

# Hemophagocytic lymphohistiocytosis with B-cell lymphoma, a rare lethal cause for fulminant hepatic failure

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## Abstract

55-year-old Caucasian male presented with fevers (39.4C), resting tremors, and influenza- like symptoms. Two months prior he had a febrile illness, presumed to be viral, which persisted for two weeks. On admission, the patient was found to encephalopathy, asterixis and fever. Laboratory studies demonstrated pancytopenia, renal and hepatic failure. No specific cause of hepatic failure was identified despite extensive evaluation. An extensive immunological, metabolic and infectious disease work-up was negative. Abdominal ultrasound and CAT scan and MRI of the chest and abdomen revealed mild ascites with pleural effusion and hepatosplenomegaly. Subsequent liver biopsy demonstrated nonspecific acute hepatitis. The clinical picture then raised suspicion for HLH. A bone marrow biopsy demonstrated histiocytes without hemophagocytes with concomitant B-cell lymphoma in brain biopsy.

## Introduction

HLH is a rare lethal disease caused by mutations in genes crucial to the cytolytic secretory pathway, resulting in induced apoptosis of target cells by perforin and granzymes [1]. This results in dysfunction in natural killer and cytotoxic T-cells [2,3]. Few patients worldwide are reported to have HLH associated with B-cell lymphoma [4,5].

## Case presentation

A 55-year-old Caucasian male presented with fevers (39.4C), fine resting tremors, and influenza- like symptoms. Two months prior he had a febrile illness presumed to be viral that was followed by fatigue, malaise and wasting, which persisted for two weeks. On admission, the patient was found to have encephalopathy, asterixis and fever. Laboratory studies demonstrated pancytopenia; white blood cell of 1.1 thou/cmm, haemoglobin 9.9 g/dL, platelets 35 thou/cmm. Acute renal failure; creatinine 5.23 mg/dL, BUN 101 mg/dL. Furthermore, the patient acute liver failure manifested with encephalopathy and coagulopathy. His AST 800 U/L, ALT 510 U/L, Alkaline Phosphatase 608 U/L, Bilirubin 14.5 mg/dL, INR 3.9. Moreover, his ferritin >40000 ng/mL, Fibrinogen 51 mg/dL, triglycerides 955 ng/mL. An Extensive infectious work up including Pan-Cultures, viral hepatitis, HIV and tuberculosis was negative. Hepatotoxic drug, autoimmune and hemochromatosis were also excluded. Abdominal ultrasound and CAT scan and MRI/MRCP of the chest and abdomen revealed mild ascites with pleural effusion and hepatosplenomegaly. Subsequent liver biopsy demonstrated acute nonspecific hepatitis. The clinical picture then raised suspicion for HLH. A bone marrow biopsy demonstrated histiocytes without hemophagocytes with concomitant B-cell lymphoma in brain biopsy. The fever, pancytopenia, and multiple organs dysfunction then raised suspicion for HLH. A bone marrow biopsy demonstrated histiocytes without hemophagocytes. The patient was transferred to a tertiary center, where a brain biopsy demonstrated B-cell lymphoma. Unfortunately, the patient died shortly after the diagnosis (Figure 1).

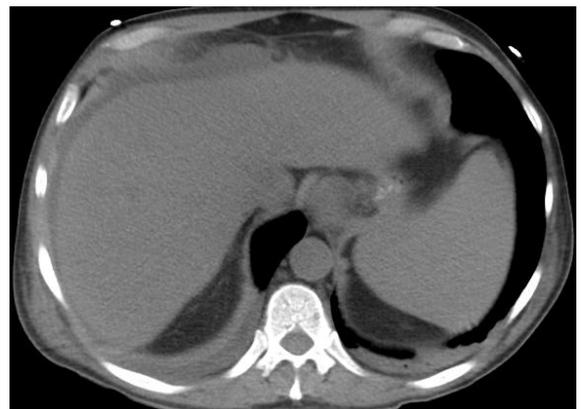


Figure 1. Hepatosplenomegaly on CT scan

## Discussion

We present a case of acute liver failure as a part of multi organ failure due to secondary HLH. The causes of secondary HLH are infection, rheumatologic disorders and neoplasms with marked regional variations in cause [2,3]. HLH is diagnosed if patients fulfil one of the two following criteria; molecular diagnosis of HLH or the presence of five of these eight sub-criteria: fever, splenomegaly, pancytopenia, hypertriglyceridemia >3 time's normal, hypofibrinogenemia, high ferritin, soluble CD 25 >2,400 U/mL and hemophagocytosis in BM, spleen, or lymph nodes [3,6] (Table 1). Our patient met seven out

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**Table 1.** Molecular diagnosis consistent with HLH OR<sub>SEP</sub>(B) Fulfillment of 5/8 criteria

Fever <sub>SEP</sub> Temperature > 38.5 C for > 7 days
Splenomegaly <sub>SEP</sub> Spleen tip palpated > 3 cm below left costal margin
Cytopenias involving 2 or more lines <sub>SEP</sub> Hb < 9 g/dL, or Plt < 100 000/mL, or ANC < 1000/mL
Hypertriglyceridemia and/or hypofibrinogenemia <sub>SEP</sub> Fasting triglycerides > 2 mmol/L, or >3SD above age-adjusted <sub>SEP</sub> normal; fibrinogen < 1.5 g/L, or < 3SD below age-adjusted normal
Hemophagocytosis in bone marrow, spleen, or lymph nodes
Low or absent NK-cell activity <sub>SEP</sub> determined by 51-Cr release assay
Ferritin > 500 mg/L (84% sensitivity) <sub>SEP</sub> >10 000 (90% sensitivity, 96% specificity)
Soluble CD25 (IL-2 receptor) > 2400 U/mL <sub>SEP</sub> or >2SD above the age-adjusted mean

of the eight sub-criteria. A recent review article pooled several case series' together and found that hepatic involvement was seen in 67% of patients with HLH. Another study demonstrated that almost one third of pediatric patients presenting with hepatic failure of unknown origin had features of HLH [2,3]. HLH should be considered in all patients with idiopathic hepatic failure<sup>3</sup>. It is crucial to start treatment with corticosteroids, cyclosporine A and etoposide<sup>6</sup> once clinical suspicion HLH has been raised and prior to fulfilling the complete diagnostic criteria as early diagnosis and subsequent early treatment significantly reduce mortality [3]. Other findings supporting a diagnosis of HLH include neurological symptoms, cerebrospinal fluid pleocytosis, elevated D-dimer. Certain malignancies have association with HLH [7], most commonly seen in different types of T-cell lymphomas [3]. Studies have shown that it may occur close to 20% of the time in certain type of lymphomas. The association between HLH and B-cell lymphoma is more common in Asians [8], however among Caucasians is extremely rarely [9,10].

The absence of hemophagocytosis from a bone marrow biopsy does not exclude the diagnosis of HLH. This case demonstrates that B-cell lymphoma should be investigated even after the diagnosis of HLH has been made.

## Conclusion

Gastroenterologist should carry a high index of suspicion for HLH in patient presenting with acute liver failure. This becomes especially important in patients presenting with fever, pancytopenia and idiopathic fulminant hepatic failure after ruling out other more common differential diagnosis.

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