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Hemophagocytic Syndrome in Patients Living with HIV

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Abstract

Hemophagocytic syndrome is a clinical condition characterized by non-malignant proliferation and activation of lymphocytes and macrophages (histiocytes); hemophagocytosis in the reticuloendothelial system; and the clinical findings of fever, hepatosplenomegaly, cytopenias, and hyperferritinemia. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening and rapidly progressive condition caused by excess activation of the immune system. This syndrome is classified as familial or acquired; the latter is more frequent and is associated with diverse conditions, such as infections, malignancies, and rheumatic diseases. HLH associated with human immunodeficiency virus (HIV) is rare, most often being described in those with chronic HIV infection or with the presence of concomitant opportunistic infections. In immunocompromised patients, HLH is an aggressive condition and a fulminant syndrome with high rates of mortality. Patients presenting with a clinical picture of fever and highly elevated inflammatory markers should raise the suspicion for HLH. Treatment usually requires chemotherapy and even with standard treatments prognosis is poor with approximately 50% survival. Rapid diagnosis and treatment of the underlying disorder is necessary to prevent progression to multiorgan failure and death.

Keywords: Hemophagocytic syndrome; Human immunodeficiency virus; HIV; Hemophagocytic lymphohistiocytosis.

Introduction

The Hemophagocytic lymphohistiocytosis syndrome (HLH) was first described by Farquhar and Claireaux in 1979 in immunosuppressed patients with viral infections [1, 2, 3]. It is a clinicopathological entity characterized by unregulated macrophage activation resulting in overproduction of inflammatory cytokines and hemophagocytosis [2, 4]. The decrease in cytotoxicity of natural killer cells and cytotoxic T cells with up-regulation of γ-interferon probably plays a role in the pathogenesis of HLH, leading to an increase in macrophage activation and plentiful secretion of proinflammatory cytokines [5]. HLH is traditionally considered a rare event, but recent studies have suggested that this condition is under-diagnosed. It is characterized by fever, hepatosplenomegaly, cytopenias, and hyperferritinemia. HLH can be idiopathic or secondary to various conditions [6, 7]. The familial form is related to genetic immune defects, while the acquired form is due to an underlying disease process such as infection, autoimmune disease, or malignancy. Human immunodeficiency virus (HIV) infection is also found associated with HLH [2, 6, 7]. HLH can occur due to HIV itself or associated opportunistic infections [1]. HLH is a rapidly progressive and often fatal illness [2, 3]. It is arduous to diagnose; clinical feature includes fever, lymphadenopathy, hepatosplenomegaly, and jaundice, as well as cytopenia and impaired liver function [2, 8]. In this review, we aim to give an overview of the diagnosis and management of HLH in patients living with HIV.

Epidemiology

HLH is traditionally considered a rare event, but recent studies have suggested that this condition is underdiagnosed [1]. The association of HLH and HIV has been described; however, it occurs less frequently than previously expected [9]. Hemophagocytosis itself may not be an uncommon finding in patients living with HIV either, as demonstrated in an autopsy case series of 56 patients, of whom 54 consecutive cases had HIV and 11 had hemophagocytosis. Another study reported hemophagocytosis in bone marrow biopsy in around 10% of patients living with HIV prior to the initiation of antiretroviral therapy. The presence of hemophagocytosis has also been described in non selected populations of patients with severe sepsis and multiple organ dysfunction syndromes. Of 107 autopsies of critically ill medical patients, 64.5% had hemophagocytosis in bone marrows. This overlap of clinical and laboratory features between AIDS and HLH as well as between sepsis syndromes and HLH has given rise to significant diagnostic challenges in identifying HLH in patients living with HIV and has probably led to HLH being significantly underdiagnosed in this population [3].

Physiopathogeny

The pathogenesis of secondary HLH in the setting of HIV infection is probably related to acquired defects in cellular cytotoxicity [8]. HLH has similar pathophysiology of immune reconstitution inflammatory syndrome (IRIS) and characterized by over-proliferation of mature histiocytes, hemophagocytosis, and upswing of inflammatory cytokines [5]. Althrough the immune cells in HLH are functionally normal, it is throught to be the result of proliferation or activated T cells that go on to activated macrophages, as well as the lack of appropriate apoptosis of immunogenic cells. As these overly activated macrophages and histiocytes proloferate and run rampant, they phagocyties other cells including erythrocytes, leucocytes, and platelets, leading to the clinical symptoms. This highly stimulated immune system results in life-threatening [10]. This syndrome is a result of damage caused by the cytotoxic activity of natural killer (NK) cells and T cells; thus the ineffective immune system is constantly stimulated to generate high levels of cytokines, such as tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ), which stimulate the defense cells. High levels of cytokines are responsible for the clinical picture [1, 2, 4].

Etiology

Secondary HLH occurs after strong immunologic activation, such as with severe infection, immunodeficiency or underlying malignancy. Infectious agents, mostly viruses of the herpes family, usually are the triggers [5, 10]. Infections contribute to the initiation of hemophagocytosis in 2 types of scenarios. They have been often identified as the triggers for the onset of HLH in genetic disorders or autoimmune diseases, with an increased propensity for HLH. They can also act as the primary drivers for the onset of HLH in patients without those underlying disorders [3]. A wide variety of bacterial, viral, fungal, and parasitic infections have been associated with HLH [8]. HIV infection has been associated with HLH with a wide range of disorders, namely viral, bacterial, mycobacterial, fungal and protozoal infections, malignancy, autoimmune diseases, related therapy and even HIV itself [1, 8]. In patients living with HIV, The main etiology for HLH is opportunistic infections [3, 8]. The viral pathogens are notoriously known as a cause of infectious associated HLH [2]. EBV is the most common etiology, while CMV is associated with 30% to 40% of all virus-associated HLH cases [1]. However, HIV itself, without opportunistic infections, has been attributed to be the cause of HLH in several reported cases [3]. Naturally, the diagnosis of HLH secondary to HIV itself infection is only possible in the absence of other plausible causes [8]. In the largest study to date, only 5% of patients were

found to have no underlying cause of HLH other than HIV itself [8]. The association between bacterial infection and HLH is poorly documented, and most case reports indicate that it is due to intracellular bacteria (Mycobacteria, Legionella sp.) [1]. HLH has also been described in the settings of IRIS [3]. Recent reports have suggested that HLH may be a manifestation of acute HIV infection [5, 6]. HIV- positive patients with lymphoma are at high risk for HLH [1]. Another disorder on the spectrum of this disease state includes macrophage activation syndrome, which is a form of HLH associated with rheumatological diseases [10].

Diagnostic of HLH

HLH is difficult to diagnose clinically [6]. It is an uncommon and frequently undiagnosed event, recently described in critically ill patients. HLH remains a diagnostic challenge, as the clinical presentation of this condition mimics sepsis, a frequent syndrome in patients living with HIV [1]. With HLH, consideration of all its etiologies with appropriate diagnostic testing is required. While the differential for secondary HLH is broad, consideration of the clinical context can help dictate what kind of testing needs to be done [6]. The Histiocyte Society has released guidelines that outline specific clinical and laboratory criteria for the diagnosis of HLH and specific algorithms for its management [6, 8]. HLH is diagnosed by fulfilling a minimum of 5 of 8 of the following criteria: fever, splenomegaly, cytopenia in 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent NK cell activity, ferritin >500 μg/L, and soluble CD25> 2400 U/mL [4, 10]. Five of the eight criteria must be met for the diagnosis, but a ferritin level> 10 000 ng/mL is highly suspicious [10]. Central nervous system involvement, cutaneous manifestations, severe coagulation disturbances, and multiple organ dysfunctions occur less frequently [1]. Notably, the criteria only require a ferritin level > 500 ng/ml, but a level > 10 000 ng/ml is thought to be highly suspicious for HLH, with a specificity of 96%. The ferritin level upon diagnosis has also been found to have prognostic value, and its decline correlates with response to treatment. The soluble IL-2 receptor was found to be a more sensitive marker than ferritin with a sensitivity of 93% and also carries prognostic implications [10]. The manifestations of HIV-associated HLH are not different from those of other virally associated HLH. Interestingly, those who developed HIV- associated HLH tend to have higher viral loads, co-commitment opportunistic infections or underlying malignancies such as lymphoma [2]. A study evaluating how applicable the diagnostic criteria and treatment algorithm laid out in these guidelines are to adult HIV- infected patients has not been reported so far [3]. Most of the features listed as the diagnostic criteria for HLH such as fever, splenomegaly, bicytopenias, hypertriglyceridemia, and hyperferritinemia are often present in patients with advanced HIV with or without opportunistic infections and with or without antiretroviral therapy [3]. For most of the cases reviewed in HIV infected patients, the typical presentation was of fever of unknown origin, although in several cases there were other coexistent causes for fever such as other opportunistic infections or acute infections. Fever in an AIDS patient has a very long list of differential diagnoses [3]. These nonspecific features have a wide differential diagnosis in the context of HIV. Indeed HLH may be mistaken for many other disorders, most frequently lymphoproliferative diseases or infections [8].

Table. Diagnostic Criteria for HLH [3]

The diagnosis of HLH can be established if either 1 listed below is fulfilled

1. A molecular diagnosis consistent with HLH

2. Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

A. Initial diagnostic criteria (to be evaluated in all patients with HLH)

- Fever
- Splenomegaly
- Cytopenias (affecting2 of 3 lineages in the peripheral blood): Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L) Platelets <100 10^9/L Neutrophils <1.0.109/L
- Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides3.0 mmol/L(ie,265mg/dL) Fibrinogen 1.5 g/L
- Hemophagocytosis in bone marrow or spleen or lymph nodes No evidence of malignancy B.

B. New diagnostic criteria

- Low or absent NK cell activity (according to local laboratory reference)
- Ferritin 500 mg/L
- Soluble CD25 (ie, soluble IL-2 receptor) _2,400 U/mL

(Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NK, natural killer)

Management of HLH

Although HLH is a rare complication of HIV, it presents a difficult challenge for treatment. Without treatment, HLH is invariably fatal, but the consequence of immunosuppressive treatment regimen in the setting of an underlying opportunistic infection can also have fatal outcomes [3, 10]. Treatment includes supportive care, immunomodulatory therapy, and treatment of any underlying condition. The treatment backbone is an induction phase involving chemotherapy, typically etoposide,

combined with immunotherapy, such as cyclosporin A and steroids. This is followed by a continuation phase that is to be maintained until stem cell transplant is available, as transplant is the only curative treatment for familial HLH [10]. In the context of HIV, HLH requires high dose steroids and IV immunoglobulin to quell the life-threatening inflammatory response, underlying opportunistic infections may prove to be fatal if they go unrecognized there are no current guidelines on antibiotic use in HIV patients with confirmed HLH, and it may be of value to treat these patients empirically for opportunistic infections in the setting of critical illness [10]. It's preferred to stop antiretroviral therapy [2, 5]. Immunomodulatory therapy may be perilous in the setting of underlying infection. Currently, there are no guidelines on empiric antibiotic use for patients with HIV and HLH, but one must be vigilant in searching for underlying infections given the risk of the immunosuppressive regimen required to treat HLH in the setting of HIV [10]. It is controversial when immunosuppressive therapy is indicated versus the treatment of the underlying infection alone [3]. In contrast, EBV-associated HLH is successfully treated with immunosuppressive agents alone [4]. In patients with HLH associated with HIV, early initiation of ART may provide an effective clinical option for reversing the hematological abnormalities associated with the syndrome [11].

Conclusion

In conclusion, a thorough investigation should be done in an immunosuppressed patient with persistent fevers and suspicion for HLH, because prompt initiation of treatment for the specific trigger may improve outcomes and limit the use of cytotoxic chemotherapy. Physicians taking care of patients with HIV infection should be vigilant regarding the increased incidence of HLH. Efforts to exclude infections and lymphoproliferative disorders must be made. The clinical findings of fever, hepatosplenomegaly, cytopenias, bone marrow haemophagocytosis, and hyperferritinemia, fulfilled five of the above-mentioned criteria, suggesting HLH as the most probable diagnosis.

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