80 IU, SGPT 33 IU, alkaline phosphatase 234 IU, hypoalbuminemia (2.8g/dl) and AKI (creatinine 1.4mg/dl). His IgM HEV was positive and rest all viral markers (IgM HAV, HBsAg, anti HCV and HIV) were negative. Pyrexia workup including blood cultures, LN biopsy, malarial antigen/smear and amoebic, scrub and leptospira serology were all negative. Patient's Hb and platelet count fell down (8.5 to 3.4 g% and 5,19,000 mm<sup>3</sup> to 2,10,000mm<sup>3</sup> respectively) on subsequent estimation at day 4, while TLC count remained on lower side (3500mm<sup>3</sup>). There was no obvious bleeding from any site. Serum LDH levels was 715IU s/o hemolysis but DCT and ICT were negative. Radiological investigations (CXR, USG abdomen,

CECT abdomen) were suggestive of hepatomegaly and splenomegaly with normal portal vein and no occult abscess. Patient was started at admission on empirical broad spectrum antibiotics with supportive therapy including blood transfusion. When, even after 7 days of antibiotics patient stayed febrile and counts remained low, bone marrow examination (BME) was done to rule out visceral leishmaniasis. BME didnot reveal LD bodies but showed focally reticuloendothelial cells with hemophagocytosis (Figure 1). At this stage, possibility of HLH was kept and further investigation were done to rule it out- fibrinogen level: 324 mg/dl, S.ferritin: 13578 µg/L, fasting S.TGs: 316 mg/dl. Our patient fulfilled 6 out of 8 diagnostic criteria for HLH (Histiocyte Society 2004).<sup>3</sup> So final diagnosis of secondary HLH etiology: acute HEV hepatitis was kept. After definitive diagnosis patient was started on iv dexamethasone and antibiotics were continued. He responded to treatment and fever and counts improved (Hb 8.3 g/dl, TLC 4500/mm<sup>3</sup>) icterus decreased (bilirubin 10.51 mg/dl, C. bilirubin 2.95 mg/dl). He was discharged on oral dexamethasone for 8 weeks, was asked to come for follow up after 2 weeks but he didnot come. Unfortunately he expired after 2 months when enquired on telephone.

## Discussion

HLH is a rare entity of immune activation, which may be familial or sporadic, manifesting as symptoms and signs of severe inflammatory response. It has been associated with viral infections (29%), other infections (20%), malignancies (27%), rheumatological disorders (7%). Most common associated viral infection is EBV. Its association with HEV virus has been rarely documented. Less than 5 cases have been documented till date.<sup>4-7</sup> Co-morbidities have been documented

in three cases (hepatitis A co-infection,<sup>2</sup> splenic lymphoma,<sup>5</sup> and rheumatoid arthritis treated with tocilizumab infusion.<sup>6</sup> Three patients recovered with supportive treatment while the fourth one died due to fulminant hepatitis.

HLH is characterised by phagocytosis of blood cells and their precursors, mostly by monocytes and macrophages. Excessive activation of monocytes may be due to stimulation by high levels of activating cytokines, IFN- $\gamma$ , IL-2 receptor, TNF- $\alpha$ , IL-1 and IL-6. The exact mechanism by which abnormal cytokine elaboration by T-lymphocyte results in HPS remains unclear.

It presents with cytopenias due to uncontrolled hemophagytosis and laboratory findings resulting from disseminated immune regulation and cytokine storm. Clinically, HLH is characterized by high fever, lymphadenopathies, hepatosplenomegaly, liver dysfunction, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, as well as coagulopathy and neurological manifestations (cerebral HLH) in many cases and is diagnosed based on HLH 2004 criteria.<sup>3</sup> The diagnosis of HLH can be established if one of the two criteria is fulfilled 1) A molecular diagnosis consistent with HLH 2) Diagnostic criteria for HLH fulfilling 5 out of 8 criteria: 1) fever 2) splenomegaly 3) cytopenias (at least 2 of 3 lineages in peripheral blood, 4) hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL) 5) haemophagocytosis in bone marrow, spleen or lymph nodes 6) low

or absent NK-cell activity 7) serum ferritin >500  $\mu$ g/L 8) soluble CD25  $\geq$  2400 U/ml. but these criteria are not very sensitive. Treatment of HLH involves immunosuppression and modulatory agents and treatment of the inciting illness, if it is secondary. Infection as such are most common cause of secondary HLH also common triggering factor in familial HLH. So, genetic mutations to rule out familial HLH must be done in very case. There is no standard protocol for treatment in infections. One must treat underlying infection. The HLH-94 and HLH-2004 trials protocols (dexamethasone, etoposide cyclosporine and methotrexate) used for genetic HLH can be applied to secondary severe or non responding cases. Although steroids have been commonly used in treating virus associated HLH, there have been cases reported showing failure<sup>8</sup>. Our patient showed a drastic improvement with steroids initially. Patients without a clear diagnosis of familial HLH, bone marrow transplantation should be considered if remission is not attained by 8 weeks of chemotherapy and immunotherapy and patients in remission without a clear diagnosis of familial HLH should be monitored for signs of relapse. Without treatment, HLH has poor prognosis and with treatment also mortality ranges from 50-75% in acquired cases. EBV related HLH has mortality of 25-100% and other infections has recovery in 60%-70% cases.

### Conclusion

HLH is an uncommon life threatening condition due to uncontrolled immune

activation and bears high mortality. HLH is a rare extra-hepatic manifestation in acute HEV hepatitis and must be suspected if patient develops fever, hepatosplenomegaly and cytopenia. Early aggressive therapy with steroids must be started and patient must be followed closely.

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