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Letter to the Editor

Please, do not forget secondary hemophagocytic lymphohistiocytosis in HIV-infected patients

We found the paper by De Santis et al. on the hematological abnormalities in HIV-infected patients very interesting.[1] However, we think that the possible diagnosis of secondary hemophagocytic lymphohistiocytosis (HLH) should also have been considered in HIV-infected patients with cytopenias (affecting ≥2 or 3 lineages in the peripheral blood).

HLH is a potentially fatal hyperinflammatory syndrome characterized by histiocyte proliferation and hemophagocytosis. HLH may be inherited (primary, familial), occurring generally in infants, or may be secondary to any severe infection, malignancy, or rheumatologic condition, occurring at any age. HLH is diagnosed using clinical criteria developed by the HLH Study Group of the Histiocyte Society (Table 1).[2,3] The mechanism behind secondary HLH is not well understood, and its clinical picture may be identical to primary HLH, but there is more variability in severity and outcome.[4] HLH is considered to be due to a deficiency in cytolytic activity resulting in persistent activation of lymphocytes and histiocytes. This uncontrolled immune response leads to hypersecretion of pro-inflammatory cytokines, an up-regulation of adhesion molecules and MHC I and II molecules on mono/macrophages, and an expansion of inflammatory monocytes. This exaggerated inflammatory response is responsible for necrosis and organ failure, and results in uncontrolled proliferation and phagocytic activity of histiocytes.[5]

HIV alone or in the presence of other opportunistic and non-opportunistic infections or malignancies has been associated with HLH, and HLH has also been described in the setting of immune reconstitution inflammatory syndrome.[5] In PubMed there are at least 82 papers in which the association of 'HIV' with 'hemophagocytic' or 'haemophagocytic' is present. Five studies report series with more than five cases, with a mortality ranging from 31% to 100%.[6–10] A recent retrospective study by Fardet et al. describes the characteristics of 58 HIV-infected patients with secondary HLH. At the time of HLH, the median duration of HIV infection was 4 years and 57% were receiving highly-active antiretroviral therapy. The median CD4 lymphocyte count was 91/μl and 35% of patients had a plasma HIV-1 RNA less than 50 copies/ml. An underlying hemopathy/malignancy (Hodgkin lymphoma $n = 10$) or infection (tuberculosis $n = 9$, cytomegalovirus $n = 5$) was present in 31 patients.[9]

Clinicians need to be aware of the occurrence of HLH in HIV-infected patients. Further studies are needed to understand whether an immunosuppressive treatment such as treatment with steroids or with an etoposide-containing regimen could be beneficial in those cases that do not respond promptly to anti-infective therapy.

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Table 1
Hemophagocytic lymphohistiocytosis (HLH) 2004 diagnostic criteria (modified from Henter et al.[3])

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH are fulfilled (five out of the eight criteria below):
   - Fever
   - Splenomegaly
   - Cytopenias (affecting ≥2 or 3 lineages in the peripheral blood):
     Hemoglobin <90 g/l (in infants <4 weeks: hemoglobin <100 g/l)
     Platelets $<100 \times 10^9$/l
     Neutrophils $< 1 \times 10^9$/l
   - Hypertriglyceridemia and/or hypofibrinogenemia:
     Fasting triglycerides ≥265 mg/dl
     Fibrinogen ≤1.5 g/
   - Hemophagocytosis in bone marrow or spleen or lymph nodes
   - Low or absent NK-cell activity
   - Ferritin ≥500 μg/l
   - Soluble CD25 ≥2400 U/l

Comments:

If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.

The following findings may provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein, (b) histological picture in the liver resembling chronic persistent hepatitis (biopsy). Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, and skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, increased VLDL, decreased HDL.

VLDL, very low density lipoprotein; HDL, high density lipoprotein.

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