Case report

Haemophagocytic Lymphohistiocytosis in a Malay infant: Rare, Old and Often Forgotten Disease

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Abstract:

Haemophagocytic lymphohistiocytosis (HLH) is a rare disease but potentially life threatening clinical syndrome. It is caused by a multisystemic hyperinflammatory process secondary to severe hypercytokinemia with excessive and uncontrolled activation of the immune response. We report a case of familial HLH with no apparent causes in 6 months-old Malay girl presented with recurrent fever associated with severe anaemia and bleeding tendency requiring extensive treatment but refractory to the treatment which lead to mortality due to neutropenic sepsis indicating of poor prognosis of this disease. This familial type of HLH should be suspected in all children after excluding all the secondary causes with collective laboratory features and requiring extensive management as it associated with high mortality.

Keywords: Familial; haemophagocytic lymphohistiocytosis; infant

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Introduction:

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by fever, cytopenia, splenomegaly and hemophagocytosis activity in bone marrow, spleen, or lymph nodes which can be familial or acquired.[1,2]Familial HLH is associated with genetic mutation contribution, meanwhile acquired HLH can be secondary to viral, bacterial, fungal or parasitic infection, autoimmune disorder, malignancies or post transplants recipients.[3] HLH is life threatening disorder and if diagnosis or treatment is delayed, it can be associated with high mortality. Approximately 20-40% mortality rate was reported which can rise up to 70-85% in certain subtypes.[4,5]

The incidence of HLH is 1.0 per million children per year in Europe and 1 in 8 million in Japan.[4,5] This disease entity is rare but has been recognized long time ago and been reported way-back in 1940s. Farquhar and Claireaux described the first example of familial HLH which also involved infant age.[6] The incidence in Malaysian population is not well established and to the best of our knowledge, this is the first reported case of HLH in young children in North-east coast of peninsular Malaysia.

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Because of the rarity of the disease with life threatening condition, early diagnosis and prompt treatment is important. We decided to present this case as we consider it will useful for pediatricians in this region as the disease has very important implications arising from early diagnosis and management. Under diagnosis of this condition is highly likely, which further compromised the epidemiological data of this rare disorder. Due care was taken for ethical issues by taking parental consent and ensuring that the institute has no objection for publishing this case report.

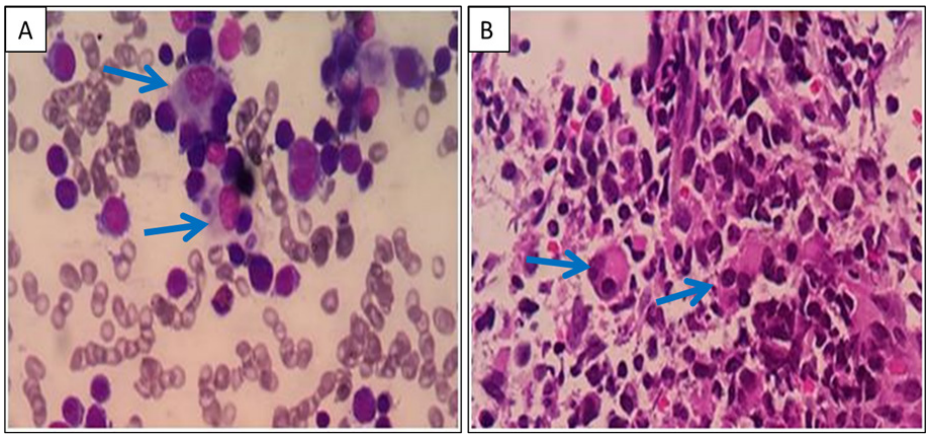

Figure 1: Bone marrow aspiration and trephine biopsy show haemophagocytosis (blue arrow): A. Bone marrow aspiration shows predominantly erythroid precursors with mild dyserythropoiesis, presence of many macrophages which arrange in cluster, vacuolated, foamy and plum-like appearance and increase in haemophagocytic activity. B. Bone marrow trephine showed reverse myeloid to erythroid ratio, presence of sprinkle of macrophages/ histiocytes with few showing haemophagocytic activity.

Case Report:

The patient is a Malay girl who initially presented at the age of 4 months with history of 2 days high grade fever associated with generalised bruises and abdominal distension. She also had history of passing out fresh blood in stool. There were no symptoms associated with upper respiratory tract, urinary tract, central nervous system or gastrointestinal tract infection. She was born at term from non-consanguineous marriage and had normal growth and development according to age. She is the youngest out of 3 siblings and from poor socio-economic family background. There was no significant family history of similar problem.

Physical examination revealed she was conscious, active, febrile with pallor but not jaundiced. There were no dysmorphic features. There were multiple bruises at trunk, upper and lower limb. There was large hepatosplenomegaly (liver was 7cm and spleen 5 cm palpable) but no lymphadenopathy. Examinations of other systems were unremarkable. She was treated as bacterial infection with a course of antibiotic (intravenous cefotaxime for 1 week and oral azithromycin for 5 days) and received packed red cells and platelet transfusion and recovered with the initial treatment. She had regular follow up as outpatient for investigating the cause of hepatosplenomegaly until presented again at the age of 6 months with similar problem of high grade fever, generalized bruises and worsening of abdominal distension.

Her blood count showed persistently bicytopenia with haemoglobin level ranging from 4-7g/dL and platelet counts ranging from 8-11x10^9/L with increased reticulocytes count. Blood film revealed features of haemolysis with leucoerythroblastic picture. The biochemical test results supported the haemolytic activity with increased indirect bilirubin and lactate dehydrogenase (LDH). Blood culture did not isolate specific microorganism and all infectious screening results were negative (TORCHES, HBV, HCV, HIV, Leptospirosis, EBV, Mycoplasma, dengue, malaria, and parvovirus). Bone marrow aspiration and trephine biopsy (BMAT) was done due to persistent bicytopenia and revealed macrophages/ histiocytes proliferation with significant increased of haemophagocytic activity (Figure 1). As HLH was suspected, further investigations showed markedly increased serum ferritin (5931 ng/ml), serum cholesterol and triglyceride (7.71 and 4.35 mmol/L respectively) and low serum fibrinogen (1.34 g/L). The summary of all laboratory investigations results are shown in Table 1.

She was diagnosed with familial type HLH based on clinical presentation at very young age, blood count, biochemical results and BMAT findings, and

Table 1 Summary of laboratory test throughout the admission and treatment of the patient

Test	Reference range	Result		
		1st admission, at 4/12 old	2nd admission, at 6/12 old	Post 1st induction therapy
Hb (g/dL)	11.5-15	6.2	4.4	7
TWBC/N/L (x10^9/L)	4-10/1.5-9/4-10	21.8/3.3/11.9	26.5/3.3/11.6	10.2/1.3/7
Platelet (x10^9/L)	150-400	11	13	11
Retic count (x10^9/L)	0.4-1.0	2.5	2.7	
Coagulation profile				
PT/INR/APTT (sec)			17.0/1.38/35.1	
D-Dimer (µg/ml)	<0.5		3.35	
LFT				
Albumin (g/L)	38-42	37	38	46
TB/ DB/IB (µmol/L)	<17/<3.4/-	37/10/27	49/15/34	10/-/-
ALT/AST (U/L)	15-60/13-45	334/133	42/53	44/30
LDH (U/L)	<480	7592	7657	4282
HLH workout				
Sr fibrinogen (g/L)	2.3-4.4		1.5	4.3
Sr ferritin (ng/mL)	14.5-87.6	782.4	5981.2	1309.4
Sr C/TG (mmol/L)	<4.4/<1.7		7.7/4.4	3.6/0.8
Infection screening				
CRP (mg/L)	<10	Negative	Negative	
Blood/urine C&S		NG	NG	
Dengue IgG/IgM		NR		
HBs Ag		NR		
Anti-HCV		NR		
Anti-HIV 1/2		NR		
Mycoplasma IgM		NR		
CMV IgM/IgG (titre, U/mL)		NR /Reactive (61.9)		
Parvovirus		Negative		
Toxo IgM/IgG		NR/NR		
HSV-1/2 Ig G		Reactive/ NR		
EBV IgM		NR		
Syphilis		NR		
CTD screening				
Rheumatoid factor	Negative	Negative		
C3/C4 (g/L)	0.7-1.3/ 0.2-0.6	0.8/0.3		

Hb=haemoglobin, TWBC=total white blood cell; N=neutrophil; L=lymphocyte; Retic=reticulocytes; PT=prothrombine time; APTT=activated partial thromboplastin time; sec=second; LFT=liver function test; TB=total bilirubin; DB=direct bilirubin; IB=indirect bilirubin; ALT=alanine transaminase, AST=aspartate transaminase; LDH=lactate dehydrogenase; Sr=serum; C=cholesterol; TG=triglyceride; C&S=culture and sensitivity; CRP=C-reactive protein; Ag= antigen; HBs=hepatitis B surface; HCV=hepatitis C virus; HIV=human immunodeficiency virus; CMV=cytomegalovirus; Toxo=toxoplasma; HSV=herpes simplex virus; EBV=Epstein Bar virus; CTD=connective tissue disease; NR=non reactive; NG=no growth

there were no secondary causes had been identified. However molecular diagnosis for confirmation was not performed due to logistic and limited resource for further testing. She was treated with chemotherapy using HLH 2004 protocol regime (dexamethasone, etoposide and cyclosporine A) and required 2 cycles of induction therapy when she did not show much improvement clinically (persistent bicytopenia and hepatosplenomegaly). She able to tolerate the chemotherapy for 8 months until succumbed to death at the age of 14 months-old due to neutropenic sepsis.

Discussion

HLH is characterized by multisystem inflammation. It is a reactive process from prolonged and excessive activation of antigen-presenting cells and CD8+ T cells, which also include excessive proliferation and ectopic migration of T cells.[7] This disease also known as histiocytic medullary reticulosis.[8,9] HLH can be subdivided into 1. primary (genetic) which can be due to familial or immune deficiency syndromes; and 2. secondary (acquired) which can be due to infection, autoimmune disease, malignancy or immunosuppression.[10] The genes that are involved in the pathogenesis of primary familial HLH include PRF1 (type 2), UNCD13D (type3), STX11(type 4), STXBP2 (type 5) and unknown (type 1).[11] These mutations lead to defect in the cytotoxic activity of the natural killer cells and the cytotoxic T lymphocytes which contribute to excessive and uncontrolled immune response with activated macrophages and histiocytes. Both genetic and familial cases of HLH are often precipitated by acute infections.[12]

HLH is life threatening disorder which required early diagnosis and prompt treatment for better outcome. Delay in the diagnosis or treatment associated with high mortality rate, approximately 20-40% and even higher in certain subtypes. [4,5]Although this patient presented early at the age of 4 months old, but the diagnosis and treatment was quite delay, as HLH was not suspected initially and this patient showed some clinical improvement with antibiotic treatment but hepatosplenomegaly was not resolved. She later represented at the age of 6 months with worsening of the the cytopenias and hepatosplenomegaly indicating of disease progression, requiring further investigations including BMAT study which lead to the diagnosis of HLH. The diagnosis of HLH is based on HLH diagnostic criteria 2004 as shown in the Table 2.[3] This patient fulfilled the criteria included such as fever, splenomegaly, cytopenias, hypertriglyceridaemia, hypofibrinogenemia, high ferritin level and haemophagocytosis in the bone marrow. However HLH-2004 criteria has some limitation in which not all criteria are fulfilled at disease presentation and lead to misguide physician towards a negative diagnosis.[11] For early detection of HLH, close monitoring of all investigation results are required and high index of suspicion in the diagnosis list. Due to rarity of HLH, this condition might not in the list of differential diagnoses.

Table 2: Diagnostic guidelines for HLH[3]

Criteria		The diagnosis of HLH can be establish if one of either criteria 1 or 2 is fulfilled
1		A molecular diagnosis consistent with HLH
2		Diagnostic criteria for HLH *
	A	*Initial diagnostic criteria (to be evaluated in all patients with HLH)*
		Fever
		Splenomegaly
		Cytopenias (affecting ≥2 of 3 lineages in peripheral blood)
		Haemoglobin<90 g/L
		Platelets <100x10^9/L
		Neutrophils <1.0x10^9/L
		Hypertiglyceridemia and/or hypofibrinogenemia
		Fasting triglycerides ≥3.0 mmol/L
		Fibrinogen ≤1.5 g/L
		Haemophagocytosis in bone marrow or spleen or lymph nodes
		No evidence of malignancy
	B	*New diagnostic criteria*
		Low or absent NK- cell activity
		Ferritin ≥500 µg/L
		Soluble CD25 ≥2400 U/ml

* five out of eight criteria are required.

In this patient, the definite diagnosis of familial HLH cannot be confirmed by detection of genetic abnormalities related to this disease.Due to the rarity of HLH, no specific research group to be referred for confirmation at that time hence it was not planned for the specific mutation analysis. However, based on history of a very young age at presentation (< 1 year old), characteristic of laboratory abnormalities[11] and absence of infections sources, malignancies or autoimmune diseases, it is most likely primary HLH.

Conventional therapy for HLH involved chemotherapy and supportive care to resolve bleeding problem and correct severe cytopenia. This patient was treated with HLH-2004 chemotherapy

protocol, which based on chemo-immunotherapy to limit the proliferation and activation of immune cells and to halt the cytokine storm.[11] However, about 30% of HLH patients do not respond to conventional therapy as shown in this reported case. Patient did not show clinical improvement as shown by persistent hepatosplenomegaly and cytopenias throughout the treatment period. The ultimate final solution for this patients as well as refractory secondary HLH is allogenic haemopoietic stem cell transplantation,[11] and unfortunately this patient died due to neutropenic sepsis before this option of treatment could be offered. In addition this patient also faced socioeconomic constraints for further definitive management.

In conclusion, adequate knowledge and high suspicion of this disease are compulsory for early diagnosis and treatment of HLH. It is crucial to report this case in favor of familial HLH after all secondary causes were excluded. Delayed in diagnosis and treatment might lead to higher mortality rate from various complications including sepsis and multiple organ failure.

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Authors' contribution:

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Writing and submitting manuscript: Norpazila Yaacob, Mohd Nazri Hassan, Faezahtul Arbaeyah
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