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CASE SERIES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory syndrome characterized by fever, hepatosplenomegaly, bone marrow, skin, and central nervous system infiltration. Incidence of HLH is 1 per 50,000 live births worldwide. In this case series, we present 13 cases of HLH in adults; their presentation, course, and outcome over a period of three years **Materials and Methods:** We retrospectively looked at 13 cases of HLH who presented to our hospital. Data was collected from computerised electronic medical records in addition to referring to hard copies of patients' records. The median age at diagnosis was 42.5 years (age range 25 years–60 years). Diagnosis was based on fulfilling clinical and laboratory criteria. **Results:** All patients initially presented with unremitting prolonged fever, splenomegaly and bicytopenia or pancytopenia. Blood investigations showed elevated ferritin (n = 13), elevated liver enzymes[6] and high lactate dehydrogenase (LDH),[8] hypertriglyceridemia and hypofibrinogenemia in (n = 10). The main causes were Epstein barr virus,[5] malignancy(b cell lymphoma),[3] abdomen tuberculosis[2] **Conclusions:** HLH is a rare but rapidly fatal disease and may present in a wide range of different presentations. A persistent and prolonged fever with associated progressive abdominal distention (hepatosplenomegaly) and cytopenias over an acute phase should raise the suspicion of HLH. Accordingly, early diagnosis and prompt aggressive treatment are vital for patients' survival and favorable outcome.

KEYWORDS: Hemophagocytic lymphohistiocytosis, hyperinflammatory syndrome, pancytopenia.

INTRODUCTION

Haemophagocytic syndrome is a disorder characterised by fevers, lymphadenopathy, hepatosplenomegaly, cytopenias, and hyperferritinaemia due to dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes, and their haematopoietic precursors throughout the reticuloendothelial system. Primary or familial haemophagocytic syndrome appears to have a genetic aetiology, FHLH (primary), five genetic defects have been identified which account for 90% of all FHLH cases: Type 1 is due to a gene defect on chromosome 9, type 2 is due to mutations in the perforin gene, type 3 is due to mutations in the Munc-13-4 (UNC13D) gene, type 4 is due to mutations in the syntaxin 11 (STX11) gene, and type 5 is due to mutations in the gene encoding syntaxin binding protein 2 (STXBP-2). Whereas secondary haemophagocytic syndrome may be associated with infection, malignancy, or autoimmune disease. Epstein-Barr virus is the most common infectious aetiology implicated in haemophagocytic syndrome, but the syndrome has been associated with a variety of other viral, bacterial, and parasitic pathogen.

MATERIALS AND METHODS

Cases of hlh were recognised from computerised electronic medical records in addition to referring to hard copies of patients' records from hospital mrd section after taking permission from medical superindent of hospital between 2015 to 2018. Diagnosis was based on fulfilling clinical and laboratory criteria dictated by guidelines of the Histiocyte Society in the Revised Diagnostic Criteria for HLH. Fulfilling at least five out of a total of eight criteria would elect for a diagnosis of HLH.

RESULTS

All patients initially presented with unremitting prolonged fever, most being referred cases from primary health clinics after failing to respond to several courses of antibiotics and antipyretics. All 13 patients had splenomegaly at presentation, while only five had

concomitant hepatomegaly. The most common laboratory abnormalties were hyperferritinemia,[13] pancytopenia,[9] bicytopenia,[4] deranged LFT,[6] hypertriglyceridemia.[10] The presumed causes were viral EBV,[5] Lymphoma,[3] abdomen tuberculosis,[3] hiv,[1] adult onset stills disease,[1] CTD.[1] For treatment corticosteroids were frequently used. lymphoma patients received etoposide. Two patients received att. two patients died. two patient lost follow up.

S. No.	Age	Gender	Diagnosis
1	55	M	EBV
2	58	M	LYMPHOMA
3	28	F	CTD
4	40	M	EBV
5	47	M	ABDOMEN TB
6	25	M	EBV
7	55	F	ABD TB
8	40	M	HIV
9	43	F	EBV
10	50	M	LYMPHOMA
11	32	M	EBV
12	46	M	LYMPHOMA
13	29	F	STILLS DISEASE

S no.	Fever	Splenomegaly	Hepatomegaly	Cytopenia	Increased ferritin	Increased TG	Decreased fibrinogen	Deranged LFT
1	y	Y	N	bi	2200	765	Y	N
2	y	Y	Y	Pan	1200	546	N	Y
3	Y	Y	N	pan	4000	129	Y	N
4	Y	Y	N	pan	1100	180	Y	N
5	Y	Y	N	pan	13000	567	Y	Y
6	Y	Y	N	pan	3000	1097	Y	Y
7	Y	Y	N	pan	2500	1233	N	n
8	Y	Y	Y	pan	1000	112	Y	Y
9	Y	Y	N	pan	1300	543	Y	N
10	Y	Y	Y	bi	9000	819	N	Y
11	Y	Y	N	bi	2000	926	Y	n
12	Y	y	Y	pan	1339	554	Y	Y
13	y	y	Y	bi	3547	676	y	n

Y: yes, n:no, pan: pancytopenia, bi; bicytopenia

DISCUSSION

In our study, results were closely comparable with general literature statistics. Most of our cases proved to be viral in origin with a male predominance. Clinical presentation of HLH varies widely; which makes it an even more abysmal syndrome, as a delay in diagnosis often leads to fatal consequences. Most of our patients fulfilled the classical clinical criteria for HLH.

Molecular diagnosis compatible with hemophagocytic lymphohistiocytosis.

At least five out of the eight following criteria:
Fever
Splenomegaly
Cytopenia (involving at least two lines)
Hemoglobin <9 g/dL or <10g/dL in newborn babies
Platelets <100 x 109/L
Neutrophils <1.0 x 109 /L
Hypertriglycerides (>265 mg/dL) or hypofibrinogenemia (<150mg/dL)
Evidence of hemophagocytosis in a bone marrow, liver or node biopsy
Decreased or absent NK-cell activity
Elevated ferritin >500 ug/L
Elevated soluble IL-2 receptor alpha (> 2400 U/mL)

CONCLUSION

HLH is rapidly progressive and fatal and may masquerade as a sepsis syndrome, CNS infection, or other hematological malignancy. Therefore, physicians, essentially those working in primary healthcare centers should be made aware of the signs and symptoms of HLH as to initiate early referral to higher care systems (tertiary care). Early diagnosis and prompt aggressive treatment are vital for patients' survival and favorable prognosis. In addition, initial response to chemotherapy is important and probably predictive of subsequent clinical progression. Finally, hematopoietic stem cell

transplant (HSCT) remains the sole rescue for familial cases and relapsing disease.

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