



## Case report

# Acute human immunodeficiency virus infection associated hemophagocytic lymphohistiocytosis

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## ABSTRACT

Although acute HIV-induced HLH is rare in literature, HIV is an important differential diagnosis in patients with HLH. In our study, a 33-year-old previously healthy male patient was admitted with fever of unknown origin, lymphadenopathy, generalized edema, transaminitis, acute renal failure, oliguria, myalgias, night sweats, unintentional weight loss, and leukopenia. Disease course was indicative of a viral-like prodrome of roughly 2-month duration. At an outside hospital, full viral work-up (including EBV, CMV, HIV antibodies, hepatitis panel) was negative. HIV p24 antigen assay was not available at the outside facility. Outside liver chemistry and lymph node biopsy were suggestive of HLH. HLH was confirmed via serum ferritin, white cell receptor, and cytokine studies. Repeat viral and rheumatologic studies revealed a positive p24 antigen with indeterminate HIV antibody. We demonstrate efficacy of a specific treatment plan as well as importance of p24 antigen studies in patients with HLH and/or the HIV window-period, adding to available literature/documentation of a rare disease process.

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## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is defined as hyperacute activation of the immune system, resulting in high grade fevers, hepatosplenomegaly, and heightened hemophagocytosis and natural killer cell activity. Researchers speculate that HLH may be induced via a number of diseases, all which lead to cytotoxic lymphocyte dysfunction [1]. HLH may be either primary (genetic predisposition based on Mendelian-defined mutations) or secondary (triggered by an acute event/immune system insult such as malignancy, infection, or autoimmune flare). It is suspected that genetic predisposition and acquired insults are not mutually exclusive, however, and thus, these terms are losing favor [1].

Acute human immunodeficiency virus(HIV)-induced HLH is rare in literature [2]. However, it is an important differential

diagnosis in patients with HLH. While the mechanism of HLH induction (by HIV) is not well understood, it is important to understand the relationship between HIV and acute HLH in order to appropriately diagnose and treat HIV-induced HLH. Patients with such aggressive and acute HIV infections (with early AIDS) often present with fulminant organ failure and immune dysfunction [2–12]. This presentation of HLH can be addressed uniquely via prompt anti-retroviral therapy (ART), improving patient prognosis [2–12].

## Case presentation

A 33-year-old previously healthy African American male was transferred from an outside hospital (OSH) with 2-month history of unexplained leukopenia, generalized lymphadenopathy, fever of unknown origin and transaminitis. Symptoms onset initially as a virus-like prodrome with 4 weeks of dry cough, generalized myalgias, fatigue, rash, bilateral posterior cervical lymphadenopathy, and high-grade fevers (103–104 F). Labs were initially unremarkable, so he was treated with oral antibiotics for 1 week and sent home from the OSH. Three weeks later, he returned with complaints of worsening night sweats, 10-lb weight loss, diffuse muscle and joint pain, and loss of appetite. Examination revealed 103.1 F and diffuse anterior, posterior cervical and inguinal lymphadenopathy. Repeat labs showed 2200 white blood cell

*Abbreviation:* AIDS, acquired immunodeficiency syndrome; AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine transaminase; ART, anti-retroviral therapy; ATN, Acute tubular necrosis; AST, aspartate transaminase; CMV, cytomegalovirus; FTA-ABS, Fluorescent treponemal antibody; HHV, human herpes virus; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy; HLH, hemophagocytosis lymphohistiocytosis; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; RPR, rapid plasma regain.

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count, 82,000 platelet count. He also had transaminitis with aspartate transaminase (AST) 128, alanine transaminase (ALT) 69, alkaline phosphatase (ALP) of 63, and bilirubin of 0.4. Serum work-up for hepatitis (A,B, and C), HIV-1 and 2 antibodies, Epstein-Barr Virus (EBV) IgM, cytomegalovirus(CMV) IgM. Syphilis studies: rapid plasma reagent (RPR), and fluorescent treponemal antibody (FTA-ABS) were positive. The patient was treated with full-course of intramuscular penicillin g. However, he continued to have intractable fevers, monocytosis with leukopenia, and worsening lymphadenopathy. Left anterior cervical node biopsy was negative for malignancy, but significant for diffuse reactive macrophages. Patient was transferred to our facility for higher level of infectious disease care given unclear etiology. Day 0 (arrival) of hospitalization, maximum temperature was 102.5 F and white count was 5.22, platelet count was 131,000, hemoglobin was 10.4, and liver function panel was worsened with AST 179, ALT 186, ALP 393 and total bilirubin 2.0 (direct 1.4). He also had an azotemia/acute kidney injury (AKI) with Cr of 2.5, BUN 30. All hepatitis, EBV, CMV work-up was repeated and negative. Human herpes virus(HHV)-6,7,and 8 as well as Rickettsial serum assays were negative. Herpes simplex virus (HSV) 1, 2 IgG antibodies were positive. On further investigation of sexual history, patient endorsed multiple female partners over the proceeding 2–3 months. Sexual promiscuity (acute v. chronic) is the likely source of his HSV-2. Serum ferritin was elevated to 37,286. Repeat HIV studies were ordered (including p24 antigen). Transaminitis, ferritin, lymphadenopathy, and lymph node biopsy were concerning for macrophage activating syndrome/hemophagocytic lymphohistiocytosis (HLH).

Day 1 of hospitalization, the patient's white count dropped to 3.03. Day 2 repeat HIV assays resulted positive for HIV antibodies with addition of p24 antigen. HIV-1 antibody assay was indeterminate. During processing time for HIV-1 confirmatory viral load and CD4 T-cell counts (approximately 36 h), patient's leukopenia nadired at and nadired at 1.60 on Day 4. Azotemia/AKI and oliguria continued to worsen despite aggressive IV hydration and Cr peaked Day 4–6.5 with a BUN of 87. He complained of significant lower and upper extremity edema, which was 3+, non-pitting on exam. Urine studies were obtained, showing muddy brown casts, urine sodium of 19, and nephrotic range proteinuria (>999). He also developed acute blurring of his vision. Nephrology and ophthalmology were consulted for concerns of HIV-associated nephropathy / acute tubular necrosis (ATN) and HIV-retinopathy.

## Investigation

Clinical picture and elevated ferritin strongly supported diagnosis of HLH. Prior lymph node biopsy showed diffuse reactive macrophages strongly suggesting HLH. This biopsy was performed roughly 4 days prior to transfer to our facility. Patient refused repeat lymph node biopsy and/or bone marrow biopsy, so HLH was further confirmed via the HLH-specific serum markers (Table 1).

IL-2, natural killer/CD8<sup>+</sup> cell studies supported HLH suspicion. Trigger for HLH appeared to infectious on initial presentation

which prompted mononucleosis (with hepatitis), HIV, and syphilis work up.

Mononucleosis is a common infectious process associated with HLH. Transaminitis, fever, and diffuse lymphadenopathy in an adolescent/young adult may be suspicious for mononucleosis with viral hepatitis. However, all serum studies for EBV, hepatitis A, B, C, and CMV were negative.

Because the patient reported open sexual relationship with his spouse and multiple high-risk sexual partners, syphilis and HIV were both high on differential diagnosis. RPR and FTA-ABS were negative, but pathophysiology progressed despite systemic antibiotics and complete syphilis treatment with intramuscular penicillin. Lack of improvement with syphilis treatment led us to pursue other possible sources of fever, lymphadenopathy, and leukopenia.

Prior to obtaining our confirmatory HIV-1 viral load, various organ system assessments were suspicious for HIV-induced pathology (e.g. HIVAN, HIV retinopathy). Urinalysis showed nephrotic proteinuria with many muddy brown casts, consistent with acute tubular necrosis. Hospital day 3, patient underwent renal biopsy. Five glomeruli were acquired. No usual type or collapsing type glomerulosclerosis was seen (Fig. 1). Myoglobin positive protein casts were noted, suggesting acute tubular injury may be related to rhabdomyolysis (Fig. 2). Electron microscopy showed evidence of podocyte effacement (Fig. 3). Findings were consistent with minimal change/focal segmental glomerulosclerosis category. Pathology suggested segmental sclerosis may not be seen due to focal nature of the disease.

On repeat testing, HIV-1 antibody reactivity was indeterminate. HIV-2 antibody was nonreactive. p24 antigen was positive. Hospital day 5, HIV-1 viral load (quantitative RNA) resulted at 7,747,342 (RNA copies per mL). CD4<sup>+</sup> count was 79 cells/mm<sup>3</sup>. Definitive diagnosis was reached: HLH triggered from acute retroviral syndrome (HIV/AIDS) in the window period.

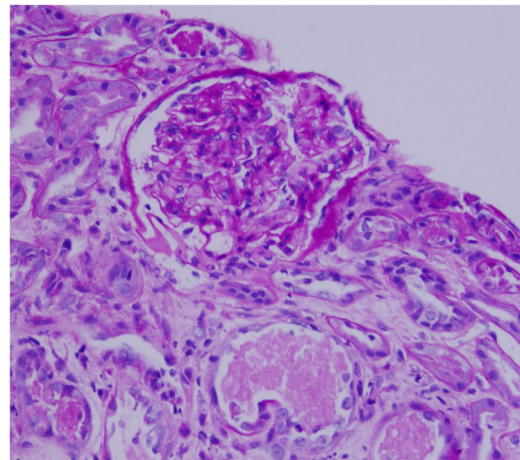


Fig. 1. Hematoxylin and eosin stain of renal cross section, glomerulus.

**Table 1**  
HLH-specific serum antibody, leukocyte, and cytokine studies.

Lab Study	Result	Normal Range	Units
Interleukin-2(IL-2)-Receptor Antibody	8525	< 700	U/mL
Soluble IL-2 Expression	7833	45–1105	U/ mL
Natural killer cell granzyme B Flow cytometry	1438	98–181	Mean Channel Fluorescence
Natural killer cell perforin Flow cytometry	199	98–181	Mean Channel Fluorescence
Perforin expression	55	2–15	% CD8 <sup>+</sup> cells
Granzyme B expression	84	0–61	% CD8 <sup>+</sup> cells
CD56 expression, NK cells	1.2	1.7–13.4	% of total WBCs

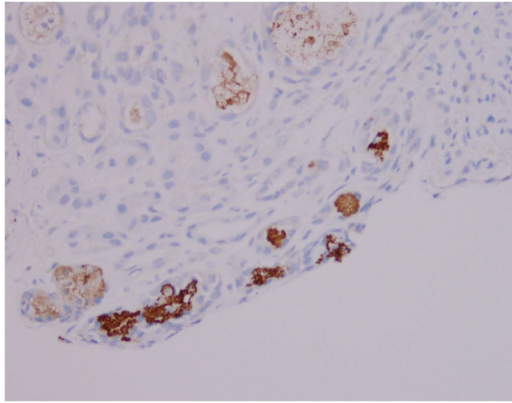


Fig. 2. Renal biopsy showing myoglobin deposition.

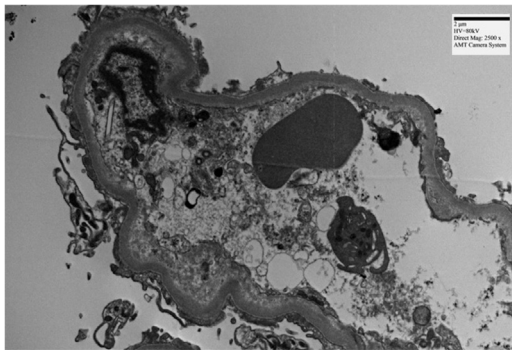


Fig. 3. Electron microscopy with evidence of podocyte effacement.

## Treatment

HLH treatment in non-HIV patients usually mandates systemic steroids; however, given a high suspicion of HIV, steroids were withheld in favor of superior treatment with ART (in AIDS-induced HLH). Day 5 of hospitalization: viral load and CD4 count confirmed HIV-1 infection with AIDS. Hemodialysis was initiated. ART regimen was also initiated with rilpivirine 25 mg daily, lamivudine 50 mg daily, and dolutegravir 50 mg daily, pending HLA B-5701 results for abacavir response. Day 20 of hospitalization, HIV genosure showed pansensitivity. HLA B-5701 was negative. Patient's regimen was adjusted to abacavir 600 mg daily, dolutegravir 50 mg daily, lamivudine 300 mg daily. Creatinine peaked at 7.4 on Day 5 of hospitalization just prior to dialysis and ART initiation.

## Outcome and follow-up

Day of 10 hospitalization, WBC (4680) and platelet (95,000) counts improved significantly. After 10 days of dialysis, patient's kidney function stabilized. Hemodialysis was stopped hospital day 15. Urine output consistently increased to 2–3 L daily by day 12 of ART and day 17 of hospital stay. Hospital day 19, patient was discharged home without further indication for hemodialysis. WBC was 3,710, hemoglobin was 8.5, and platelet count was 196,000. One month after discharge he was seen by nephrology clinic, where repeat labs showed improved white blood cell count of 8,610, hemoglobin of 10.5, platelet count of 290. Renal function stabilized back to patient's admission baseline with Cr 2.40, BUN 7. Glomerular filtration rate was 38. He was started on low dose angiotensin converting enzyme inhibitor and continued on ART for HIVAN. Patient did not resume further follow up with HIV clinic

locally, so HIV and hepatic panel labs were not available for follow up at our facility.

## Conclusions

- Acute HIV infections (in the window period) should be ruled out in all patients who present with FUO, high risk lifestyle, transaminitis, multiple cytopenias, and hepatosplenomegaly and/or suspicion of HLH.
- HLH should ideally be diagnosed via biopsy techniques; however, alternative serum studies such as soluble IL-2 expression, ferritin, and NK cell activity may be beneficial in achieving diagnosis with or without biopsy.

Patients with HIV-induced HLH are likely to improve with ART for treatment unlike patients with primary HLH (who require systemic immunosuppression).

## Consent for publication

Obtained from patient during time of hospitalization. Available upon journal request.

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N/A.

## Authors' contributions

Egge – Manuscript, literature review, direct patient care/assessment of patient

Cheeti – Literature review

Hayat – Rheumatology advisory role and attending physician who spear-headed patient diagnosis and treatment.

## CRediT authorship contribution statement

**Stephanie L Egge:** Project administration, Writing - original draft, Writing - review & editing, Data curation. **Apoorva Cheeti:** Resources. **Samina Hayat:** Conceptualization, Supervision.

## Declaration of Competing Interest

None.

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