CASE REPORT

HHV-8-associated haemophagocytic lymphohistiocytosis in a patient with advanced AIDS

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SUMMARY

We present a patient with advanced AIDS admitted with recurrent shock of unclear aetiology, fevers, altered mental status and refractory cytopenias. His case posed a diagnostic challenge because evaluation of septic shock in the setting of advanced AIDS requires a time-consuming work-up for broad infectious aetiologies that can delay consideration of other diagnoses, including primary or secondary haemophagocytic lymphohistiocytosis (HLH). After this patient did not improve with supportive care and empiric antimicrobials, there was concern for HLH given that he met ≥ 5 of the HLH consortium criteria. He underwent bone marrow biopsy, which was non-diagnostic. Empiric therapy for HLH was initiated, but unfortunately, the patient died. Autopsy revealed extensive haemophagocytosis in the spleen, bone marrow and liver, confirming the diagnosis of HLH. Postmortem, his soluble CD-25 returned 18 890 pg/mL (< 1033 pg/mL), and his serum HHV-8 PCR resulted positive. The diagnosis was HLH secondary to Human Herpes Virus 8 (HHV-8) in a patient with advanced AIDS.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory condition characterised by reactive macrophage proliferation and activation leading to cytokine storm. There are both familial and acquired, or secondary, forms, and the secondary form is less well characterised and can derive from a wide array of primary conditions including infection, immunodeficiency such as HIV/AIDS, haematological malignancy or autoimmune conditions.¹ HLH does commonly occur in patients with AIDS and is frequently secondary to either malignancy or opportunistic infection.^{2–3} Diagnosing HLH requires ≥ 5 of the HLH consortium criteria for the diagnosis of HLH: fever, splenomegaly, cytopenia, elevated ferritin, hypofibrinogenaemia/hypertriglyceridaemia, evidence of haemophagocytosis, low natural killer cell activity and increased levels of the interleukin-2 receptor soluble CD-25. These criteria are notoriously non-specific and manifest late in the illness course, making it a challenging and elusive diagnosis. Our case illustrates the challenge in diagnosing HLH: it mimics septic shock and other inflammatory conditions that are far more common and therefore makes it difficult to consider HLH on the early differential diagnosis. Additionally, HLH secondary to HHV-8 is rare and not as well known; there is limited literature on its

epidemiology and management. In review of literature, we found only eighteen cases of HHV-8-related HLH which included both patients with and without HIV/AIDS.^{4–5} Finally, in this case, HLH secondary to HHV-8 was a postmortem diagnosis, which highlights the value of autopsy.

CASE PRESENTATION

A man in his mid-40s with AIDS, with last CD4 count of 31 cells/ μ L and last viral load of 349 copies/mL, presented with 5 days of recurrent fevers up to 40°C, rectal pain and watery diarrhoea. He had restarted antiretroviral therapy approximately 2 weeks prior, after a period of prolonged non-compliance. He denied other medical conditions, surgeries, sick contacts, travel and alcohol, drug or tobacco use. He was sexually active with men and had multiple sexual partners. His home medications included abacavir/dolutegravir/lamivudine, atovaquone, azithromycin, valacyclovir, pantoprazole and folic acid.

On examination, he was noted to be hypotensive (blood pressure 90s/50s mm Hg), tachycardic (heart rate 130s/min) and febrile (oral temperature 39.5°C). He was drowsy, displayed anasarca with bibasilar crackles, ascites, lower extremity pitting oedema and splenomegaly palpable 4–5 cm below the costal margin. He did not have any skin rashes.

The patient was admitted to the intensive care unit (ICU) for resuscitation, pressor support and broad spectrum antibiotics including intravenous vancomycin, levofloxacin and piperacillin-tazobactam. Initial work-up is summarised below.

INVESTIGATIONS

Initial laboratory evaluation was notable for CD4 count of 17 cells/ μ L, HIV viral load of 33 copies/mL, haemoglobin 7.9 g/dL; leucocyte count of 3.6×10^9 /L and platelet count of 126×10^9 /L. Serum ferritin level was 2671 ng/mL. Bacterial blood cultures, urine culture, sputum culture, acid fast bacilli sputum smear $\times 3$, stool culture, stool ova and parasite examination and stool *Clostridium difficile* PCR for toxin B gene were negative. CT scans of the chest, abdomen and pelvis revealed scattered pulmonary and subpleural nodules (< 4 mm in size), bronchial wall thickening and peribronchovascular opacities in bilateral lung bases, mediastinal and hilar lymphadenopathy (largest 1.4 cm), upper abdominal lymphadenopathy (largest 1.5 cm) and splenomegaly (splenic diameter 23 cm) (figure 1).

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Figure 1 CT chest/abdomen/pelvis without contrast. Figure part A is the coronal view and demonstrates hepatosplenomegaly (asterisks); the inset image of this figure demonstrates hepatomegaly in the axial view. Figure part B demonstrates splenomegaly in the sagittal view. Figure parts C and D show significant paratracheal lymphadenopathy (yellow arrows). Figure parts E and F demonstrate bilateral nodular pulmonary infiltrates consistent with Kaposi's sarcoma (yellow arrows), small bilateral pleural effusions and pericardial effusion.

Table 1 Summary of broad infectious work-up performed after second clinical decompensation

Test for bacterial aetiologies		Test for fungal aetiologies	
Legionella urine antigen	Negative	<i>Histoplasma capsulatum</i> Urine antigen	Negative
Acid Fast Bacillus blood cultures	Pending	<i>Blastomyces dermatidis</i> Serum antibody	Negative
<i>Brucella melitensis</i> serum antibody	Negative	<i>Histoplasma capsulatum</i> Serum antibody	Negative
<i>Bartonella henselae</i> antibody	Negative	<i>Coccidioides immitis</i> serum antibody	Negative
Test for viral aetiologies		Fungal blood culture	Negative
Serum Epstein-Barr Virus PCR	Negative	Cryptococcal antigen	Negative
Serum herpes simplex virus PCR	Negative	Beta D glucan assay	Negative
Serum Cytomegalovirus PCR	Negative	Sputum <i>Pneumocystis jirovecii</i> direct fluorescent antibody	Negative
Serum Human Herpes Virus-6 PCR	Negative	Test for parasitic aetiologies	
Parvovirus B-19 PCR	Negative	<i>Strongyloides stercoralis</i> antibody	Negative
Respiratory virus panel		Stool studies:	
Influenza virus	Negative	Shiga toxin, cyclospora, microsporidia, isospora, cryptosporidium, giardia antigen	Negative
Serum Human Herpes Virus-8 PCR (resulted post-mortem)	Positive – 210 000 DNA copies/mL		

He was adequately fluid resuscitated and his clinical condition improved initially; however, his shock recurred and prompted a more extensive infectious work-up detailed in [table 1](#).

A lymph node biopsy could not be performed because of access limitations of image-guided techniques, and the patient was not a candidate for surgical lymph node resection. In light of a negative infectious work-up, the consideration of HLH and haematological malignancy was entertained. A bone marrow biopsy was performed. The specimen was considered suboptimal but revealed a polytypic plasma cell population without immunophenotypic aberrancy (40% of total marrow cellularity), which was not diagnostic of B-lineage non-Hodgkin's lymphoma or plasma cell neoplasm. HLH work-up was initiated. Soluble CD-25 level was 18 890 pg/mL; a repeat serum ferritin was 7125 ng/mL; fibrinogen was 106 mg/dL; and fasting triglyceride level was 131 mg/dL.

DIFFERENTIAL DIAGNOSIS

The patient had advanced AIDS, and there was inevitable ongoing suspicion for opportunistic infection despite the extensive negative work-up. As such, the differential included disseminated mycobacterium avium complex (MAC) and disseminated fungal infection with bone marrow infiltration, given that it would also explain the cytopenias. Additional considerations with respect to non-infectious aetiologies included haematological malignancy, immune reconstitution syndrome, multicentric Castelman's syndrome (MCD) and HLH.

TREATMENT

The patient initially improved and was transferred out of the ICU; however, 1 week later, he developed recurrent high fevers (temperature of 39.5°C–40°C) and hypotension. He also had developed progressive somnolence, disorientation and anaemia and thrombocytopenia, which required frequent blood product transfusions. While completing the infectious work-up above, he was restarted on empirical intravenous vancomycin, piperacillin-tazobactam and levofloxacin in addition to empirical treatment for disseminated MAC with intravenous azithromycin, rifampin and ethambutol while acid fast bacilli blood cultures were in process as well as empirical treatment for disseminated HSV with intravenous acyclovir while the serum HSV PCR was in process. The patient intermittently refused antimicrobial and antiviral therapy and transfusion of blood products; he also refused NG tube placement to supplement nutrition. His course was additionally complicated by unstable supraventricular tachycardia requiring emergent cardioversion.

At this point, there was a high clinical suspicion for HLH given negative thorough infectious work-up and because the patient met almost five of the HLH consortium criteria including recurrent fever, splenomegaly, refractory cytopenias in >1 lineage, elevated ferritin and low fibrinogen with a pending CD-25 level. The patient's HScore at this point in time, calculated using a scoring system that was developed to estimate an individual's risk of having reactive HLH, was 223, which corresponded to a 96.8% risk of having HLH.⁶ Secondary HLH was highest on the differential, and because we did not find an underlying infection or malignancy, high-dose dexamethasone was initiated for empirical treatment of HLH with plans to initiate etoposide within a few days. Shortly afterwards, soluble CD25 resulted as severely elevated 18 900 pg/dL and ferritin had increased to 7125, which was consistent with HLH.

OUTCOME AND FOLLOW-UP

With dexamethasone therapy, the cytopenias briefly improved in that the patient did not require transfusions of platelets and packed red blood cells. However, the patient continued to decline with progressive somnolence, worsening malnutrition and anasarca and worsening renal and liver failure in the setting of recurrent hypotension. In consultation with our haematology colleagues, it was determined that the risks of etoposide in the setting of critical illness with multiorgan dysfunction were too great, so empirical etoposide was not initiated. With continued clinical decline, the patient's family elected for comfort care and he died 2 days later.

An autopsy was performed to determine cause of death. Significant findings included hepatomegaly (liver weight 2540 g), splenomegaly (spleen weight 1260 g) and Kaposi's sarcoma (KS) in both lungs. Other notable findings included generalised icterus and lymphadenopathy. On histology, haemophagocytosis was present in the bone marrow, spleen and lymph nodes (figure 2A–C). In each lung, there was a spindle cell vascular proliferation with extravasated red blood cells, classic histological features of KS (figure 3A,B). HHV-8 by immunohistochemistry performed on a lung section highlighted many of the scattered spindled cells (figure 3C,D). In addition, sections of the spleen, lymph nodes and bone marrow revealed florid polytypic plasmacytosis without plasmablast proliferation (figure 2A–C). The marked plasmacytosis, HHV-8 positivity, advanced AIDS and generalised lymphadenopathy raised the possibility of HHV-8-associated MCD and generated debate regarding the

Figure 2 (A) Bone marrow. This section of bone marrow demonstrates plasmacytosis (green asterisks) and the presence of abundant macrophages, many of which are undergoing haemophagocytosis (green arrows) in a background of trilineal haematopoiesis (double green asterisks). (B) Lymph node: high-power image of a lymph node section shows the same florid plasmacytosis seen in the spleen (inside green circles). Hemosiderin-laden macrophages are also present (green boxes). Haemophagocytosis is also observed (green stars). (C) Spleen: higher power view of spleen section shows marked haemophagocytosis (green arrows), hemosiderin-laden macrophages (green circles) and plasmacytosis (green asterisks).

diagnosis of HLH versus MCD. As such, the case was introduced to and discussed at length between haematopathology at our institution and at the Massachusetts General Hospital. After much discussion, the following considerations were raised: there was indeed a polytypic plasma cell population that could be consistent with MCD but which is not specific to MCD and can be seen in HLH. Review of lymph node, spleen and bone marrow sections demonstrated a lack of plasmablast cell population

Figure 3 (A) Section of lung displaying a vaguely nodular spindle cell vascular proliferation with extravasated blood cells and increased vasculature in a background of emphysematous change. (B) Higher power view of lung demonstrating infiltrative short fascicles of spindle cells with abundant extravasated red blood cells and hemosiderin in between. (C) Immunohistochemistry highlighting the prominent nuclear staining of the spindle epithelial cells in this HHV-8-driven process. (D) Higher magnification image of HHV-8 staining.

which was felt to be unusual for MCD. Additionally, only focal rather than more pronounced vascular proliferation was noted in the lymph nodes, which is atypical of MCD. Finally, there was very scattered to almost no staining of HHV-8 in the lymph node and spleen sections where typically in MCD, there is much more impressive staining for HHV-8. Due to these reasons, the diagnosis of HLH was favoured over the diagnosis of MCD. Interestingly, in our case, the clinical diagnosis of MCD was favoured until autopsy after which the cause of death was deemed to be HLH secondary to HHV-8 in the setting of advanced AIDS. The serum HHV-8 level eventually returned at 210 000 DNA copies/mL, supporting the postmortem diagnosis.

DISCUSSION

This case brings to attention HLH, a life-threatening haematological condition caused by an overwhelming inflammatory response of macrophages leading to a cytokine storm causing clinical symptoms of fever, vasoplegia and cytopenias. The HLH diagnostic criteria are notoriously non-specific and do not become apparent until late in the disease course, making the syndrome a diagnostic challenge and leading to delays in diagnosis and initiation of treatment, as was the case for our patient. HLH occurs more frequently in the HIV/AIDS population and is increasingly recognised as a cause for a septic shock-like presentation among these patients.⁷ While literature on HLH in HIV is limited to case series and retrospective studies, it has been shown that HLH in advanced AIDS is frequently driven by an underlying process ('secondary HLH').⁸ One of the largest case series of HLH in HIV included 58 patients and found that haematological malignancy accounted for 55% of patients while underlying infection accounted for 41% of patients. The most frequently encountered aetiologies of secondary HLH in this case series included Hodgkin's lymphoma, tuberculosis, other B cell lymphoma and MCD.⁸

Another large retrospective case series included 162 HIV and non-HIV-infected patients with HLH and found underlying haematological malignancy (56.8% of cases) to be more common than infection (40% of cases) and again noted Hodgkin's lymphoma, B cell lymphoma and MCD to be the most common underlying causes.³ In this study, infectious aetiologies included bacteria, mycobacteria, viruses such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), toxoplasmosis, leishmaniasis, *Plasmodium falciparum*, *Pneumocystis jiroveci* and histoplasmosis.³ *Mycobacterium tuberculosis* and cytomegalovirus infections were the most common and accounted for 8% and 3.7% of HLH cases, respectively.³ Remaining literature describing reactive HLH secondary to underlying infection is limited to single-centre case series and case reports. For example, there is a single-centre case series of disseminated histoplasmosis causing secondary HLH, one including 11 patients^{9 10}; however, disseminated histoplasmosis was not a frequent cause of HLH in the multicentre 162-patient case series raising the concern that relative frequency of underlying infection may be difficult to ascertain without a multicentre study across national or regional boundaries, reflecting variable prevalence of these infections in different populations. EBV is a more frequently cited trigger of haemophagocytic syndrome with multiple case reports and case series noted in the literature.¹¹⁻¹³ Other herpes viruses, including HHV-8, are less frequently cited in the literature. While MCD is a well-known cause of reactive HLH, HHV-8 associated HLH in the absence of MCD is much less well known, and in our review of the literature, we found a total of 18 adult cases of HHV-8-related HLH that varied significantly in clinical characteristics.

These 18 patients included both HIV-positive and HIV-negative patients as well as patients who had previously received renal transplant. They additionally include both cases of HLH caused by HHV-8 in association with MCD, KS or primary effusion lymphoma (PEL) as well as cases caused by HHV-8 infection in the absence of associated malignancy, like our patient's case.^{4 14–22} It has been shown that HHV-8 viral load correlates with disease activity.^{4 18} Over half of these patients died despite treatment frequently due to delays in diagnosis and, where treatment information is available, 4–5 of these cases demonstrated good responsiveness to etoposide or to foscarnet followed by chemotherapy for KS.^{4 17} The cases of HHV-8-associated MCD were successfully treated with etoposide, rituximab±splenectomy and successfully attained remission.⁵

Unfortunately, our patient's illness had progressed to advanced stages before we could treat him with chemotherapy, and we attribute this at least in part to the delays in diagnosis caused by the bias towards infection and the recommendation by our specialists that infection be ruled out extensively prior to consideration of HLH. Subsequently, we were hesitant to initiate etoposide because of concern regarding the toxicities of chemotherapy in a critically ill patient and preferred to trial dexamethasone first to help mitigate chemotherapy associated risks and still assess the clinical response to treatment. By the time the decision was made to treat HLH empirically with etoposide, the patient's disease process had progressed too far to be reversible. The challenge in treatment-related decision making is that at present, there is little consensus on treatment of secondary HLH, which is usually handled on a case-by-case basis. Occasionally, no immunosuppressive or cytotoxic therapy is necessary.^{9 23 24}

Our case is important because it reintroduces HHV-8 as an important cause of HLH in the patient with advanced AIDS, where other opportunistic infections have been ruled out. It demonstrates the diagnostic challenge that HLH poses in a patient with advanced AIDS when the risk of infection is high

and so the tendency to diagnose septic shock is high. Though treatment methods are suggested by the literature, initiating treatment posed a challenge at first because of diagnostic uncertainty and, subsequently, because of the patient's critical illness and multiorgan dysfunction. Finally, it illustrates the value of autopsy in providing diagnostic clarity. Our postmortem clinical suspicion for HHV-8-associated MCD was high, but on autopsy, was felt to be much less likely than primary or reactivation HHV-8-associated HLH. We propose that providers maintain a high index of suspicion for secondary HLH in patients with AIDS and consider viral aetiologies, which may not be readily apparent on presentation and so cannot easily be ruled out. Holding treatment to identify the trigger for HLH can lead to progressive illness and death, as it did in our patient.

Contributors All authors were involved in the conception and design, acquisition and analysis of data, drafting the article or revising it critically for important intellectual content and gave final approval of the version published.

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Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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Learning points

- Haemophagocytic lymphohistiocytosis (HLH) is a relatively rare hyperinflammatory disorder diagnosed by meeting five or more of the following eight criteria: recurrent fever, splenomegaly, cytopenia involving >1 cell line (hemoglobin <9 g/dL, absolute neutrophil count <100/μL, platelets <100 000/μL), hypertriglyceridaemia (fasting triglyceride >2.0 mmol/L or >3 SD above normal value) or hypofibrinogenaemia (fibrinogen <1.5 g/L or >3 SD below the normal value), haemophagocytosis on biopsy of bone marrow/spleen/lymph nodes, low or absent natural killer cell activity, serum ferritin >500 μg/L and elevated soluble interleukin-2 (CD25) levels (>2400 U/mL or very high for age).
- HLH frequently occurs in immunosuppressed populations and among patients with HIV/AIDS; HLH is most frequently driven by underlying malignancy or infection.
- HHV-8, particularly in the absence of multicentric Castleman's syndrome, is a rare cause of HLH that should be recognised.
- Limited literature on HHV-8-associated HLH suggests good responsiveness to etoposide-based therapies, but these need to be initiated before critical stages of illness course to be effective.
- As such, early diagnosis of HLH is important, and a high index of suspicion should be maintained by clinicians.

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