Hemophagocytic Lymphohistiocytosis (HLH) in Children Presenting as Liver Disease

Nomisha Amin, Ira Shah, Sushmita Bhatnagar

Pediatric Liver Clinic, B.J. Wadia Hospital for Children, Mumbai, India

Hemophagocytic lymphohistiocytosis (HLH) is a rare acute hyperinflammatory condition presenting with high fever, pancytopenia, splenomegaly with the pathologic finding of hemophagocytic lymphohistiocytosis in bone marrow and other tissues. Predominant hepatic manifestations at presentation are rare. We report a series of three cases which showcase the spectrum of liver disease as presentation in hemophagocytic lymphohistiocytosis. (J Clin Exp Hepatol 2014;4:175–177)

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder in children and characterized by multisystem inflammation. The predominant features are cytopenias, high fevers and splenomegaly along with hepatitis.[1] Due to life threatening nature of the disease, urgent diagnosis is essential. To assist with the rapid diagnosis of HLH, the Histiocyte Society has developed a set of diagnostic guidelines that encompass both clinical and laboratory findings.[2] With additional experience these diagnostic criteria have been modified. These include either a molecular diagnosis of HLH or at least 3 of 4 clinical parameters such as fever, splenomegaly, cytopenias (minimum 2 cell lines reduced) and hepatitis along with at least 1 of 4 such as hemophagocytosis, raised ferritin, increased sIL2Rα or absent or very decreased NK function. Other results supportive of HLH diagnosis are hypertriglyceridemia, hypofibrinogenemia and hyponatremia.[1]

HLH may be due to genetic causes or secondary due to autoimmune disorders or viral infections. (1) The liver is often involved in both the conditions.[1,2] Concentrations of serum liver enzymes are abnormal in 80% of the patients.[3] While hepatic manifestations are common, predominant hepatic manifestations at presentation is rare. We thus report 3 cases which presented as active hepatitis and liver failure in a case of HLH.

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Address for correspondence: Ira Shah, Co-Incharge, 1/B Saguna, 271/B St Francis Road, Vile Parle (W), Mumbai 400056, India.
E-mail: irashah@pediatriconcall.com
Abbreviations: CMV: cytomegalovirus; EBV: Epstein Barr virus; HLH: hemophagocytic lymphohistiocytosis; LKM: liver–kidney-microsomal; MAS: macrophage activation syndrome; PT: prothrombin time; PTT: partial thromboplastin time; VAHS: virus associated HLH
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CASE PRESENTATION

Case 1

A 9½ years old boy was referred for elevated liver enzymes on regular screening. He was diagnosed to have virus associated HLH (VAHS) 6 months ago and had received 3 doses of etoposide and 3 weeks of dexamethasone along with blood transfusion and fresh frozen plasma. At that time, he had fever for one month with hepatosplenomegaly pancytopenia and lymphadenopathy with coagulopathy and hepatitis (SGOT = 364 IU/L, SGPT = 314 IU/L). Bone marrow examination was suggestive of VAHS. Cytomegalovirus (CMV) & Epstein Barr virus (EBV) were negative though Dengue IgM was positive. Child improved with above therapy and was currently asymptomatic. On examination, he was well nourished and had a firm hepatomegaly. Other systems were normal. Investigations showed. Bilirubin of 0.8 mg%, SGOT of 254 IU/L, SGPT of 243 IU/L, Albumin of 2.8 g/dl, alkaline phosphatase of 4665 IU/L. Hemoglobin was 12.4 g/dl, white cell count of 4800/cumm [46% polymorphs, 48% lymphocytes], platelet count of 2,70,000/cumm. Ultrasound abdomen showed hepatosplenomegaly with portal hypertension. His HIV, HBsAg, HCA ELISA were negative and ANA, dsDNA, Anti Liver–Kidney-Microsomal (LKM) antibody and anti smooth muscle antibody were also negative. 24 h urine copper and serum ceruloplasmin were normal. Liver biopsy was suggestive of significant microsteatosis with portal triaditis and infiltrates consisting of lymphocytes and eosinophils with hepatic activity index of 6 and active hepatitis. His repeat EBV IgM was negative. He was started on oral prednisolone (1.5 mg/kg/day) following which liver enzymes gradually normalized in next 6 months (SGOT = 55 IU/L, SGPT = 28 IU/L) and is on regular follow up. Though this child did not fulfill the criteria for HLH (2) at the time of presentation of the liver dysfunction, he did have VAHS earlier and the current liver dysfunction responded to steroids suggestive of continued inflammation in the liver that needed immunosuppression for control.

Case 2

A 3 months old boy born of non-consanguineous marriage presented with abdominal distension for 15 days, fever for 8 days and 5 episodes of generalized tonic clonic convulsions for one day, with altered sensorium. There was no vomiting or bulging anterior fontanelle or jaundice. He was a full term delivered child with normal milestones. He had only been immunized with BCG at birth. He was on exclusive breast feeds. On examination, weight was 4.5 kg, height was 59 cm, heart rate was 140/min, respiratory rate was 48/min, blood pressure was 78 systolic. There was jaundice, pallor, splenohepatomegaly with ascites. Other systems were normal. Investigations show hemoglobin of 4.9 g/dl, WBC count of 4700/cumm and platelet count of 27,000/cumm. Bilirubin was 5 mg/dl with direct bilirubin of 2.4 mg/dl, SGOT was 230 IU/L, SGPT was 96 IU/L, Total proteins were 4.8 g/dl with albumin of 2.4 g/dl. Both prothrombin time (PT) and partial thromboplastin time (PTT) were prolonged more than 3 min. Serum ammonia was 98 μg/dl and CSF examination was normal. In view of pancytopenia with liver disease and CNS involvement, a clinical suspicion of HLH was considered and serum ferritin was done which was elevated [2885 mg/ml (Normal = 28–365 ng/ml)] serum fibrinogen was low [71 (Normal = 150–360)] and serum triglycerides were 112 mg/dl (Normal < 150 mg/dl). Bone marrow examination showed absent megakaryocytes with macrophages engulfing RBCs. His serum perforin levels were 97.6% and cytomegalovirus IgG was 100 AU/ml. Other TORCH titers were negative. Epstein Barr virus could not be sent as patient was not affording the same. In view of fever, pancytopenia, splenomegaly and high ferritin along with hemophagocytes on the bone marrow, the child was diagnosed as HLH. The presentation as fulminant liver cell failure was unusual. He was treated with Etoposide, Dexamethasone but continued to have pancytopenia and ascites which required frequent blood transfusions and recurrent ascitic tap. The child finally succumbed to a fatal bout of hematemesis after 15 days.

Case 3

A 2½ months old boy born of third degree consanguineous marriage presented with abdominal distension for 2 days and increased respiratory movement for a day. There was fever with loose motions 5 days ago that had subsided on its own. He was a full term caesarean section delivered boy with birth weight of 3.75 kg and there were no antenatal or post-natal complications. He was on formula feeds, was immunized till date and had achieved milestones appropriate for age. On examination, weight was 6 kg, length was 59 cm, heart rate was 140/min and respiratory rate was 52/min with systolic blood pressure of 90 mm of Hg. He had jaundice, pallor and large hepatosplenomegaly with ascites. There was cardiomegaly without any murmur. Other systems were normal. Investigations showed hemoglobin of 6.4 g%, white cell count of 6600 (35% polymorphs, 66% lymphocytes, 4% monocytes and 1% eosinophil), platelets of 23,000/cumm, bilirubin of 5.6 mg/dl (direct bilirubin = 2.5 mg/dl), SGOT = 1960 IU/L, SGPT = 824 IU/L, Total proteins of 4.6 g/dl with albumin of 2.8 mg/dl with severe metabolic acidosis (pH = 7.2, bicarbo nate = 9.5 mmol/L) and creatinine of 0–5 mg/dl. Chest X-ray and serum ammonia were normal. ESR was 2 mm at end of 1 h. In view of anemia with congestive cardiac failure, child was treated with blood transfusion and IV antibiotics. Ultrasound abdomen showed hepatosplenomegaly with ascites and right sided pleural effusion. Both prothrombin time (PT) and partial thromboplastin time (PTT) were deranged (36 s and 60 s respectively). The child had a generalized tonic clonic convulsion next day and hemogram showed decreasing WBC count as well. The child also started running fever. Thus in view of pancytopenia, fever, liver dysfunction and CNS involvement, a clinical suspicion of HLH was considered with macrophage activation syndrome (MAS). A bone marrow examination showed presence of hemophagocytes, serum fibrinogen levels were <150 (Normal = 150–360), serum ferritin was 60,000 (Normal = 4.2–62) and triglycerides were normal [97 (Normal = 35–160)]. Patient's was started on Etoposide and Dexamethasone. However, 7 days later serum creatinine also was elevated. Perforin levels were 0%. Child subsequently died 15 days later.

DISCUSSION

In HLH, the underlying problem is a T and Natural Killers cells dysfunction, which leads to an uncontrolled immunological response[4] due to inability to eliminate the triggering agent. The liver dysfunction is central in HLH, with hepatomegaly occurring in half cases, liver enzyme elevation and/or cholestasis are very frequent, cholestasis is a prognostic factor and liver biopsy may often be necessary to confirm HLH and diagnose underlying disorders in secondary HLH.[5] Biopsy of the liver may reveal chronic persistent hepatitis; there may be large portal infiltrates of lymphocytes, immunoblasts and histiocytes.[6] The liver in macrophage activating syndrome (MAS) has shown activated CD8 lymphocytes through production of IFNγ and macrophages with HLH and production of IL-6 and TNFα, sharing a common effector pathway with HLH syndrome.[7] Elevated serum ferritin can make the distinction from neonatal hemochromatosis and other forms of neonatal liver failure difficult. HLH should be considered in the differential diagnosis of neonatal liver disease especially fulminant hepatic failure.[8] Both our patients (case 2 and case 3) presented with fulminant hepatic failure and presence of hemophagocytes along with other criteria for diagnosis of HLH[2] confirmed the diagnosis and possibility of neonatal hemochromatosis was ruled out.

While hepatic manifestations being common in HLH, it is uncommon to find it as the main presenting sign.[9] In

fact, there has been only 1 report of a pediatric series in which HLH might have directly caused fulminant hepatic failure itself owing to an associated hepatic cytokine storm[10] and one of hepatic encephalopathy as a presentation reported by us earlier.[11] Our 3 cases of HLH presented with signs suggestive of liver failure as a main feature of which the first one had continuation of liver dysfunction as part of the VAHS diagnosed earlier and other 2 presented with fulminant hepatic failure. Case 3 had a low perforin level suggestive of familial HLH whereas case 2 also had an early age of presentation suggestive of familial cause but we were unable to do the perforin levels due to unaffordability. A high index of clinical suspicion for HLH must thus be kept in mind especially when these patients present with cytopenias.

Aggressive immunochemotherapy is the treatment of choice. Liver transplantation for acute liver failure was considered a contraindication in acute phase of HLH due to hyperactivated immune system, multiorgan failure and critical condition of the patient and is associated with poor outcome.[8]

In conclusion, HLH is a frequently lethal disease with a high variability in clinical presentation. It must be considered a differential in patients presenting with clinical signs of acute liver failure especially when it is accompanied by cytopenias.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. *Hematology*. 2009;1:127–131.
2. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124–131.
3. Leber B, Mayrhauser U, Rybczynski M, Stadlbauer V. Innate immune dysfunction in acute and chronic liver disease. *Wien Klin Wochenschr*. 2009;121:732–744.
4. Goransdotter EK, Fadeel B, Nilsson-Ardnor S, et al. Spectrum of perforin gene mutations in familial hemophagocytic lymphohistiocytosis. *Am J Hum Genet*. 2001;68:590–597.
5. Larroche C, Ziol M, Zidi S, Dhote R, Roulot D. Liver involvement in hemophagocytic syndrome. *Gastroenterol Clin Biol*. 2007;31:959–966.
6. Favara BE. Histopathology of liver in histiocytosis syndromes. *Pediatr Pathol Lab Med*. 1996;16:413–433.
7. Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C. Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha producing macrophages. *Blood*. 2005;105:1648–1651.
8. Parizhskaya M, Reyes J, Jaffe R. Hemophagocytic syndrome presenting as acute hepatic failure in two infants: clinical overlap with neonatal hemochromatosis. *Pediatr Dev Pathol*. 1999;2(4):360–366.
9. Wright G, Wilmore S, Makanyanga J, et al. Liver transplant for adult hemophagocytic lymphohistiocytosis: case report and literature review. *Exp Clin Transpl*. 2012;10:508–512.
10. Ýleri Talia, Azýk Fatih, Uysal Zümrüt, et al. Severe acute hepatic failure as an initial manifestation of hemophagocytic lymphohistiocytosis. *J Ankara Univ Fac Med*. 2009;62:119–123.
11. Shah I, Bhatnagar S. Hepatic encephalopathy-a presentation of hemophagocytosis. *Trop Gastroenterol*. 2010;31:125.