HEMOPHAGOCYTIC SYNDROME PRECIPITATING ACUTE ON CHRONIC LIVER FAILURE A CASE REPORT AND REVIEW OF LITERATURE.

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Abstract:
Hemophagocytic syndrome is a disconcerting clinical dilemma characterised by a combination of clinical and biochemical features. Hepatologists may be consulted early in the disease when patient presents with abnormal liver enzymes, coagulopathy or hepatomegaly. Furthermore, some gastrointestinal infections, diseases and medications may trigger the syndrome. Herein we report a case of hemophagocytic syndrome in a chronic liver disease patient.

Keyword:
Hemophagocytic syndrome, macrophages, acute on chronic liver failure.

INTRODUCTION:
Hemophagocytic syndrome (also known as hemophagocytic lymphohistiocytosis or macrophage activation syndrome), is characterized by proliferation of benign macrophages showing phagocytosis of blood cells in hematopoietic organs including bone marrow, spleen, or lymph nodes, together with fever, splenomegaly, cytopenia, and hypertriglyceridemia. This syndrome, was first described in patients with viral infections, but is now known to be associated with various conditions of altered immunity, e.g. lymphoproliferative disorders, severe bacterial infections, acquired immune deficiency syndrome, systemic lupus erythematosus, immune suppressive therapy, or neoplastic diseases. Familial erythrophagocytic lymphohistiocytosis with an autosomal recessive mode of inheritance has also been described. Herein we describe a patient with hemophagocytic syndrome precipitating acute on chronic liver failure.

CASE HISTORY:
57 years old male patient presented with history of prolonged low grade, intermittent, daily fever since 1 year. Investigations done elsewhere were inconclusive. He was also treated empirically with anti tuberculous therapy with no response. Fever was still persisting at presentation. He presented to our department with an additional
complaint of progressive, painless and non-cholestatic jaundice for 1 month and abdominal distension associated with pedal edema for 10 days. He was drowsy since 4 days prior to admission. There was no history of GI bleed, pain abdomen or indigenous drug intake.

He was a known diabetic, hypertensive and bronchial asthma patient for last 10 years. There was no history of surgery in the past. He had no addiction to alcohol or nicotine in any form and the family history was unremarkable. His general examination revealed pallor, icterus and pedal edema with normal hemodynamic parameters. On per-abdominal examination, spleen was palpable 3 cm below the left costal margin. He was drowsy with slurring of speech. He had no focal neurological deficits or asterixis. The other systems were normal on examination. His investigations were as follows Total bilirubin at admission was 5.7 (direct fraction 5) mg/dl which increased to 10.6 (direct fraction 8.5) mg/dl, SGOT was 412, SGPT was 106, alkaline phosphatase was 299. Hemoglobin was 10.2 gms at admission which decreased to 7.7 gms within 5 days. Total count was 2500 and platelets were 13,000. Sr. Creatinine was 0.5 mg/dl at admission and it increased to 2 mg/dl in 5 days. Prothrombin time (INR) was 14.3 (1.3) at admission and after 5 days it was 25.1 (2.3). APTT was 42.4 at admission and 62.4 after 5 days. Fibrinogen was 106.2 mg/dl, Viral markers (HBV, HCV, HIV, HAV, and HEV) were Negative. Sr Sodium was 117 mmol/L, Potassium was normal. Sr Creatinine was normal. Sr LDH was high (951 u/l). Total cholesterol was 188 mg/dl; Triglyceride was 307 mg/dl. Sr Ferritin was 13041.7, Cultures were negative. TSH—1.4 µIU/ml, ANA was negative. ESR was 54 after 60 secs. Bone marrow aspiration was done with a possibility of hemophagocytic syndrome as there was bcytopenia, very high ferritin, high triglycerides and low fibrinogen. Bone marrow was aspirated from postero-superior iliac spine with adequate precautions (prolonged manual compression over the site after procedure). Blood products were arranged, but no post procedure bleeding was noted. The trephine biopsy showed moderately hypercellular marrow with adequate megakaryocytes and evidence of hemophagocytosis.

Figure 1--Bone marrow trephine biopsy showing macrophages with hemophagocytosis. Ultrasonography of the abdomen showed shrunken, coarse, irregular liver with volume redistribution. It also showed ascites with splenomegaly, Portal vein diameter was 14 mm. CT Scan abdomen showed volume redistribution of liver, moderate ascites and significant adenopathy, size of the largest lymph node being 28x19 mm. Detailed etiological work up for chronic chronic liver disease, including screening for Hepatitis B/C virus infection, was negative. Worsening coagulopahty precluded a liver & lymph node biopsy. The patient was managed with
measures for hepatic coma – low protein intake, empiric broad spectrum antibiotics and antifungals, lactulose, gut decontamination and gradual correction of hyponatremia. Hemophagocytic syndrome with acute on chronic liver failure was diagnosed based on clinical, laboratory, radiological and bone marrow findings. He was started on steroids. He continued to deteriorate with recurrent hypoglycemia, continuous fever, hypotension, altered sensorium and respiratory distress. He succumbed to his illness and expired 6 days after hospital admission.

DISCUSSION:
Hemophagocytic syndrome can be primary, familial and secondary (or acquired). Distinctive feature is the proliferation of histiocytes and active phagocytosis of other blood cells - primarily observed in the bone marrow, but can also be seen in the liver, spleen, and lymph nodes. The hemophagocytosis can be intermittent and thus may not be evident in all specimens at all time points. In our patient, hemophagocytosis was noted in bone marrow smear. The clinical features include skin rash, hepato-splenomegaly, persistent fever, and neurologic abnormalities which can range from mental status change to seizures or coma. Renal function impairment and pulmonary infiltrates can be part of this syndrome. Serum ferritin level greater than 10,000 mcg/dL, is often helpful as a screening measure. In our patient, as well, a high serum ferritin level gave us a clue to the diagnosis. The diagnostic criteria for primary hemophagocytic syndrome are summarised below. (2004 Criteria for the diagnosis of HLH; Pediatr Blood Cancer 2007; 48:124–131).
Molecular diagnosis or five out of eight of the following is required for the diagnosis.

1. Fever
2. Splenomegaly
3. Cytopenia, Haemoglobin < 10 gms, Neutrophils < 1000, Platelets < 100,000
4. Hypertriglyceridemia (<265 mg/dl) or hypofibrinogenemia (<150 mg/dl)
5. Evidence of Hemophagocytosis either in bone marrow, spleen, lymph node or CSF.
6. Low or absent NK cell activity
7. Ferritin > 500 µg/dl

Caroline de et al in their study, described hepatic manifestations of hemophagocytic syndrome in 30 patients. Fever, jaundice, and hepatomegaly or splenomegaly was present in 50% of the patients. Twelve (40%) of these patients died. Almost all (i.e. 29/30) the patients had an underlying medical condition potentially contributing to immune dysregulation. Liver biopsy was helpful in diagnosing disorders like lymphoma, Hodgkins disease, chronic lymphocytic leukemia, herpes virus hepatitis, CMV infection and tuberculosis. In our patient, fever, organomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia and presence of hemophagocytosis prompted us to make a diagnosis of hemophagocytic syndrome. Imaging showed presence of chronic liver disease. He had evidence of acute hepatic insult in the form of jaundice and coagulopathy which was complicated by ascites and encephalopathy within a period of 10 days. So he had acute on chronic liver failure. Etiology of chronic liver disease could not be established in this
patient. The possible etiology could be non alcoholic steatohepatitis as he was a long term diabetic and other etiological work up of chronic liver disease being negative. Liver and lymph node biopsy was precluded due to various reasons and thus we were not able to diagnose an underlying condition contributing to hemophagocytic syndrome. This underlying disorder could be viral infection or lymphoproliferative disorder as suggested by large intra abdominal lymphadenopathy. Mainstay of treatment for hemophagocytic syndrome remains high-dose corticosteroids. Anecdotal reports suggest various agents may be tried in steroid unresponsive cases - cyclosporin A, Etanercept, Anakinra, Intravenous immunoglobulin, Etoposide, Plasmapheresis, Abatacept, Anti inflammatory globulin, Naproxen and splenectomy. In addition, a concerted effort has to be made to diagnose and treat the cause of hemophagocytic syndrome. Our patient did not respond to high dose steroids. Rescue therapy could not be give and the patient finally succumbed to his illness.

CONCLUSION:
Hemophagocytic syndrome, a potentially life-threatening condition, can precipitate liver failure. This should be considered as differential diagnosis in patients with unexplained fever and hyperferritinemia. Increased awareness, early diagnosis and prompt initiation of treatment, may facilitate better outcome.

REFERENCES:


