International Journal of Research in Medical Sciences
Balamurugan V et al. Int J Res Med Sci. 2019 May;7(5):1963-1967
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20191710

Case Report

Secondary hemophagocytic lymphohistiocytosis: a rare case report

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Received: 26 February 2019
Revised: 23 March 2019
Accepted: 04 April 2019

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a clinicopathologic syndrome, characterised by hyperinflammation due to inherited or acquired defects in the immune function, leading to unchecked proliferation of histiocytes and lymphocytes resulting in multiorgan dysfunction. HLH can be primary (familial) occurring in young children caused by underlying genetic defects in natural killer cells/cytotoxic T cells or secondary HLH occurring in older children or adults following infections, rheumatological disorders or malignancies. HLH is a medical emergency, having varied clinical presentations and lacks a pathognomonic clinical or laboratory abnormality. Clinical presentations include unexplained fever, hepatomegaly, splenomegaly, skin rash, cytopenias, liver dysfunction, coagulation abnormality and neurological manifestations. It carries a poor prognosis. Early diagnosis based on HLH 2004 criteria and initiation of treatment is crucial in the management strategy, which is likely to improve the outcome of this life-threatening disease. The treatment strategies include immunosuppressive drugs, immunomodulatory therapy and autologous hematopoietic stem cell transplant in selected cases. Here with authors report a case of young adult, presenting with fever, thrombocytopenia, splenomegaly, and multi organ dysfunction, diagnosed as a case of secondary HLH based on the HLH 2004 guidelines.

Keywords: Cytopenia, Haemophagocytic lymphohistiocytosis, HLH, Splenomegaly, Unexplained fever

INTRODUCTION

Haemophagocytic lymphohistiocytosis is an aggressive and life-threatening syndrome characterized by excessive immune activation. Farquhar J W et al, and Claireux AE et al, first described in siblings affected by this disease in the year 1952.[1] This disease was originally described as 'familial hemophagocytic reticulosis'. The other terminologies include Autosomal recessive familial HLH, familial erythrophagocytosis HLH, viral associated hemophagocytic syndrome, Infection associated hemophagocytosis.[2-5] The term hemophagocytosis refers to the engulfing (literally meaning 'eating') of blood cells and its precursors by activated macrophages and is seen in bone marrow, spleen, liver, lymph node.[6] Primary HLH or familial HLH is caused by underlying genetic mutations in the genes encoding HLH or primary immune deficiencies.[5] Secondary or acquired HLH, occurs in individuals without identifiable HLH gene mutations or genetic predisposition triggered by auto immune diseases, infections or malignancies.[5]

CASE REPORT

A 26-year-old male, with no known co-morbidities admitted with history of fever, for 5 days duration. History of abdominal pain was present. No history of cough with expectoration, joint pain, bleeding manifestation or altered sensorium. No history of chronic drug intake. On examination, the patient was obese,

febrile and icteric. No generalized significant lymphadenopathy. The patient was evaluated for fever, splenomegaly with thrombocytopenia.

Table 1: Clinical pathology investigations.

Parameter	Value	Units
WBC count	2500	per cumm
RBC count	3.35	x 10^6/cumm
Haemoglobin	7.9	g/dl
Packed cell volume	24.2	%
Mean cell volume	86.2	fl
Mean cell haemoglobin	30.5	pg
Mean cell haemoglobin concentration	35.4	g/dl
Platelet count	8000	per cumm
Immature platelet fraction	1.4	%
Erythrocyte sedimentation rate	120	mm/ hour
Prothrombin time	32	seconds
Activated partial thromboplastin time	93.9	seconds
INR	2.40	
Fibrinogen	73.7	mg/dl

The patient was evaluated for fever, splenomegaly with thrombocytopenia.

Table 2: Clinical biochemistry investigations.

Parameter	Value	Units
Random plasma glucose	149	mg/dl
Urea	98	mg/dl
Creatinine	4.2	mg/dl
Total bilirubin	13.2	mg/dl
Direct bilirubin	8.7	mg/dl
Aspartate transaminase	2985	IU/L
Alanine transaminase	1294	IU/L
Alkaline phosphatase	119	IU/L
Total protein	5.8	g/dl
Albumin	3.2	g/dl
C-reactive protein	235.6	mg/L
Ferritin	>2000	mcg/L
Lactate dehydrogenase	6010	U/L
Creatine phosphokinase	15010	U/L

Table 3: Clinical microbiology investigations.

Test performed	Results
Widal (*Salmonella typhi*)	Titres insignificant
Dengue - serology ELISA (NS1 antigen, IgM antibody)	Negative
Hepatitis B and Hepatitis C - serology ELISA	Negative
HIV I and II antibodies - Tridot	Non-reactive
Blood culture (after 48 hours)	No growth
Urine culture (after 48 hours)	No growth

Patient had a rapid downhill course in clinical and laboratory parameters, over a period of four days, progressing to multi organ dysfunction. The laboratory workup is summarized in (Table 1, 2 and 3).

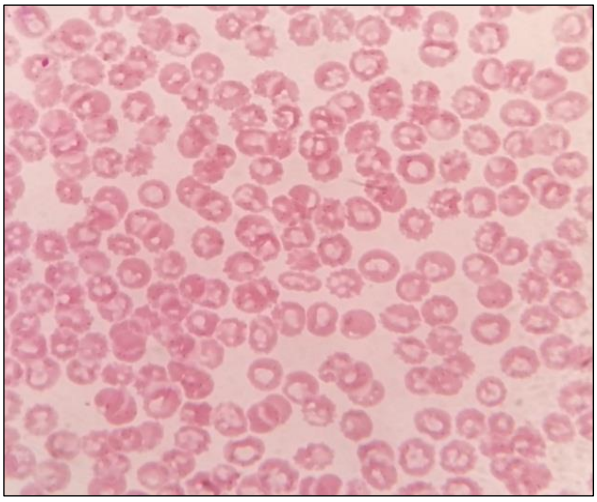

Figure 1:100x (Leishman stain) peripheral smear shows severe thrombocytopenia.

Peripheral smear study (Figure 1) showed RBC-microcytic hypochromic admixed with normocytic normochromic RBCs. No inclusions, no circulating normoblasts seen, no hemo parasites seen. WBC - mildly reduced in count with normal morphology and following distribution neutrophils 41%, band forms 2%, lymphocytes 52 %, eosinophils 5%. Platelets-markedly reduced in number, manual count of 7000 cells/cumm. Occasional giant platelets seen. Impression: dimorphic anaemia, mild leukopenia, severe thrombocytopenia and smear negative for malarial parasite was given.

In combination of clinical parameters of fever, splenomegaly, coagulopathy , liver and renal dysfunction, supported by the laboratory parameters of elevated serum ferritin levels, low fibrinogen levels , markedly elevated serum transaminases , deranged renal function, a working diagnosis of suspected haemo phagocytic lympho histiocytosis with disseminated intravascular coagulation, acute liver failure, acute renal failure and rhabdomyolysis was offered.

At that time, bone marrow aspiration, bone marrow biopsy, core needle biopsies of liver and kidney were performed.

Bone marrow aspiration (Figure 2, 3, 4 and 5) revealed a partially diluted marrow, with reduction in erythroid precursors, myeloid precursors and occasional megakaryocytes. Also seen in clusters and singly dispersed histiocytes with abundant vacuolated cytoplasm, exhibiting intracytoplasmic erythroid, myeloid precursors and platelets, indicating evidence of hemo phagocytosis.

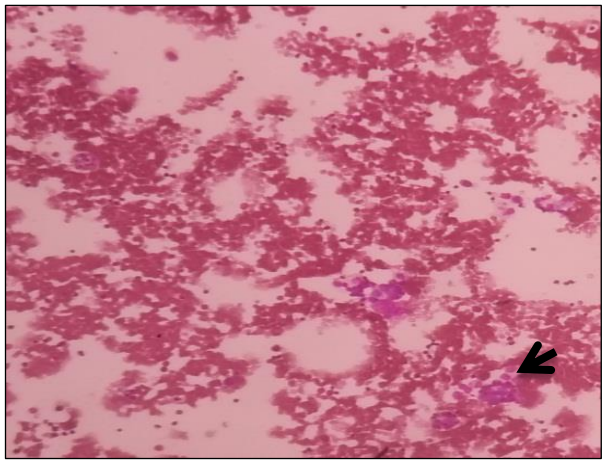

Figure 2: 4x (Leishman stain) bone marrow aspirate shows partially diluted marrow with histiocytes in clusters (↓).

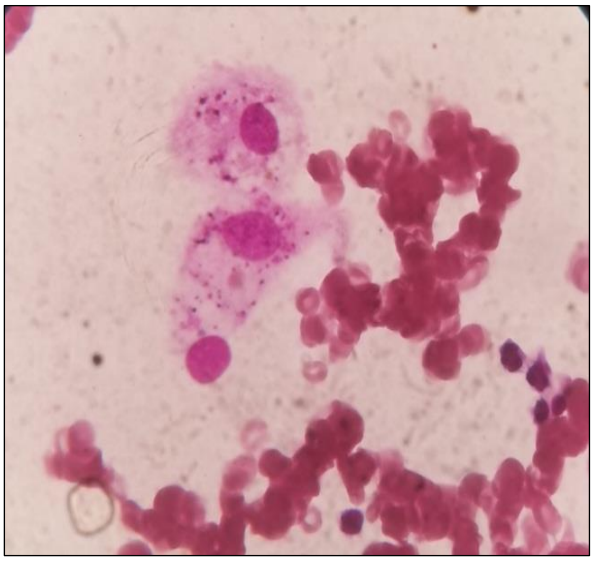

Figure 3: 100x (Leishman stain) bone marrow aspirate shows increase in histiocytes.

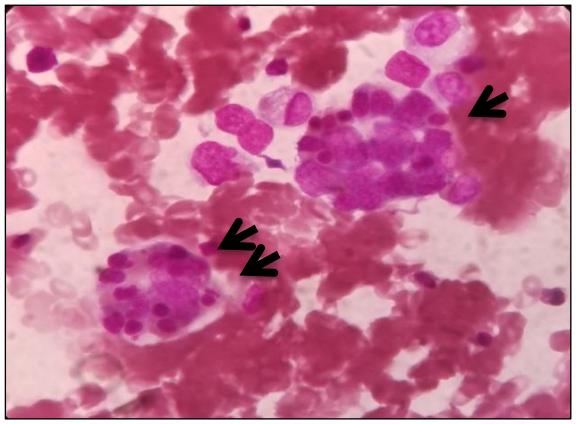

Figure 4: Figure 4: 100x (Leishman stain) bone marrow aspirate shows histiocytes engulfing erythroid (↓) and myeloid precursors (↓↓).

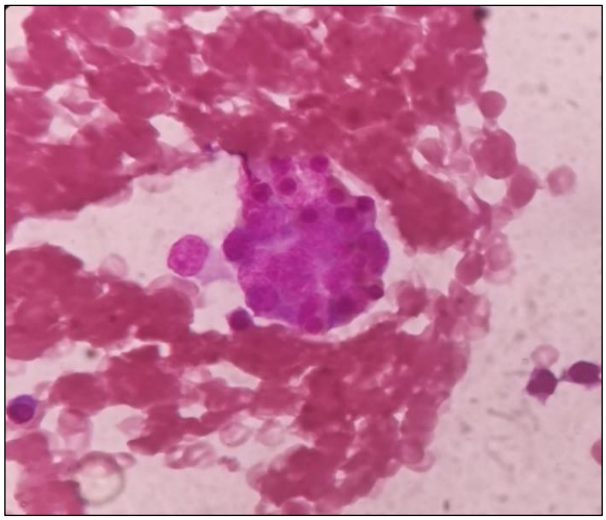

Figure 5: 100x (Leishman stain) bone marrow aspirate shows histiocyte engulfing erythroid precursors.

Based on the histiocyte society treatment protocol HLH 2004 guidelines, the following criteria for the diagnosis of haempohagocytic lymphohistiocytosis were fulfilled (minimum of five parameters is adequate for diagnosis) fever, splenomegaly, haemoglobin-7.9g/dl, platelet count-8000cells/cumm, fibrinogen-73.7mg/dl, ferritin->2000mcg/L, bone marrow aspirate showing hemophagocytosis.

However, shortly after the confirmatory diagnosis of secondary haemophagocytic lymphohistiocytosis was arrived and before appropriate management could be initiated, the patient succumbed to the illness, at the end of 4th day following admission.

The bone marrow trephine biopsy (Figure 6 and 7) showed hypocellular marrow, with reduced trilineage hematopoiesis with an increase in histiocytes as confirmed by positive staining by immunohistochemistry marker for histiocytes, namely CD 68 (Figure 8).

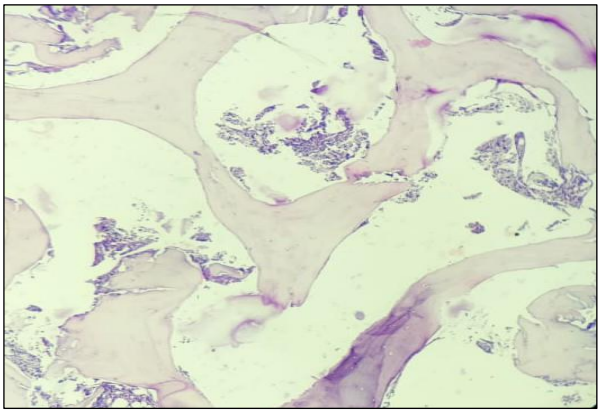

Figure 6: 10 x (H and E) shows a hypocellular marrow.

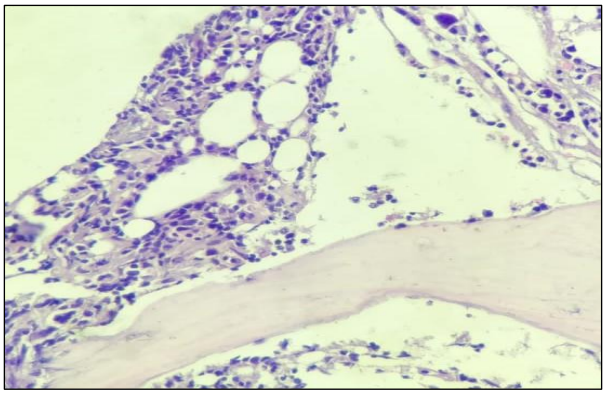

Figure 7: 40x (H and E) shows scattered large cells with abundant eosinophilic cytoplasm, ovoid nuclei, suggestive of histiocytes.

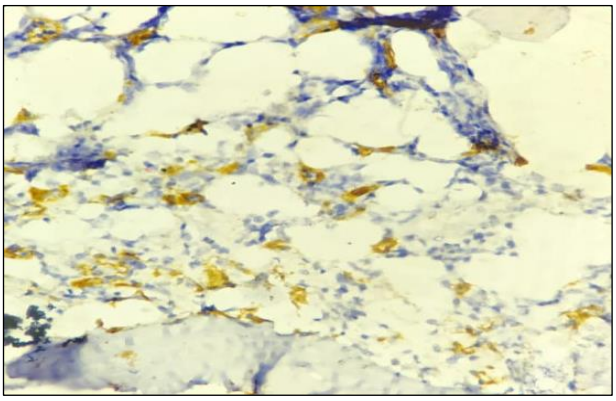

Figure 8: 40 x (IHC) CD 68 shows positive staining for histiocytes in bone marrow.

DISCUSSION

Haemophagocytic lymphohistiocytosis is a rare disease of immune dysregulation, characterized by hypertyrosinemia, hemophagocytosis, hyperferritinemia, hypo fibrinogenemia, variable cytopenias, multiorgan dysfunction that may lead to death.[7]

HLH is more common in pediatric patients, with infants less than 3 months of age. It has equal sex predilection; however, it affects patients of all ages. A slight male predisposition is seen in adults.[2]

The etiopathogenesis involves defects in natural killer cells/cytotoxic T-cells along with excessive activation of histiocytes.[8-10] It leads to excessive cytokine production by macrophages, NK cells, and cytotoxic T-cells resulting in tissue damage. The cytokines elevated in blood of patients with HLH are interferon gamma (IFN), tumour necrosis factor alpha (TNF), interleukins (IL) such as IL 6, IL 10 and IL 12 and the soluble interleukin 2 receptor (sCD25).[11] HLH is classified as primary or familial HLH and secondary or acquired HLH. Primary HLH is caused by gene mutations mapping to loci such as FHL 1, FHL 2, FHL 3, FHL 4, FHL 5, GS 2, XLP 1, and XLP 2.[5] Certain congenital immunodeficiency syndromes like Griscelli syndrome. Chediak Higashi syndrome, X linked lympho proliferative disease, and Hermansky pudlak syndrome are associated with increased risk for primary HLH. Secondary or acquired HLH usually denotes a patient without a familial gene mutation and is particularly triggered by some viral illness, auto immune disease, and lymphoma.

The clinical features are often non-specific, and it mimics common infections, pyrexia of unknown origin, hepatitis or encephalitis. It includes fever, splenomegaly, bi-cytopenia, neurological symptoms like seizures, mental status changes and multi organ dysfunction.[12] HLH can affect other organ systems that include acute respiratory distress syndrome (ARDS) requiring ventilatory support, severe hypotension, SIADH, skin manifestations like rashes, purpura, petechiae, edema, bleeding manifestations or underlying immunodeficiency syndrome specific findings. Associated features include viral infections like Ebstein barr virus (EBV), cytomegalovirus (CMV), parvo virus, human immuno deficiency virus (HIV) or rarely with bacterial, parasitic or fungal infections. Associations with lymphoid neoplasms including B cell, T-cell and NK cell neoplasms are also reported. Laboratory abnormalities include cytopenia involving 2 cell lines like anaemia and thrombocytopenia in majority of the patients.[13] A very high serum ferritin level >2000mcg/L is considered highly sensitive and specific for the diagnosis of HLH.[14] All patients with HLH have hepatitis, manifested by abnormal liver function tests, characterized by elevated liver enzymes, lactate dehydrogenase, bilirubin, increased triglycerides and abnormal coagulation parameters (disseminated intravascular coagulation). Cerebrospinal fluid may show pleocytosis, hyperproteinemia and or hemophagocytosis. MRI of brain may show hypodense or necrotic areas. Bone marrow evaluation is must for all patients with HLH. HHemophagocytosis is characteristic of HLH, it is not diagnostic or pathognomonic. Bone marrow cellularity can be high, low or normal.[15] Specialized tests include immunological assay of soluble IL-2 receptor alpha (sCD25), flowcytometric evaluation of NK cell function/degranulation, cell surface expression of perforin and granzyme B proteins. Genetic testing for HLH gene mutation is indicated for all patients who meet the criteria for HLH and in relatives of patients with a known genetic syndrome. Diagnosis is based on diagnostic criteria of HLH 2004 trial.[16] It includes five of the following eight findings

- Fever >38.5°C,
- Splenomegaly,
- Peripheral blood cytopenia -with at least 2 of the following: hemoglobin <9g/dl, platelets <10000/cumm, absolute neutrophil count <1000/cumm,
- Hypertriglyceridemia (>265mg/dl) and/or hypofibrinogenemia (<150mg/dl),

- Hemophagocytes in bone marrow, spleen, lymph node or liver,
- Low or absent NK cell activity,
- Ferritin >500 ng / ml,
- Elevated soluble CD25, (or)
- HLH associated gene mutation.

Since HLH is associated with high mortality in the absence of appropriate treatment, the diagnostic criteria need not be strictly adhered to, while initiating therapy in critical case scenarios. Differential diagnosis includes macrophage activation syndrome (MAS), systemic infections/sepsis, liver failure, multiorgan dysfunction syndrome, encephalitis, Kawasaki disease, transfusion associated graft versus host disease. Treatment include immunosuppressive drugs like dexamethasone, immune modulators like podophyllotoxin derivatives, combination of both as induction and continuation phases, oral cyclosporine, intravenous anti thymocyte globin (ATG), intrathecal methotrexate for CNS involvement and autologous hematopoietic stem cell transplant in resistant disease, recurrent disease, familial HLH patients, CNS disease and in patients with gene defects.

CONCLUSION

Haemophagocytic lymphohistiocytosis is a disease characterized by systemic hyperinflammatory response, which shows rapid clinical deterioration and may potentially prove fatal. Evidence of hemophagocytosis in bone marrow, spleen, liver or lymph node by histopathological examination is of vital importance to physicians, evaluating patients with unexplained fever, multi organ dysfunction and coagulation abnormalities. Hence high index of suspicion with early diagnosis is the key, to start appropriate intervention and promote survival of patients with this uncommon disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Balamurugan V, Bharathi VJ. Secondary hemophagocytic lymphohistiocytosis: a rare case report. Int J Res Med Sci 2019;7:1963-7.