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 familial[2] or secondary to other diseases including infection,[3] rheumatologic disorders[4] or malignancy related.[5] The reported incidence of familial HLH from Sweden is one case per every 50,000 live births[6]; 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 ≥38.5 °C, (2) splenomegaly, (3) peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL; platelets <100,000/μL; absolute neutrophil count <1000/μL, (4) hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL), (5) hemophagocytosis in bone marrow, spleen, lymph node, or liver, (6) low or absent NK cell activity, (7) ferritin >500 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 (≥38.5 °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 (±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		

[a]Figure indicate mean (±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.