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An Unusual Case of Hemophagocytic Lymphohistiocytosis Presentation in Acute Human Immunodeficiency Virus

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) in acute human immunodeficiency virus (HIV) patients has been scarcely reported in the English literature. To the best of our knowledge, only 12 cases have been described. We present a case of a 27-year-old male with no past medical history who was admitted with a new-onset headache, fever, night sweats, and chills. Further laboratory tests revealed transaminitis, leukopenia, thrombocytopenia, positive HIV antigen/antibody test, and markedly elevated ferritin levels, which promoted our suspicion of HLH. This case demonstrates HLH as an unusual presentation of HIV during its seroconversion stage. This report adds a rare disease process to the available literature, and we emphasize that markedly elevated ferritin levels in acute HIV patients should raise suspicion toward a diagnosis of HLH.

Keywords

hemophagocytic lymphohistiocytosis, HIV, infectious disease, case report, hematology oncology, ferritin

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening condition marked by immune dysregulation resulting in cytokine storm, abnormal function of T lymphocytes, with activation of macrophages leading to hemophagocytes in the reticuloendothelial system.[1-3]

HLH has been reported at all stages of HIV infection.[4] In the majority of cases, AIDS is the main underlying etiology during which opportunistic infections trigger the onset of HLH. However, HIV itself has been reported as the cause of HLH.

In this report, we highlight HIV as a triggering agent of HLH and propose antiretroviral therapy (ART) as a viable option in managing acute HIV-HLH. We emphasize hyperferritinemia as an important clue toward the diagnosis of HLH.

Case Presentation

A 27-year-old male with no past medical history presented to the emergency department with headache for the past 2 days. He also endorsed photophobia, chills, night sweats, decreased appetite, 10-pound unintentional weight loss, and fevers. The patient reported being sexually active with men only with the last unprotected sexual intercourse 2 weeks ago. He denied any illicit drug use.

In the emergency department, the patient had a temperature of 38.2 °C, a heart rate of 103 beats/minutes, respiratory rate of 20 breaths/minutes, blood pressure of 100/60 mm Hg, and O_2 saturation of 100% on room air. Physical examination was unremarkable with no meningeal signs. Given his headache and a fever of 38.3 °C, the patient was started on empiric meningitis treatment with vancomycin and ceftriaxone. Computed tomography of the head without contrast showed no acute intracranial process. Magnetic resonance imaging of the brain with and without contrast was unremarkable.

Initial laboratory findings (Table 1) were significant for leukopenia of 2.2 × 10^3/μL, thrombocytopenia of 81 × 10^3/μL, hemoglobin of 12.3 g/dL, transaminitis, elevated C-reactive protein of 3.16 mg/dL, and hypoalbuminemia. Chest X-ray did not reveal any active infection or any other pathology. Blood cultures were negative. Lumbar puncture revealed the following: white blood cells 3 cells/cm^2, red blood cells 378 cells/cm^2, glucose 54 mg/dL, and elevated protein 51 mg/dL. Cerebrospinal fluid (CSF) was

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Table 1. Laboratory Values at Presentation.

Laboratory tests	Patient laboratory values	Reference laboratory values
Hemoglobin, g/dL	12.3	11.1-15.4
White blood cell, $10^3/\mu L$	2.2	4.5-11
Platelets, $10^3/\mu L$	81	150-450
Sodium, mmol/L	133	136-145
Potassium, mmol/L	3.7	3.5-5.1
Bicarbonate, mmol/L	25	21-32
Creatinine, mg/dL	0.89	0.51-0.95
Alkaline phosphatase, units/L	114	45-117
Aspartate aminotransferase, units/L	663	15-37
Alanine transaminase, units/L	597	13-61
Total bilirubin, mg/dL	0.3	0-1
C-reactive protein, mg/dL	3.16	<0.30
Lactic acid plasma, mmol/L	0.8	0.4-2
Ferritin, ng/mL	>40 000	26-388
D-dimer, ng (FEU)/mL	>5000	<500
Fibrinogen, mg/dL	246	150-450
Triglycerides, mg/dL	115	<150
Partial thromboplastin time, seconds	43.5	25.4-37.6
Ceruloplasmin, mg/dL	24	18-36
HIV 1,2 antigen/antibody	Prelim reactive	Nonreactive
Syphilis antibody qualitative	Reactive	Nonreactive
Soluble interleukin 2 receptor/CD25 (pg/mL)	4194	532-1891

negative for cryptococcal antigen, herpes simplex virus, and CSF VDRL. Accordingly, vancomycin was discontinued. Ceftriaxone was decreased to 1 g every 24 hours for 2 weeks, followed by intramuscular benzathine penicillin G 3 million units to treat presumed neurosyphilis due to elevated protein in the CSF. HIV antigen/antibody test was positive, with an HIV-RNA level over 10 000 000 copies/mL, CD4 T-cell count of 201 cells/μL, and CD8 T-cell count of 93 cells/μL. These results along with fatigue, fever, pancytopenia, and transaminitis supported the diagnosis of acute retroviral syndrome; therefore, ART was initiated consisting of darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

Additional laboratory values (Tables 1 and 2) showed hyperferritinemia >40 000 ng/mL, D-dimer >5000 ng/dL, bi-cytopenia, transaminitis, and hypertriglyceridemia, which raised concern for HLH. H-score showed a 93% to 96% probability of having HLH (Table 3). A collaborative decision was made by the patient and the physicians to defer bone marrow biopsy and we chose to confirm our suspicion by performing noninvasive tests such as interleukin (IL)-2 receptor and natural killer (NK) cell activity.

Computed tomography of the abdomen and pelvis with contrast showed borderline prominent right hepatic lobe, slight hypodensity of the liver suggesting fatty hepatocellular changes, and mesenteric adenitis. The patient's symptoms of headache had self-resolved on the third day of admission and he left against medical advice. Following discharge, IL-2R returned >4000 pg/mL. The suspicion of HLH secondary to acute HIV was confirmed as the patient met 4/8 criteria for the diagnosis including fever, bi-cytopenia of thrombocytopenia and neutropenia, elevated ferritin, elevated IL-2R along with the high probability of H-score. The patient followed-up outpatient and he reported complete resolution of his symptoms.

Discussion

Hemophagocytic lymphohistiocytosis was first described by Scott and Robb-Smith in 1939.[5] Primary or genetic HLH occurs in infants and young children due to mutations in genes responsible for the cytotoxic function of NK cells and T lymphocytes. Secondary HLH occurs in adults, and it is often secondary to infections, malignancies, autoimmune conditions, and acquired immunodeficiency states like HIV/AIDS.[6] Among infections, viruses are the most common triggering agents (especially Epstein-Barr virus and cytomegalovirus), followed by bacteria (particularly mycobacterium tuberculosis), protozoa (mainly *Leishmania* spp), and fungi (typically *Histoplasma* spp).[7-10] The most frequent malignancies associated with HLH are lymphoma, and related autoimmune diseases such as systemic lupus erythematosus and adults Still's disease.[11]

The diagnosis of HLH was based on the HLH-2004 criteria proposed by the Histiocyte Society. This HLH-2004 criteria requires 5 out of 8 criteria to make the diagnosis:

Table 2. Serological Tests for Other Viral Infections.

IgG VCA EBV	+	IgG HAV	+
IgM VCA EBV	−	IgM HAV	−
IgG EBNA	+	HCV Ab	−
IgG EBV	+	DR-HBs A	
IgG CMV	+	IgG HBs	−
FTA ABS	+	IgM HBc	−
IgM Cocci	−	IgG Cocci	−
GC rRNA	−	Chlamydia rRNA	−
SARs CoV 2 RNA	−	Influenza A antigen	−
Influenza B antigen	−	CSF *Cryptococcus* antigen	−
CSF Cocci IgM	−	CSF Cocci IgG	−
HLA B*5701	−		
HIV 1 RNA Qn PCR	>10 000 000	HIV 1 RNA Qn PCR	>7000 log/mL
HIV 1 DNA PCR	+	QuantiferonGold	−
RPR	+	RPR titer	1:64
Anti-smooth muscle antibody	−	Toxoplasma Ab IgG	−
West Nile Ab CSF, IgM	−	West Nile Ab CSF, IgG	+

Abbreviations: IgG, immunoglobulin G; VCA, viral capsid antigen; EBV, Epstein-Barr virus; HAV, hepatitis A virus; EBNA, EBV nuclear antigen; HCV, hepatitis C virus; Ab, antibody; HBs, hepatitis B surface antigen; CMV, cytomegalovirus; FTA ABS, fluorescent treponemal antibody absorption; Cocci, coccidiomycosis; GC rRNA, Neisseria gonorrhoeae ribosomal RNA; SARS CoV 2, severe acute respiratory syndrome coronavirus 2; CSF, cerebrospinal fluid; HLA B, human leukocyte antigen; HIV, human immunodeficiency virus; Qn PCR, quantitative polymerase chain reaction; RPR, rapid plasma regain.

Table 3. H-Score Criteria.[25]

Fever (°C)	0 (<38.4) or 33 (38.4-39.4) or 49 (>39.4)
Organomegaly	0 (no) or 23 (hepatomegaly or splenomegaly) or 38 (hepatomegaly and splenomegaly)
Cytopenia	0 (1 lineage) or 24 (2 lineages), 34 (3 lineages)
Ferritin (ng/mL)	0 (<2000) or 35 (2000-6000) or 50 (>6000)
Triglycerides (mmol/L)	0 (<1.5) or 44 (1.5-4) or 64 (>4)
Fibrinogen (g/L)	0 (>2.5) or 30 (<2.5)
Hemophagocytosis in bone marrow biopsy	0 (no) or 35 (yes)
Aspartate aminotransferase (IU/L)	0 (<30) or 19 (>30)
Known underlying immunosuppression	0 (no) or 18 (yes)

fever, at least 2 lineages of cytopenia, hypertriglyceridemia (>265 mg/dL), and/or hypofibrinogenemia (<1, 5 g/L), hyperferritinemia (>500 ug/L), low/absent natural-killer cell (NK-cell) activity and increased levels of CD25 (soluble IL-2 receptor/sIL-2).[1] A retrospective analysis of adult HIV patients considered a diagnosis of HLH if the patient met 3 of 8 criteria of the HLH-2004 classification instead of 5 of 8 criteria in the HLH-2004 definition.[12] Our patient achieved 4 out of 8 HLH-2004 criteria (fever, marked elevated ferritin, bi-cytopenia, and high levels of IL-2) and he had an H-score of 211 with a 93% to 96% probability of having HLH.

The ideal diagnosis of HLH requires biopsy with histopathological documentation of hemophagocytosis in bone marrow biopsy showing activated histiocytes. But bone marrow biopsy results may also be inconclusive as these findings may be absent in a significant portion of patients, even during fulminant disease.

Acute HIV is usually known to have high levels of viremia that is associated with alteration of cytokine levels.[13] The presence of viremia and the subsequent changes of cytokine levels may be associated with the HLH occurrence. HLH is rare in HIV patients with most cases described in chronic HIV or with the presence of opportunistic infections. Only 14 case reports described HLH in HIV acute retroviral syndrome in the English literature[14-22] (Table 4). Our case further confirms that HLH can occur during the seroconversion stage of acute HIV infection.

In our case, the markedly elevated ferritin levels, along with thrombocytopenia and transaminitis in this patient with newly diagnosed HIV raised our suspicion toward HLH. Even though the elevation of serum ferritin may occur in acute inflammatory syndrome due to infectious, neoplastic, autoimmune, and iron overload such as hemochromatosis, a cutoff of >10 000 increases the specificity of HLH.[23]

Table 4. Summary of Previously Reported Cases of Acute HIV With HLH.

Source	Age (years)/sex	Fever	WBC (g/μL)	CD4 count (cells/μL)	Treatment	Prognosis/ complications
Adachi et al[14]	48/Male	+	12 050	90	ART	Recovered
Egge et al[15]	33/Male	+	22 000	79	ART	Recovered
Martinez et al[16]	31/Male	+	1500	300	Unknown	Unknown
Chen et al[17]	18/Male	+	9700	630	ART	Recovered
Sun et al[18]	27/Male	+	10 085	500	NL	None
Sun et al[18]	28/Female	+	1400	NL	Acetaminophen, ketoconazole	Oral candidiasis, encephalopathy
Sun et al[18]	31/Male	+	1600	NL	Steroids, flucanozole	Acute renal failure, encephalopathy
Sun et al[18]	18/Male	+	2800	NL	IVIG, antibiotics	Blurred vision
Castilletti et al[19]	27/Male	+	3400	138	ART	Recovered
Park et al[20]	44/Male	+	3900	157	ART	Recovered
Ferraz et al[21]	27/Female	+	1720	NL	ART	Recovered
Allen et al[22]	25/Male	+	5600	237	ART	Recovered

Abbreviations: HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; WBC, white blood cells; ART, antiretroviral therapy; NL, not listed; IVIG, intravenous immunoglobulin.

To identify the triggering agents of HLH in our patient, we performed numerous imaging studies along with various cultures and serological markers for a number of pathogens and rheumatological and immunological markers. Despite the extensive workup, we were unable to find another triggering agent for HLH except for the HIV infection itself. Subsequently, the most likely explanation is that HLH was a manifestation of the inflammatory storm occurring during acute HIV infection.

HLH in acute HIV patients is thought to have a better prognosis compared with HLH due to malignancy.[24] Another difference is that HLH in HIV patients has good prognosis with initiation of ART. Admittedly, all the reported 12 cases attained complete resolution from HLH after the introduction of ART or supportive therapy like steroids or intravenous immunoglobulin. Of 12 cases, 7 cases included the administration of ART during acute HIV infection (Table 4). Just like in our case, where the patient had complete resolution of symptoms with ART therapy.

Conclusion

Acute HIV infection should be included in the differential diagnosis of HLH. Since our patient recovered with ART without the need for any further intervention, screening for HIV should be performed as it can affect the patient's outcome significantly.

A missed diagnosis of HIV in young adults who are diagnosed with HLH may lead to exposure to immune-modulating therapy that comes with their own side effects. We emphasize that histopathological presence of hemophagocytosis is not a prerequisite to making a clinical diagnosis of HLH. We further stress the importance of hyperferritinemia as an important clue toward the diagnosis of HLH in HIV patients.

Authors' Note

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of Conflicting Interests

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Ethics Approval

Ethical approval to report this case was obtained from the Kern Medical Institutional Review Board (Study ID #20088).

Informed Consent

Informed consent for patient information to be published in this article was obtained.

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