Hemophagocytic Lymphohistiocytosis Masquerading as Acute Liver Failure: A Single Center Experience

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Background/aim: Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening disorder of extreme inflammation and unregulated immune response which require prompt recognition and early introduction of definitive therapy. HLH can present with wide range of hepatic dysfunction ranging from mild elevation of transaminases to liver failure. This study is carried out to describe the clinical and laboratory presentation of HLH. **Methods:** Patients who were diagnosed with HLH between January 2013 and December 2015 were retrospectively included in this study. **Results:** Six patients were diagnosed as secondary HLH with median age of 28.5 years at diagnosis. All patients were presented with history of deep jaundice and high grade fever with pancytopenia and splenomegaly. Underlying diagnosis was viral infections in 4 and probable viral infection in remaining two. Bone marrow hemophagocytosis was present in 3 cases. Three patients were treated with corticosteroids only and one each with corticosteroids with cyclosporine or intravenous immunoglobulin (IVIG) and HLH treatment protocol. One patient died due to acute respiratory distress syndrome (ARDS); another patient died in follow-up due to respiratory failure due to pneumonia. **Conclusions:** HLH is rare and potentially life-threatening cause of prolonged fever, jaundice and pancytopenia. Early diagnosis and initiation of specific therapy can improve clinical outcome. (J CLIN EXP HEPATOL 2017;7:184-189)

Hemophagocytic lymphohistiocytosis (HLH) is potentially life threatening disorder associated with extreme inflammation and unregulated immune activation.¹ HLH is either familial² or secondary to other diseases including infection,³ rheumatologic disorders⁴ or malignancy related.⁵ The reported incidence of familial HLH from Sweden is one case per every 50,000 live births⁶; however incidence of secondary HLH is unknown as there were no epidemiological studies. Both types are associated with fever, hepatomegaly, splenomegaly and pancytopenia. Early recognition and prompt treatment of HLH is associated with improved clinical outcome.

Primary HLH is associated with various genetic abnormalities and often manifests during infancy and early childhood. Being autosomal recessive disorder, it is more commonly seen in consanguineous parenthood.² In majority of cases, genetic abnormalities are responsible for fixed defects in cytotoxic cell function.² Various mutations in

perforin, Munc 13-4, Syntaxin 11, Munc 18-2 and others are associated with primary HLH, which may allow genetic testing and can help in reaching early diagnosis.⁷ Secondary HLH is more common in older children and adults, often associated with viral infections, rheumatological conditions and malignancies.³⁻⁵ However, classifying patients as having primary or secondary HLH is often not possible due to non-availability of genetic testing or absence of family history. HLH has been considered as differential diagnosis of ALF. In study by Amarapurkar et al. evaluating differential diagnosis of ALF described one case of HLH as the differential diagnosis of ALF out of 28 cases.⁸ HLH can present with variable degree of hepatic dysfunction ranging from mild elevation of transaminases to liver failure; whereas diagnosis of HLH without hepatic dysfunction should be considered unusual.⁹ HLH is one of the rare causes of prolonged fever, deep jaundice with pancytopenia and splenomegaly, it is essential to consider HLH as differential diagnosis of ALF. Hence we carried out retrospective study to describe the clinical and laboratory presentation with treatment of HLH patients from January 2013 to December 2015, who were initially admitted with provisional diagnosis of ALF at admission.

METHODS

After approval institutional review board, hospital records from Hepatology database January 2013 to December 2015 were retrieved. All patients with provisional diagnosis of

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Abbreviations: ARDS: acute respiratory distress syndrome; CMV: cytomegalovirus; CSA: cyclosporine; EBV: Epstein Barr virus; HLH: hemophagocytic lymphohistiocytosis; IVIG: intravenous immunoglobulin; MAS: macrophage activation syndrome

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ALF at admission were screened. Patient who were ultimately diagnosed as HLH were included in our study.

Diagnosis was based on Histiocyte Society criteria, in which, in the absence of family history or of specific genetic tests, five out of eight criteria should be present in order to establish a diagnosis and initiate treatment.¹⁰ The criteria are listed as follows: Diagnosis of HLH was made if five of following eight findings are present (1) fever $\geq 38.5^{\circ}\text{C}$, (2) splenomegaly, (3) peripheral blood cytopenia, with at least two of the following: hemoglobin $< 9\text{ g/dL}$; platelets $< 100,000/\mu\text{L}$; absolute neutrophil count $< 1000/\mu\text{L}$, (4) hypertriglyceridemia (fasting triglycerides $> 265\text{ mg/dL}$) and/or hypofibrinogenemia (fibrinogen $< 150\text{ mg/dL}$), (5) hemophagocytosis in bone marrow, spleen, lymph node, or liver, (6) low or absent NK cell activity, (7) ferritin $> 500\text{ ng/mL}$

and (8) elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms.

Demographic, etiology, clinical features, laboratory and treatment data were retrieved. Primary HLH was diagnosed in patients with younger age and presence of family history, in absence of genetic testing. Secondary HLH was diagnosed in patients with older age with evidence of precipitating disease such as viral infection, rheumatological conditions or malignancy.

Treatment received in hospital were documented as corticosteroids alone, intravenous immunoglobulin (IVIg) with steroids or combination of steroid with cyclosporine (CSA) and HLH protocol therapy (corticosteroids, etoposide, CSA).¹⁰

Table 1 Clinical and Laboratory Features of Patients.

	1	2	3	4	5	6	Overall ^a
Age (years)	26	35	47	24	31	21	30.5 (± 9.5)
Sex	F	M	M	F	F	F	2 – Males
Duration of symptoms (days)	15	30	30	45	90	7	36.1 (± 29.5)
Symptoms							
Fever	Y	Y	Y	Y	Y	Y	6/6
Rash	Y	Y	Y	Y	N	Y	5/6
Jaundice	Y	Y	Y	Y	Y	Y	6/6
Encephalopathy	N	N	N	N	Y – Hypoxic	N	1/6
Diagnostic criteria							
Fever ($\geq 38.5^{\circ}\text{C}$)	Y	Y	Y	Y	Y	Y	6/6
Splenomegaly	Y	Y	Y	Y	Y	Y	6/6
Pancytopenia							
Hb (g/dl)	7.1	9.2	6.7	8.2	8.6	6	7.6 (± 1.2)
TLC (/mm ³)	900	1900	2500	4000	2800	3600	2616.7 (± 1130)
Platelet (/mm ³)	100,000	120,000	100,000	140,000	90,000	75,000	104,166 ($\pm 22,894$)
Ferritin (ng/ml)	2256	2166	1650	1708	2000	2000	1963 (± 242)
Triglycerides (mg/dl)	594	341	734	500	581	605	599 (± 130)
Fibrinogen (mg/dl)	105	169	150	140	50.7	145	126 (± 42.6)
Hemophagocytosis	Y	Y	N	N	N	Y	3/6
NK cell activity	Na	Na	Na	Na	Na	Na	Na
sCD25 activity	Na	Na	Na	Na	Na	Na	Na
Other laboratory parameters							
Bilirubin (mg/dl)	20.7	12.4	24.7	23.7	14.8	24.6	20.15 (± 5.33)
SGOT (U/l)	342	383	175	126	95	67	198 (± 133)
SGPT (U/l)	553	512	218	177	169	154	297 (± 183)
INR	1.79	1.44	1.79	1.48	1.20	1.40	1.5 (± 0.23)
Treatment given	Steroids	Steroids + CSA	IVIg + Steroids	Steroids	HLH protocol	Steroids	
Hospital Stay (ICU stay) days	22 (6)	26	40	22	4 (4)	27	23.5 (± 11.6)
Outcome	+	Died	+	+	Died	+	2 – death 4 – improved
Cause of mortality	RF			ARDS			

^aFigure indicate mean ($\pm$ standard deviation) IVIg – IV Immunoglobulin, CSA – cyclosporine, HLH protocol – corticosteroids, etoposide, CSA, ARDS – acute respiratory distress syndrome, RF – respiratory failure, + – improvement on therapy, Na – not available.

RESULTS

During the study period, 6 patients were diagnosed and treated for HLH. All 6 patients presented with history of high grade fever, deep jaundice, and hepatosplenomegaly at admission. All patients were referred by primary care physicians for further evaluation in view of worsening LFT and to consider liver transplantation if required. Median duration to reach diagnosis of HLH after hospitalization was 14 (range 2–30) days. HLH was diagnosed based on presence of at least five out eight clinical and laboratory criteria. Clinical and laboratory data is summarized in Table 1. All six cases were diagnosed as secondary HLH in view of absence of family history, older age of onset, presence of precipitating factor and absence of recurrence during follow-up period. All patients had evidence of bone marrow histiocytosis (Figure 1) and three had bone marrow hemophagocytosis (Figure 2). Three patients were treated with tapering doses of corticosteroids. IVIG with

steroids; combination of cyclosporine with steroids and HLH protocol therapy was used in one patient each. Median hospital stay was 22 (range 4–40) days. Two patients died in this study, one due to acute respiratory distress syndrome (ARDS) and secondary to respiratory failure due to pneumonia.

Case 1

A 26 years old female was admitted with high grade fever ($\geq 38.5^\circ\text{C}$) with deep jaundice (total bilirubin–20.7 mg/dl) and coagulopathy (INR–1.79) since 15 days. In view of deep jaundice with coagulopathy possibility of ALF was considered. She also had exfoliative skin lesions since 1 week. Her Hemogram showed pancytopenia (Hb – 7.1 g/dl, TLC – $900/\text{mm}^3$ and platelets – $100,000/\text{mm}^3$). Her workup for viral hepatitis (IgM-HAV, IgM-HbcAg, HbsAg, Anti-HCV and IgM-HEV) was negative. In view of persistent high grade fever, she was evaluated for dengue, malaria, leptospirosis and brucella along with blood and urine cultures, which were inconclusive. An alternative diagnosis was considered in view of persistent fever, absence of sepsis. Her bone marrow revealed histiocytosis (Figure 1), which gave clue toward diagnosis of HLH. Her serum fibrinogen is 205 mg/dL, serum ferritin 2256 ng/mL, triglycerides 594 mg/dL and serum LDH 2995 U/L.

Her clinical and laboratory evaluation was consistent with HLH. She was treated with prednisolone (40 mg/day) for 2 weeks. Serial monitoring of hemogram and LFT showed progressive improvement. Oral prednisolone was tapered by 10 mg per two weeks in follow-up. After 18 months of follow-up, she is doing well without any evidence of recurrence.

Case 2

A 35 years old male was referred as case of severe hepatitis secondary to Hepatitis A, considering possible need of liver transplantation. He was having history of high grade fever, deep jaundice since 1 month. On examination, he was having tachycardia, icterus and hepatosplenomegaly. There was petechial rash over trunk and extremity. His blood investigations showed pancytopenia (Hb – 9.2 g/dl, TLC – $1900/\text{mm}^3$ and platelets – $120,000/\text{mm}^3$) with deranged LFT (total bilirubin – 12.4 mg/dl, INR – 1.44). After sending blood and urine cultures, he was treated with antibiotics (reports were subsequently collected as sterile). Anti-malarial treatment was added on 2nd day, due to persistent high grade fever although peripheral smears on three occasions were negative for malarial parasites. In view of persistent fever and deranged LFT, he was evaluated further for brucella, leptospira, rickettsia and EBV was negative. He underwent bone marrow examination which showed marrow histiocytosis and hemophagocytosis (Figure 2). Due to presence of hemophagocytosis, he was evaluated for HLH, which showed elevated ferritin

Figure 1 Bone marrow showing histiocytosis (arrow).

Figure 2 Bone marrow demonstrating hemophagocytosis (arrow).

(2166 ng/ml) and triglycerides (341 mg/dl) and normal fibrinogen (169 mg/dl). As patients clinical and laboratory parameters were consistent with HLH diagnostic criteria, he was treated with cyclosporine with tapering doses of corticosteroids. He improved subsequently over two weeks and tapering on steroids was started. In 3rd week of therapy, he was re-admitted with tachypnea and tachycardia secondary to bilateral pneumonia requiring mechanical ventilation. However he died on 2nd day of re-admission.

Case 3

A 47-year-old male was admitted progressive jaundice, high grade fever with vesicular rash over face since 1 month. On evaluation, he was found to have pancytopenia (Hb – 6.7 g/dl, TLC – 2500/mm³ and platelets – 100,000/mm³) with deranged LFT (total bilirubin – 24.7 mg/dl, INR – 1.79). Vesicular lesions on face were suggestive of herpes labialis. He was extensively evaluated for febrile illness in the form serological workup for brucella, leptospira and rickettsia; blood and urine culture; CECT abdomen and chest. However, all these evaluations were negative. During course of illness, he developed non-oliguric renal failure which improved with conservative management. In view of high ferritin (1650 ng/ml) and triglycerides (734 mg/dl) with low fibrinogen (150 mg/dl) along with pancytopenia; possibility of HLH was considered. His bone marrow biopsy showed histiocytosis; however hemophagocytosis could not demonstrated. He was treated with IV immunoglobulin for 5 days with tapering doses of corticosteroids. His TLC, LFT and ferritin improved over next two weeks, followed by which steroid tapering was started. He is asymptomatic after 12 months of follow-up.

Case 4

A 24-year-old female was admitted with high grade fever with itching since 45 days. She was evaluated by primary care physician and diagnosed as acute viral hepatitis due to hepatitis A. In view of persistent jaundice along with fever, she was referred to our hospital for further evaluation and management. On examination, she had maculopapular rash more on extremity with hepatosplenomegaly. On further evaluation, she was having pancytopenia (Hb – 8.2 g/dl, TLC – 4000/mm³ and platelets – 140,000/mm³) with deranged LFT (total bilirubin – 23.7 mg/dl, INR – 1.48). Viral markers were negative except IgM – anti HAV was positive. However, in presence high grade fever and pancytopenia with deranged LFT, alternative diagnosis was considered. She was further evaluated to rule out septic focus, which was inconclusive. In the presence of low fibrinogen (140 mg/dl), high ferritin (1708 ng/dl) and triglycerides (565 mg/dl) possibility of HLH was considered and bone marrow studies were done; which showed histiocytosis with orderly maturation of myeloid series. As

patient's clinical and laboratory data was satisfying HLH diagnostic criteria, diagnosis of HLH was made. She was treated with tapering doses of steroids; her TLC improved and bilirubin dropped to normal over four weeks. At 6 months of follow-up, she is asymptomatic.

Case 5

A 31-year-old female was referred with deep jaundice, high grade fever since 3 months, which was preceded by upper respiratory tract infection. At admission, she was hypoxic due to ARDS, required mechanical ventilation to maintain oxygenation. Her previous evaluation by primary care physician revealed moderate anaemia (8.6 g/dl), low TLC (2800/mm³), thrombocytopenia (90,000/mm³) with raised bilirubin (14.8 mg/dl). INR was 1.20. Workups for fever in the form of cultures (blood, urine and sputum); serology for brucella, leptospira, rickettsia were negative. Bone marrow had shown evidence of histiocytosis. In view of pancytopenia with deranged LFT; possibility of HLH was considered. Serum ferritin (2000 ng/ml), triglycerides (581 mg/dl) were high and fibrinogen was low (50.7 mg/dl). She was started on HLH protocol therapy consisting of corticosteroids, etoposide and cyclosporine; however she died on 4th day of admission due to ARDS.

Case 6

A 21-year-old female was diagnosed as case of acute viral hepatitis due to hepatitis A. However, from 5th day of diagnosis she developed high grade fever for which she was admitted. She also developed generalized petechial rash. Her laboratory evaluation showed moderate anaemia (6 g/dl), low TLC (3600/mm³), thrombocytopenia (75,000/mm³) with raised bilirubin (24.6 mg/dl) and INR was 1.4. Her further evaluation for febrile episodes in the form of peripheral smears for malarial parasite, widal test, serology for dengue, leptospira were inconclusive. Blood and urine cultures were negative. Her ferritin (2000 ng/ml) and triglycerides (605 mg/dl) were high and fibrinogen (145 mg/dl) was low. In the presence of clinical and laboratory evidence suggestive possibility of HLH, bone marrow examination was done which showed histiocytosis without hemophagocytosis. She was treated with tapering doses of steroids; over 2 weeks her TLC and bilirubin showed improving trend. Her ferritin was normalized in four weeks. At 14 months follow-up, she is asymptomatic without any evidence of recurrence.

DISCUSSION

HLH is a syndrome associated with various clinical and laboratory manifestation which results from dysregulated immune activation.⁹ This immune dysregulation is divided into primary (familial) or secondary (acquired). Primary HLH manifests in the infants or younger children with or

without family history. Unregulated activation of cytotoxic T cells and NK cells occurs due to mutations in perforin, Munc 13-4, Syntaxin 11, Munc 18-2 etc.⁷ Whereas secondary HLH manifests in older children or adults without family history or specific genetic mutations. These patients usually have concurrent infections, rheumatological or malignancies which trigger uncontrolled immune activation.³⁻⁵ However, in absence of specific gene analysis differentiation between primary and secondary HLH is entirely dependent upon age at onset and presence of family history or recurrence in follow-up. Primary and secondary HLH is associated with over activation of antigen presenting cells leading to activated macrophages and histiocytes which carry out hemophagocytosis resulting in cytokine storm and eventually multi organ dysfunction syndrome.^{10,11}

Diagnostic criteria for HLH is based upon pattern of clinical and laboratory findings. Specific genetic testing if available can not only confirm diagnosis but also can predict recurrence in index patient and predisposition in the family members.⁹ Initial HLH-94 criteria^{12,13} by Histiocyte society was later revised in 2004 which is commonly used in clinical practice and trials.¹⁰ Many common manifestations of HLH are not part of HLH diagnostic criteria such as rash, hepatic dysfunctions and neurological manifestations.⁹ In present study, all patients fulfilled at least 5 out of 8 diagnostic criteria.

In our present study, patients were referred for evaluation for need of liver transplantation in view of jaundice, splenomegaly and thrombocytopenia considering possibility of acute liver failure by primary physicians. However, presence of fever after onset of jaundice and absence of documented sepsis (negative cultures from all possible sources with normal procalcitonin) raised suspicion of alternative diagnosis. In addition, presence of median INR of 1.46 with evidence of hypoxic encephalopathy in one patient made the diagnosis of acute liver failure unlikely. So the possibility of HLH was considered. Diagnosis of HLH is usually delayed due to its rare occurrence, variable manifestations and lack of specific testing.⁹ In the present study, 14 median days (range 2–30) were required to reach final diagnosis of HLH. In HLH, almost all patients will have hepatic inflammation ranging from mild elevation of transaminases to liver failure.¹⁴ Liver biopsy in HLH can demonstrate chronic persistent hepatitis with periportal lymphocytic infiltration.¹⁵ Venooclusive disease, disseminated intravascular coagulation and platelet degranulation defects have been described in the HLH.^{16,17}

Despite the small sample size, non-availability of specific genetic tests and retrospective nature of this study, these cases demonstrate importance of HLH as differential diagnosis of prolonged fever, jaundice and pancytopenia. Limited access to genetic testing for primary HLH might be big hurdle in diagnosis, but secondary HLH can be

diagnosed with clinical and laboratory criteria.¹⁸ Secondary HLH due to viral infections are commonly occurs with Epstein Barr virus (EBV).¹⁹ Few case reports described hepatitis A induced HLH in both adult and paediatric population.^{20,21} In our study, 3 patients had serological evidence of hepatitis A and one had HSV.

Immediate goal of therapy of HLH is to suppress the hyper-inflammation with chemotherapeutic and/or immunosuppressive agents such as corticosteroids, cyclosporine, and immunoglobulin with addressing underlying triggering factor if present.²² Initial treatment for both primary and secondary HLH involves immunosuppression to control immune hyper-activation followed by hematopoietic stem cell transplantation.²³ We treated three patients with corticosteroids alone considering secondary HLH and intensification of treatment if no improvement. However all 3 patients treated with corticosteroids improved without need for intensification. One patient who has HSV infection along with HLH was treated with intravenous immunoglobulin with corticosteroids; considering addition of immunoglobulin may have addition benefit along with corticosteroid.²³

Another patient was treated with cyclosporine with corticosteroids which showed clinical improvement. However, this patient died in follow up due to respiratory failure secondary to bilateral pneumonia which could be treatment related adverse event. However, benefits of adding immunoglobulin or cyclosporine are not well established.⁹ One patient who admitted with ARDS in ICU was treated with HLH protocol therapy consisting of dexamethasone (two weekly tapering starting from 10 mg/m²), etoposide (150 mg/m²) with cyclosporine (100 mg twice day) considering clinical status patient at admission. Addition of intrathecal methotrexate and hydrocortisone is required in patients with CNS involvement.¹⁰ This patient had encephalopathy which we considered due to hypoxia rather than manifestation of HLH. HLH protocol therapy was started on 2nd day of admission however, patient died on 4th day of admission.

We advise to monitor hemogram, liver function test and serum ferritin during treatment and follow-up. Serum ferritin levels correlate with disease activity.²⁴ Primary HLH is considered to be fatal unless aggressively treated. In secondary HLH, mortality rate is reported between 20 and 40%.^{25,26} The mortality rate in our patients was 33.3% which is consistent with previous studies.

In conclusion, our case series demonstrated need to consider HLH as important cause of prolonged fever, jaundice and pancytopenia for gastroenterologists and hepatologists. High index of suspicion is required for diagnosis and early initiation of treatment. We emphasize on prospective and multicentre studies for better understanding about HLH, to improve its clinical outcome, although due to rarity of HLH, it may be difficult to conduct such studies.

CONFLICTS OF INTEREST

The authors have none to declare.

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