MedCrave
Step into the World of Research
Hematology & Transfusion International Journal

Case Report

Hemophagocytic lymphohistiocytosis in a child with sickle cell disease

Keywords: hemophagocytic lymphohistiocytosis, FHL, EBV, hemoglobin S, sickle cell disease, X-ray

Volume 6 Issue 5 - 2018

Walaa Shoman,[1] Yasmine El Chazli,[2] Asmaa Elsharkawy,[2] Neveen Mikhael,[3] Akram deghaidy,[3] Abeer Al-Battashi,[4] Yasser Wali[2]

[1]Department of Pediatrics, Immunology/Rheumatology unit, Alexandria University, Egypt
[2]Department of Pediatrics, Hematology/Oncology unit, Alexandria University, Egypt
[3]Department of Clinical pathology, Alexandria University, Egypt
[4]Department of Child Health, Royal Hospital, Oman

Correspondence: Yasser Wali, Department of Pediatrics, Hematology/Oncology unit, Alexandria University, Egypt, Email yasser_wali@hotmail.com

Received: September 02, 2018 | **Published:** September 27, 2018

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyper-inflammatory syndrome which represents the extreme end of a severe uncontrolled hyperinflammatory reaction that can occur in many underlying conditions.[1] HLH can be divided into primary and secondary HLH. Primary HLH is caused by gene mutation, either at one of the Familial HLH (FHL) loci or in a gene responsible for one of several immunodeficiency syndromes.[2] The most common form of secondary HLH is infection associated HLH. Infectious triggers include viruses (as EBV, cytomegalovirus, HHV8, HIV), bacteria (as mycobacteria, mycoplasma), parasites (as leishmania, plasmodium), and fungi (as candida, cryptococcus).[3,4] Sickle cell disease (SCD) and its variants are genetic disorders resulting from the presence of a mutated form of hemoglobin, hemoglobin S (HbS), which can be detected by hemoglobin electrophoresis. SCD is suggested by the typical clinical picture of chronic hemolytic anemia and vaso-occlusive crisis.[5,6] We present a case of HLH in an Egyptian boy who was diagnosed later as having SCD.

Case report

A 5-years-old Egyptian boy who was born to consanguineous parents (first degree cousins). His past history was free apart from cervical lymphadenitis reported at the age of 6 months which has been treated successfully with antibiotics and recurrent dental abscesses starting at the age of 2years. In August 2017, he complained of high grade fever for one week associated with mild cough, he received intramuscular antibiotics for 5 days with no improvement. Then he developed pallor, severe cough and grunting and received his first packed RBCs transfusion and was referred to our institution. At presentation, he was ill-looking with high-grade fever, pallor and cough. His weight was 15kg (5^{th} percentile), his height was 101 cm (5^{th} percentile). His examination showed decreased air entry on the right lung and hepatosplenomegaly. His initial laboratory investigations revealed, normocytic normochromic anemia, leukocytosis with neutrophilia, platelet count and elevated acute phase reactants. His blood and urine cultures were repeatedly sterile, and he had negative brucella serology, Widal and Tuberculin tests. His chest X-ray revealed a well-defined lesion in the right upper lobe and a CT chest confirmed the presence of a lung abscess (Figure 1). Parenteral antibiotics were started (vancomycin and meropenem) leading to a gradual improvement of his general condition and subsidence of fever within 4 days of initiation of antibiotics. He started to regain his appetite and activity and cough decreased markedly. Both the liver and spleen regressed in size and acute phase reactants normalized. After three weeks, while continuing his antibiotic course, he acutely developed a high-grade unremitting fever, grunting, marked pallor, jaundice, and marked re-enlargement of both liver and spleen despite improved chest condition and radiogram. His laboratory parameters deteriorated as well (Table 1), with pancytopenia, markedly elevated liver enzymes and direct hyperbilirubinemia. Ciprofloxacin was empirically added the possibility of overwhelming sepsis, and suspicion of secondary HLH was raised. Further investigations revealed markedly elevated serum ferritin and triglyceride levels with normal serum fibrinogen level. Bone marrow aspirate was normocellular with increased erythropoiesis and no apparent hemophagocytosis or evidence of hypoplasia (Of note that it was done after 2weeks from the start of HLH therapy; Figure 2). Viral studies including serology for HAV, HBV, HCV, HIV, EBV and CMV were negative. As he had been fulfilling 5 criteria for diagnosis of HLH according to the Histiocyte society 2004 protocol,[2] dexamethasone 10mg/m^2/day was promptly started and it resulted in a dramatic improvement of fever, rapid regression of the size of liver and spleen and gradual improvement of the general condition. After 14days, the dose of dexamethasone was reduced to 5mg/m^2/day then gradually discontinued as the patient's condition has completely improved. Basic immunological tests including immunoglobulins assay, lymphocyte subsets analysis, and DHR were normal making an underlying immune disorder unlikely. At the next follow up visit, although his clinical condition and routine laboratory investigations had completely normalized after discontinuation of steroids and antibiotics, he still had splenomegaly (span 12cm) and a persistent normocytic normochromic anemia with a normal blood film and serum ferritin. Further investigation of his splenomegaly and persistent anemia with hemoglobin electrophoresis showed Hb S of 62.5%, Hb F 35.7% and Hb A2 of 1.8%. The diagnosis of SCD was further confirmed by the detection of the homozygous mutation at codon 6 [A>T] of the Beta globin gene. Both siblings are sickle cell trait.

Table 1 Laboratory values of the patient from initial presentation to end of steroid treatment.

	30/8 On admission	10/9	19/9 deterioration	21/9 Starts Dexa	28/9	28/10 Treatment discontinued
Complete blood count						
Hb (g/dl)	10.5 (after transfusion)	8.6	5.4	8.5 (after transfusion)	9.9	10.2
MCV (fl)			89.8	87.5		88.7
MCH (pg)			29.1	29.5		29.4
Reticulocytes (%)	1.8		2.8			
Platelets (x10^3/µL)	630	479	85	52	291	260
WBCs (x10^3/µL)	15.2	8.7	3.43	1.66	7.6	10.5
Neutr. %/ ANC (x10^3/µL)	64/9.7	45/3.9	40/1.3	5/0.08	69/5.3	50/5.1
Lymphocyte %	24	38	56	89	13	40
Monocytes %			4	5		
Chemistry						
Creat. (mg/dl)	0.24	0.26	0.2	0.2	0.4	0.27
Sodium (N: 136-145mmol/L)	136	135	129	135	134	
ALT (N: 12-78IU/L)	20	14	242	1093	571	75
AST (N: 15-37IU/L)	41	22	625	1177	104	30
ALP (N: 46-116 IU/L)			161	127	108	77
TSB/ DSB (mg/dl)	0.2/0.1		1.72/0.55	1.5/0.4	2.3/1.3	1.4/0.4
Albumin (N: 3.4-5g/dl)				2.8	3.3	3.9
TG (mg/dl)			581	413		119
CRP (N: up to 5mg/L)	96	10	98.9	72	7	3
ESR (mm/hr)	45					
PT/PTT (sec)	13.2/35.5		14.9/46.3		12/26.2	
Fibrinogen (N: 180-400mg/dl)				336		
Ferritin (N: 7-140ng/ml)				37.579		

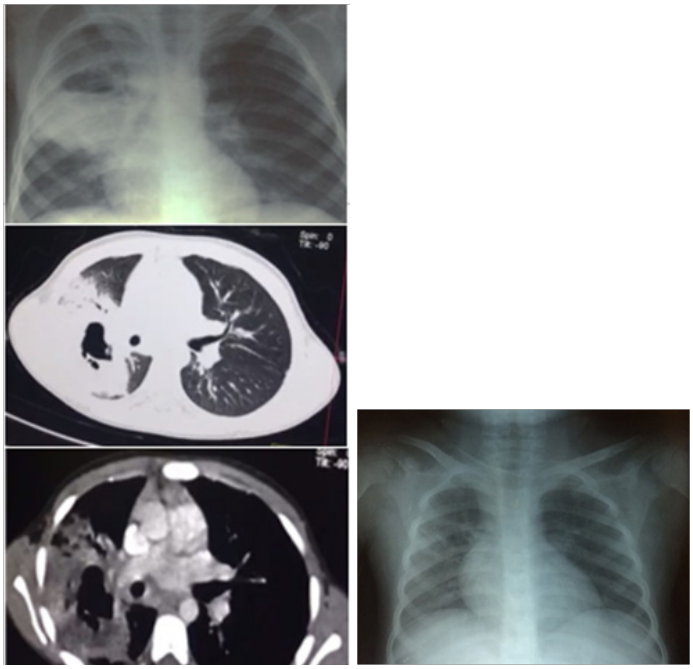

Figure 1 A Chest X-ray and CT chest at presentation, B follow up chest X-ray during the event of HLH.

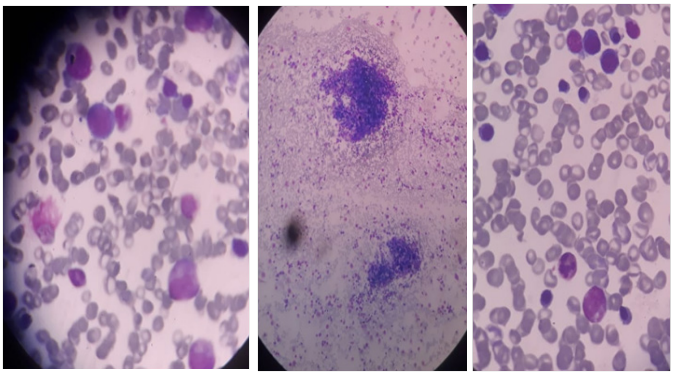

Figure 2 Bone marrow aspirate picture.

Discussion

We hereby report the first case of secondary HLH in a child with SCD. It is important to note that the SCD phenotype in this child was not severe and he has not been diagnosed except after the subsidence of the HLH episode when a persistent anemia and splenomegaly were noted on follow up. SCD is a disease associated by a chronic inflammatory state with high levels of several pro-inflammatory cytokines.[7,8] SCD patients are also more prone to infections of variable etiologies. Bacterial infections being the most common, with a particularly increased risk of invasive pneumococcal disease in patients not receiving a proper prophylaxis. Splenic dysfunction is the

Citation: Shoman W, El Chazli Y, Elsharkawy A, et al. Hemophagocytic lymphohistiocytosis in a child with sickle cell disease. *Hematol Transfus Int J.* 2018;6(5):180–182. DOI: 10.15406/htij.2018.06.00179

main mechanism of increased susceptibility to encapsulated organisms in SCD patients.[9] On the other hand, the associated complement deficiencies increase the susceptibility of these patients to infection by other organisms including Escherichia coli urinary tract infection, Mycoplasma pneumonia, Chlamydophila pneumoniae respiratory infections, dental infections and cholecystitis caused by anaerobes.[9] It is worthy to note that in this patient recurrent dental infections were a long lasting complaint. Although no specific organism was recovered by blood culture and serology, we assume that such an infection might have been the HLH trigger. The inability of his immune system to achieve a complete eradication of the infective organism, led to a persistently stimulated inflammatory response reaching the end of the spectrum of hyperinflammation in the form of HLH syndrome. An aplastic crisis in SCD would also be a possible cause of pancytopenia, however, in our patient; the BMA was normal. Moreover, there was rapid clinical deterioration, enlarging liver and spleen size, very high ferritin level and high serum triglycerides, which are all in favor of HLH. It is important to note that absence of hemophagocytosis in the bone marrow aspirate does not exclude the diagnosis of HLH, especially that it has been done after start of treatment in our case which makes this negative result hard to interpret. We can also speculate that the inflammatory state exacerbated by infection in our patient before and during the HLH episode has exaggerated his anemia leading to the discovery of his original disease. Infection is a recognized cause of worsening vaso-occlusive crises and hemolysis in SCD through increasing the circulating leukocytes and inflammatory cytokines levels with elevated expression of adhesion molecules on both the vascular endothelium and leukocytes themselves.[9] It is important in a child with HLH to look for a possible underlying disease especially in those with persistence of signs as anemia or splenomegaly.

Acknowledgements

None.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Janka GE, Lehmberg K. Hemophagocytic syndromes–an update. *Blood Rev.* 2014;28(4):135–142.
2. Janka GE. Hemophagocytic syndromes. *Blood Rev.* 2007;21(5):245–253.
3. Maakaroun NR, Moanna A, Jacob JT, et al. Viral infections associated with haemophagocytic syndrome. *Rev Med Virol.* 2010;20(2):93–105.
4. Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis.* 2007;7(12):814–822.
5. Strouse J. Sickle cell disease. *Handb Clin Neurol*. 2016;138:311–324.
6. Lanzkowsky P. Leukemias. In: Lanzkowsky P, editor. *Manual of Pediatric Hematology and Oncology*. 5th ed. USA: Elsevier Inc.; 2011. p. 518–566.
7. Bunn HF. Pathogenesis and Treatment of Sickle Cell Disease. *N Engl J Med.* 1997;337(11):762–769.
8. Conran N, Costa FF. Hemoglobin disorders and endothelial cell interactions. *Clin Biochem.* 2009;42(18):1824–1838.
9. Booth C1, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis.* 2010;14(1):e2-e12.