Human herpesvirus-8 related hemophagocytic lymphohistiocytosis with Kaposi sarcoma in an immunocompetent HIV negative adult

Talal Alnabelsi, Cecilia Jang, Ramzi Mulki, Amin Benyounes, Manju Balasubramanian, Mark Morginstin

ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening disorder characterized by proliferation of the mononuclear phagocytic system resulting in marked hemophagocytosis. While HLH may occur as a consequence of a herpes viral infection, this usually arises in immunocompromised individuals. We report a rare case of HLH with Kaposi sarcoma triggered by human herpesvirus-8 (HHV-8) infection in an immunocompetent adult.

Case Report: Our patient is a 58-year-old male with a recent diagnosis of Kaposi sarcoma of his lower extremities hospitalized for fever, chills and night sweats. Evaluation revealed pancytopenia, splenomegaly, diffuse lymphadenopathy and Kaposi sarcoma on lymph node biopsy in the absence of HIV infection. Investigations also revealed hemophagocytosis on bone marrow examination. A diagnosis of secondary Hemophagocytic Lymphohistiocytosis was made and the patient was initiated on etoposide and steroids with marked improvement of symptoms and blood counts. One month later, he was hospitalized for high grade fevers and was again found to be pancytopenic and septic with multi-organ failure. The patient's condition rapidly deteriorated and he succumbed to his illness five days later.

Conclusion: Hemophagocytic lymphohistiocytosis is a rare and devastating condition typically arising in immunocompromised individuals. Our patient had non-specific symptoms in addition to pancytopenia and lymphadenopathy in the setting of Kaposi sarcoma. While this may seldom be compatible with an HHV-8 infection, a thorough search revealed associated HLH. Although extremely rare, HLH should be considered in immunocompetent patients with HHV-8 related manifestations particularly in the presence of pancytopenia.
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Keywords: Hemophagocytosis, Kaposi sarcoma, Immunocompetent, Human herpesvirus-8

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening disorder characterized by proliferation of the mononuclear phagocytic system resulting in marked hemophagocytosis; macrophages engulfing hematopoietic cells. Familial and acquired forms of this disorder are recognized. Primary HLH refers to familial cases with underlying genetic abnormalities. Acquired forms on the other hand, are attributed to underlying infections, malignancy or autoimmune conditions. Infection-associated HLH has been documented in viral, bacterial, fungal and parasitic infections. The most notable viral cause of hemophagocytosis is Epstein-Barr virus. Human herpesvirus 8 (HHV-8), typically associated with Kaposi sarcoma, multicentric Castleman disease (MCD) and primary effusion lymphoma, is very rarely associated with HLH [1]. HHV-8 related HLH occurs mainly in immunocompromised hosts, such as post-transplant or HIV-positive individuals. Here we report on an unusual presentation of HLH related HHV-8 infection with KS in an immunocompetent, HIV negative adult.

CASE REPORT

Our patient is a 58-year-old Mediterranean male with a recent diagnosis of KS. Two months prior to his admission, the patient sought a podiatrist for abnormal skin findings on his lower extremities. He first noticed the lesions 12 months ago on his right lower back and several more developed on his lower extremities over time (Figure 1). The lesions were small and hyperpigmented papules scattered throughout both legs and feet. The largest lesion on his right foot was biopsied which showed KS with positive immunohistochemical staining for HHV-8. He was instructed to follow-up with a specialist for further workup. He then became symptomatic in the interim and presented to our hospital.

The patient presented with fevers, chills, malaise and night sweats. He also reported progressive weakness, dizziness and worsening pain in his lower extremities. His past medical history besides the recent diagnosis of KS was unremarkable. He denied receiving corticosteroids or immunosuppressant medication.

The patient was originally from Italy, but moved to the United States 10 years ago. He is recently unemployed and lives with his wife in Philadelphia, Pennsylvania. He had no allergies to medication or food substances. His family history was not significant for any hematological or oncological diseases. He was not a smoker and denied substance abuse or unprotected sexual exposure.

Vital signs on admission were: temperature 38°C, peripheral pulse 95/bpm, respiratory rate 16/min, blood pressure 102/50 mmHg. Physical examination revealed marked conjunctival pallor, inguinal lymphadenopathy, splenomegaly and hyperpigmented papules on his lower extremities. The lymph nodes were large, firm but non tender with no overlying skin changes. Respiratory and cardiac examination was unremarkable. The patient was admitted to the medical floor for further workup.

Admission labs were noted as hemoglobin of 8.5 g/dl, white cell count of 3.9x10^9/μl, platelet count 122x10^9/μl. Serum electrolytes, coagulation studies, liver and kidney function tests were all normal. Multiple HIV tests (antibody and antigen-ELISA) were performed with negative results. The peripheral smear revealed a normal distribution of granulocytes with normal red blood cell morphology. An anemia panel revealed a markedly elevated ferritin 3465 ng/ml (22–275 ng/ml). Fasting triglyceride levels were also noted to be high at 336 mg/dl (0–150 mg/dl). A search for an acute infectious etiology was unrevealing.

Computed tomography scan of the chest, abdomen and pelvis showed extensive lymphadenopathy and splenomegaly. A subsequent positron emission tomography (PET) scan revealed metabolically active lymph nodes throughout the chest, abdomen and pelvis. The patient then underwent an excisional biopsy of a right inguinal lymph node. Immunohistochemical staining was positive for HHV-8 and the findings were compatible with KS. There was no evidence of lymphoma

Figure 1: Hyperpigmented papules representing Kaposi sarcoma.

Figure 2: Bone marrow sample showing hemophagocytosis (arrow).
above eight criteria. Viral serology for EBV, CMV and HHV-6 were all negative.

Due to his persistent pancytopenia and unusual characteristics of symptoms a bone marrow biopsy was performed. Biopsy findings were consistent with a hypercellular marrow and hemophagocytosis with no evidence of lymphoma (Figure 2).

The patient met many of the diagnostic criteria for secondary HLH (Table 1), which in his case was triggered by an underlying HHV-8 infection. After consultation with the hematology and oncology service, the patient was started on the HLH-94 protocol regimen consisting of a 14-day course of 20 mg IV dexamethasone and three cycles of 300 mg of etoposide [2]. He also received supportive care with packed red blood cell transfusions.

The patient's constitutional symptoms and blood counts improved and he was discharged with planned outpatient evaluation for hematopoietic stem cell transplantation (HSCT). A month later while still undergoing etoposide chemotherapy, he presented to the emergency department with malaise and high grade fevers. He was found to be pancytopenic (hemoglobin 4.8 g/dl, WCC 0.6x10³/μl, platelet count 32x10³/μl) and in septic shock with multi-organ failure. He also had elevated ferritin 4813 ng/ml and triglycerides 1319 mg/dl. The patient was started on empiric antimicrobial therapy (intravenous vancomycin and piperacillin/tazobactam) and was admitted to the intensive care unit for circulatory and respiratory support but succumbed to his illness five days later.

### Table 1: Diagnostic criteria for HLH adopted from Henter et al. [6].
A diagnosis can be established if the patient has a molecular diagnosis consistent with HLH or fulfills at least five of the above eight criteria.

<table>
<thead>
<tr>
<th>2004 Diagnostic criteria for HLH</th>
<th>Criteria fulfilled in index case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Yes</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Yes</td>
</tr>
<tr>
<td>Cytopenia affecting ≥ 2 cell lineages:</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; 9 g/dl</td>
<td>Yes</td>
</tr>
<tr>
<td>Platelet &lt; 100 x 10³/dl</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutrophils &lt; 1,000/dl</td>
<td>No</td>
</tr>
<tr>
<td>Fibrinogen &lt; 1.5 g/L or</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypertriglyceridemia (≥256 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Ferritin ≥ 500 μg/L</td>
<td>Yes</td>
</tr>
<tr>
<td>Soluble CD25 ≥ 2,400 U/ml</td>
<td>Not done</td>
</tr>
<tr>
<td>Low or absent natural killer cell activity</td>
<td>Not done</td>
</tr>
<tr>
<td>Hemophagocytosis in bone marrow, spleen or lymph nodes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DISCUSSION

Hemophagocytic lymphohistiocytosis is broadly classified into familial cases and secondary cases, typically triggered by underlying infections. The familial cases are further divided into two groups: familial hemophagocytic lymphohistiocytosis (FHL) and immune deficiencies such as Chediak–Higashi syndrome. The FHL usually presents in infants or young children with hepatosplenomegaly and pancytopenia. This form of HLH is caused by defects in immune regulation, such as mutations in genes controlling the function of cytotoxic T-cells and NK-cells [3]. Interestingly, even patients with genetic defects for HLH often have an infectious trigger to HLH in keeping with the two-hit hypothesis required for the development of many diseases [3].

The pathophysiology of HLH involves defective cytotoxic T-cell function coupled with unregulated macrophage activity leading to excessive cytokine production, immune dysregulation and tissue damage [3]. Of particular merit is IL-6, a cytokine reported to be involved in the pathogenesis HHV-8 associated disease [4]. The exact mechanism of virus mediated HLH is not clear. It has been hypothesized that the proliferation of HHV-8 infected plasmablasts might result in a cytokine storm leading to viral associated HLH, a mechanism similar to EBV-associated T cell lymphoproliferative disorder [5]. However, the trigger of HHV-8 reactivation has not been elucidated.

The diagnosis of HLH should be based upon the published diagnostic criteria used in the HLH-2004 trial [6]. Our patient had evidence of pancytopenia on laboratory investigations as well as markedly elevated ferritin and triglyceride levels. The key for our diagnosis was the demonstration of hemophagocytosis on bone marrow examination. We did not feel the need to pursue additional testing including soluble CD25 levels and natural killer cell activity because we were confident we reached a firm diagnosis.

We hereby report the fifth case of HHV-8 associated HLH in an immunocompetent, HIV negative adult. Li et al. were the first to report a case of HHV-8 related HLH in an immunocompetent, HIV negative individual with MCD [5]. Re et al. reported two more cases in immunocompetent patients but in the absence of HHV-8 related conditions [7]. A more recent article reported HLH secondary to HHV-8 in a patient with both MCD and KS [8]. Our patient had no history suggestive of immunodeficiency or malignancy and had developed KS twelve months prior to the discovery of HLH. All the patients mentioned in the cases above, including our patient, suffered a rapid and fatal clinical course.

Treatment of HLH is aimed at suppressing the hyperinflammatory state that leads to end organ damage. Treatment regimens vary according to the cause of HLH. Infection-associated HLH is usually managed by treating the underlying cause along with the standard HLH-94 protocol consisting of high dose steroids and...
etoposide [2]. It has been shown that early introduction of etoposide is the only significant variable for improved survival [3, 9]. Nevertheless, HSCT remains the only hope for permanent control or cure of the disease [10]. Its main utility is in familial HLH, although many cases of acquired HLH should be treated with HSCT. Our patient received the appropriate therapy for HLH; however, as a result of pancytopenia these patients are prone to infections and bleeding episodes. He unfortunately died after developing severe sepsis syndrome with multi-organ dysfunction refractory to therapy with antibiotics, blood products and inotropic support.

CONCLUSION

Our patient expired despite being on evidence-based treatment for HLH. This not only highlights the aggressive nature of the disease and high mortality rates but also the need for improved therapy for these patients. Additionally, HLH presents with non-specific signs and symptoms resulting in delayed diagnosis. Therefore, HLH should be considered as a complication of HHV-8 infection particularly in the presence of pancytopenia, even in immunocompetent patients. We aim to raise awareness of this condition, as early recognition is crucial for any reasonable attempt at curative therapy to be made.

Author Contributions

Talal Alnabelsi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Cecilia Jang – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Ramzi Mulki – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Amin Benyounes – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Manju Balasubramanian – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Mark Morginstin – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

REFERENCES

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