Hemophagocytic lymphohistiocytosis in a child with human immunodeficiency virus infection – a case report

LĂCÂRĂMOAREA-ELIZA CHIPERI1), ANDRA DIANA IONESCU2), CRISTIAN TIBERIU MARCU2), CORINA ITU-MUREȘAN3), CRISTINA PANTELEMON4)

1)Department of Pediatric Cardiology, Emergency Institute for Cardiovascular Diseases and Heart Transplant, Târgu Mureș, Romania
2)Department of Pediatrics, Infectious Diseases Hospital, Cluj-Napoca, Romania
3)Department of Immunosuppression, Infectious Diseases Hospital, Cluj-Napoca, Romania
4)Department of Neurosciences, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare condition and furthermore human immunodeficiency virus (HIV)-associated HLH is rarely reported in the literature. The most frequent presentation of secondary HLH is in association with infections, malignancies or drugs. In HIV-positive patients, the viral infection itself or the antiretroviral therapy (ART) could trigger HLH. Case presentation: A 14-year-old boy was admitted for persistent diarrhea, severe weight loss and chest burns. Laboratory tests revealed important neutropenia, which led to HIV infection diagnosis. ART in combination was started associated with granulocyte-colony stimulating factor. Viral copies declined after six weeks of treatment, but the cluster of differentiation 4 (CD4) T-lymphocyte and neutrophil counts remained very low. Infections and malignancies were ruled out. The bone marrow aspirate revealed hemophagocytosis which in association with fever, bicytopenia, hypofibrinogenemia and hypertriglyceridemia established HLH diagnosis. Cortisone therapy and intravenous immunoglobulins were added. Due to lack of response, HLH-2004 protocol was initiated in collaboration with pediatric hematologist. In the first six months of treatment, CD4 T-lymphocytes and neutrophil count remained low and then they showed significant increase simultaneously. During treatment, the patient developed spontaneous severe back pain. Magnetic resonance imaging showed vertebral compression, osteomalacia and a thoracic vertebral fracture. Conclusions: Having ruled out the usual associated infections and malignancies, this is a case of HIV-associated with HLH. In this case, only the ART and immunomodulatory therapy were not enough and failed to work. Systemic immunosuppression also worked only after a prolonged course which led to an unfortunate complication: a vertebral fracture.

Keywords: secondary hemophagocytic lymphohistiocytosis, HIV infection, antiretroviral therapy.

§ Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an immunological disease in which the innate immune system became hyperactive and destructive for the body. The process is labeled as cytotoxic lymphocyte dysfunction [1]. Macrophages, natural killer (NK) cells, and cytotoxic T-lymphocytes [cluster of differentiation (CD)8 T-cells] accumulate in organs like spleen and bone marrow, attack and consume other normal cells as erythrocytes, leukocytes, and platelets. The activated immune cells produce increased levels of cytokines that affect internal homeostasis leading to multiple dysfunctions.

HLH is a condition that can be either primary, which is genetically inherited, or secondary, when other factors trigger the process.

Five types of hereditary or familial HLH were described in the literature [2] and they are caused by mutations in adaptor related protein complex 3 subunit beta 1 (AP3B1), biogenesis of lysosomal organelles complex 1 subunit 6 (BLOC1S6), Bruton’s tyrosine kinase (BTK), CD27, interleukin-2 (IL-2) receptor subunit gamma (IL2RG), IL-2 inducible T-cell kinase (ITK), lysosomal trafficking regulator (LYST), magnesium transporter 1 (MAGT1), perforin 1 (PRFI), RAB27A, member Ras oncogene family (RAB27A), SH2 domain containing 1A (SH2D1A), soluble carrier family 7 member 7 (SLC7A7), syntaxin (STX3, STX11), STX binding protein 2 (STXBP2), Unc-13 homolog D (UNC13D), and X-linked inhibitor of apoptosis (XIAP) genes. Primary HLH is autosomal recessive inherited and diagnosis is established by molecular genetic testing.

Secondary HLH is triggered by a variety of factors. Most noted are viral infections, such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus-8 (HHV-8) and, less frequently, human immunodeficiency virus (HIV). It can also be triggered by fungal infections, such as Candida albicans. Other triggers described are malignancies (lymphomas more often), autoimmune or autoinflammatory conditions and different drugs, antiretroviral therapy (ART) also being mentioned.

Diagnosis is based on fulfillment of five out of eight criteria [3], unless family history and molecular diagnosis is consistent with primary HLH [4]; fever, splenomegaly, cytopenia involving at least two cell lines, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes), low or absent NK cell activity, elevated soluble IL-2 (CD25) levels.

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HIV-induced HLH is rare reported in the literature [5] and the exact mechanism of this specific association is not fully understood. It is important to recognize the association to establish a correct and complete treatment consisting of ART [6].

**Aim**

We aimed to present an association of diseases rarely seen in pediatric pathology (HIV infection and HLH) for which no specific protocols exist to date therefore the diagnosis and management are based on “expert expertise”. In this case, only the ART and immunomodulatory therapy were not enough and failed to work. Systemic immunosuppression also worked only after a prolonged course, which led to an unfortunate complication: a vertebral fracture. Family and institutional ethical consent were obtained and are available on request.

**Case presentation**

We report the case of a 14-year-old Caucasian boy with persistent diarrhea admitted in February 2015 to Department of Pediatrics, County Hospital in Oradea, Romania, for investigations. No significant personal, familial history or physical features were observed at the time. The laboratory report showed only mild dehydration, with no inflammation and immunological deficits, the bacteriological stool exam detected no pathogen agent and abdominal ultrasonography revealed no abnormalities. In the differential, inflammatory bowel disease, celiac disease and infectious enterocolitis were ruled out and he received symptomatic treatment. Five months later, in July 2015, the patient returned to Hospital reporting weight loss (7 kg over the last month) and chest burns. Complete blood count (CBC) revealed bicytopenia: anemia and neutrophilia. Further investigations consisted of a positive HIV enzyme-linked immunosorbent assay (ELISA) test therefore he was transferred to Department of Pediatrics, Infectious Disease Hospital, Cluj-Napoca, Romania. There was no significant family history for HIV infection and from the patient’s personal medical history it is worth mentioning a surgical intervention at one year of age and several minor dental interventions.

On physical examination, he presented cachexia and white lingual deposits.

Initially, HIV ELISA test was reactive and HIV infection was confirmed through Western blot test; viral load was very high (Table 1), CD4 and CD8 T-lymphocytes levels were low [7]. CBC revealed severe neutropenia (neutrophil cells count was 0), leukopenia, lymphopenia, and normochromic normocytic anemia. Esophagitis secondary to *C. albicans* infection was found at superior endoscopy and taught to be the cause for the chest burns. Other associated opportunistic infections were ruled out.

| Parameter               | Value       | Normal range [7] |
|-------------------------|-------------|------------------|
| Viral load              | 1 872 739 copies/mL | 0               |
| CD4 T-lymphocytes level | 8 cells/mL  | 500–1200 cells/mL|
| CD8 T-lymphocytes level | 344 cells/mL | 150–1000 cells/mL|
| CD4/CD8 ratio           | 0.02        | >1               |

CD: Cluster of differentiation.

Neutropenia was interpreted as secondary to HIV injury on the bone marrow and ART was initiated consisting of Darunavir, Ritonavir, Raltegravir and Lamivudine, for a period associated with Enfuvirtide. Prophylactic antibiotic treatment of opportunistic infections and antifungal treatment of candida was associated. As a response to treatment, HIV viral load decreased from 1 872 739 copies/mL to 88 copies/mL in eight weeks of ART, but neutropenia persisted. Due to severe neutropenia, the patient received granulocyte-colony stimulating factor (G-CSF). CD4 T-lymphocytes number and neutrophil count remained low (Figure 1), with G-CSF having a prompt but brief favorable response, continuous administration of at least two doses per week being necessary.

![Figure 1 – Evolution of leukocytes, neutrophils and CD4 T-lymphocytes. CD4: Cluster of differentiation 4; HLH: Hemophagocytic lymphohistiocytosis.](image-url)
Persistence of neutropenia in parallel with favorable evolution of viremia, raised the suspicion of another responsible cause. In the differential, etiologies like infections (hepatitis B and C, EBV, CMV, parvovirus B19, tuberculosis, toxoplasmosis, and Mycobacterium avium – normal serological tests and chest X-ray) and lymphoma (normal cervical, thoracic, and abdominal computed tomography) were ruled out. A bone marrow aspirate revealed granulocytic hypoplasia, pleomorphic lymphoid population, reactive macrophages (irregular nuclear shape, increased in volume, intranuclear vacuoles, eosinophilic cytoplasm), which presented hemophagocytosis and lymphocytosis (Figures 2 and 3) and, in association with fever, bicytopenia (neutrophilia and moderate normochromic normocytic anemia), hypofibrinogenemia and hypertriglyceridemia allowed the diagnosis of HLH secondary to HIV infection.

Figure 2 – Bone marrow aspirate showing hemophagocytosis. May-Grünwald–Giemsa (MGG) staining, ×1000.

Figure 3 – Bone marrow aspirate showing hemophagocytosis. MGG staining, ×1000.

Corticosteroids (Dexamethasone) therapy and intravenous immunoglobulins were added to the treatment, but there was no improvement therefore HLH-2004 protocol was initiated. It was followed for a prolonged period due to the persistence of cytopenia. CD4 T-lymphocytes levels and the neutrophil count showed significant increase simultaneously only after a period of six months from the beginning of HLH-2004 protocol.

The patient evolution was good but suddenly, during hospitalization he presented severe back pain, which initially responded to intravenous pain killers but soon after he required bed immobilization to control the pain. Magnetic resonance imaging described a thoracic (T11) vertebral fracture line, vertebral compressions, and osteopenia. A rheumatology consult led to the finding of a low level of serum vitamin D, folic acid, and calcium. The diagnosis of osteomalacia due to calcium and vitamin D deficiency secondary to prolonged cortisone therapy was established.

### Discussions

HIV infection is a less frequent cause for HLH, and diagnosis is difficult due to its rarity. Based on the literature review, we were able to find less than 10 cases of children [7–9] and fewer than 20 cases of adults [5, 10] who presented HIV-induced HLH without other associated infection or malignancy.

When HIV-associated HLH occurs, it is seen either in acute HIV infection, or in advanced HIV infection, when other infections or malignancies are associated. In the present case, the HLH developed in the chronic phase of the HIV infection after ART was started and no other infection or malignancy were associated. We found another case in the literature when HLH is described as secondary to ART in a patient with low level of CD4 T-lymphocytes (26 cells/mL) like the present case [11].

Patients with HIV-associate HLH usually improve on ART. This result is not secondary to individual effect of antiretroviral drugs; it occurs secondary to treatment of the underlying cause, which is in this situation, the HIV infection [12]. Up to present date, there is not enough information to establish that one ART scheme is better than another in treating HIV-associated HLH [13]. Prompt ART is recommended even in critically ill patients with very low CD4 T-lymphocytes level if other infections causes were ruled out [13].

Several reports [14–16] describe positive results after five or six days of treatment but these patients had a higher level of CD4 (>100 cells/mL) than in the present case. There are also reported cases in which ART did not have a favorable effect with any improvement obtained after weeks of treatment [17]. In our patient, probably secondary to a very low CD4 T-lymphocytes count, initiation of ART was not associated with biological improvement within weeks of treatment: the CD4 and neutrophil level remained low.

For patients with HIV-induced HLH that do not improve on ART, more treatment options are necessary. Immunomodulatory therapy, such as corticosteroids and intravenous immunoglobulins were added [18]. If this approach does not improve the patient condition, systemic immunosuppression, like in primary HLH, is required [18]. HLH-2004 protocol is currently the recommended regime and consists of eight weeks of Dexamethasone daily, Etoposide twice weekly. In persistent, non-familial, non-genetically verified cases, like our patient, the protocol recommended continuation of therapy until stem cell transplantation could be offered [19]. Due to the lack of response, in our case, the regime was continued for six months until CD4 and neutrophil levels, both started to increase.

Prolonged cortisone therapy can induce osteoporosis [20] by multiple mechanisms, including bone mineral density loss and alteration of bone quality [21] in direct relation with dosage and treatment duration. Protease inhibitors are also involved in adverse bone effects, and evidence abounds in this direction. They act by decreasing bone density and increasing the risk for osteopenia,
considering their effect on the hydroxylation of the inactive form of vitamin D, which can be reduced by 80% [22]. Secondary osteoporosis was the cause for the patient vertebral fracture.

Conclusions

This was a persistent case of HLH secondary to HIV infection in which ART and immunomodulatory therapy failed to work. Systemic immunosuppression worked only after a prolonged course which led to an unfortunate complication: a vertebral fracture.

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Corresponding author

Lăcrămioara-Eliza Cipieri, MD, Department of Pediatric Cardiology, Emergency Institute for Cardiovascular Diseases and Heart Transplant, 50 Gheorghe Marinescu Street, 540136 Târgu Mureș, Romania; Phone +40265–212 111, Fax +40265–216 368, e-mail: lacramioara-eliza.pop@umfst.ro

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