Hemophagocytic lymphohistiocytosis in a child with sickle cell disease

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

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. 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. 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). 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. 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 2 years. 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 (5th percentile), his height was 101 cm (5th 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 differential white blood cell count was further confirmed by the detection of the homozygous mutation at codon 6 [A>T] of the Beta globin gene. Both siblings are sickle (S) cell carriers. The diagnosis of SCD was confirmed by the detection of the homozygous mutation at codon 6 [A>T] of the Beta globin gene. Both siblings are sickle cell trait.

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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 (x10^12/µL)  | 630               | 479  | 85                 | 52                | 291  | 260                          |
| WBCs (x10^9/µL)        | 15.2              | 8.7  | 3.43               | 1.66              | 7.6  | 10.5                         |
| Neut. %/ 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               | 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/dl)   | 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 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
main mechanism of increased susceptibility to encapsulated organisms in SCD patients. 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, Chlamydia pneumonia respiratory infections, dental infections and cholecystitis caused by anaerobes. 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. 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.

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None.

Conflict of interest
The authors declare that there is no conflict of interest.

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