Fulminant HHV-8 Associated Castleman's Disease in a Non-HIV, Kaposi Sarcoma Patient with Borderline Hemophagocytic Syndrome

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The ability to establish the etiology of fever of unknown origin (FUO) during the first days in hospital is still lacking. This is related, in part, to the fact that both serologic test results and pathologic diagnoses are far from being immediate. In the following case presentation, the combination of the patient's history, clinical course, serologic test results and pathology findings led to the clinical diagnosis, which, unfortunately, still did not help save the life of our patient.

PATIENT DESCRIPTION

A 59 year old male, Jewish of Persian descent, was admitted to our department due to fever as high as 38.4°C over 3 weeks. The fever was accompanied by shortness of breath, non-productive cough and night sweats. Upon admission, his history suggested that the febrile disease began soon after a dental procedure. Also, prior to admission, the patient had been taking antibiotics for suspected community-acquired pneumonia (sequential amoxicillin, cefuroxime and even ceftriaxone were given in an ambulatory setting) without resolution of his febrile illness. While still in an ambulatory setting, a chest computed tomography (CT) scan was performed, which showed generalized lymphadenopathy, splenomegaly and bilateral pleural effusions. Three days prior to hospitalization bipedal edema appeared and general symptoms of weakness became worse, including fatigue, anorexia, dizziness and orthostatic reactions.

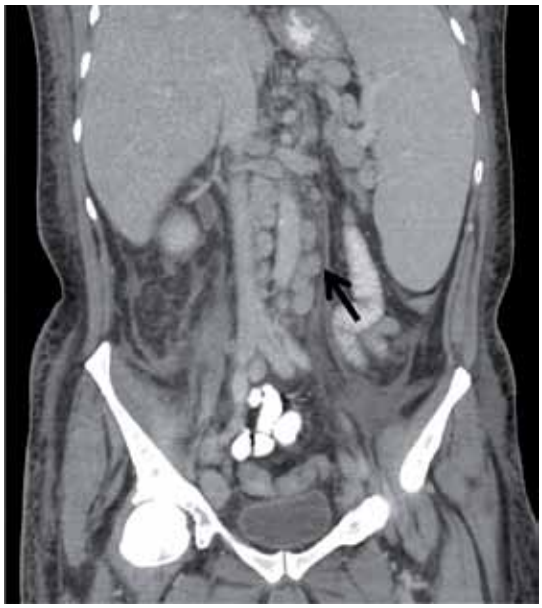
The patient's past medical history included untreated Kaposi sarcoma diagnosed 1 year prior to the current hospitalization. Kaposi sarcoma was diagnosed by a biopsy taken from a pigmented lesion on the patient's foot, found to be positive for human herpes virus 8 (HHV-8). Several subsequent serologic tests for human immunodeficiency virus (HIV) were negative. On admission the patient looked exhausted. Physical findings included enlarged, non-tender, firm lymph nodes at both the submandibular area and bilateral neck triangles. Bipedal edema was significant and there were no signs of endocarditis.

Based on the initial impression of an association between the patient's dental surgery and febrile disease, an FUO workup was initiated aimed at eliminating the possibility of endocarditis. Initial laboratory results demonstrated microcytic hypochromic anemia (hemoglobin concentration 8.5 g/dl, mean corpuscular volume 78 fl), kidney injury (serum creatinine 1.39 mg/dl and serum urea 47 mg/dl), and an anomaly on liver function test [both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were moderately increased, 127 IU/L and 106 IU/L respectively, and blood albumin was significantly low, 2.5 g/dl]. Lactate dehydrogenase (LDH) levels were within the normal range (186 IU/L). Multiple blood cultures were negative for bacteria, even after a long period of incubation. Virology workup included serologic tests for HIV, cytomegalovirus and Epstein-Barr virus, and all were negative for acute infection. Initial screening for autoimmunity was also negative [including tests for antinuclear antibody (ANA), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and perinuclear ANCA (p-ANCA)].

In parallel to our attempts to rule out infection, studies were conducted to eliminate the viable possibility of hematologic malignancy (these efforts were accelerated after a repeat history taking revealed that the fever was already present prior to the dental surgery): chest and abdominal CT scan were performed [Figure 1]. Both cervical lymph node and bone marrow biopsies were performed. Initial pathologic results of the lymph node did not show signs of malignancy, and the bone marrow demonstrated polymorphic, three-lineage hyperplasia with approximately 10% plasma cells infiltrate and no evidence of hemophagocytosis.

A few days after hospitalization the patient's condition deteriorated: fever exceeded 39°C and was accompanied by severe rigors. Progressive pancytopenia appeared with deterioration of kidney and liver function tests. During that time, empiric antibiotics were administered since the CT scan interpretation could not rule out a pulmonary alveolar infiltrate. Nevertheless, both ceftriaxone and doxicillin did not alter the course of disease and were soon stopped. The patient

Figure 1. Coronal view of a CT scan of the abdomen shows enlargement of the spleen and retroperitoneal lymphadenopathy (black arrow)



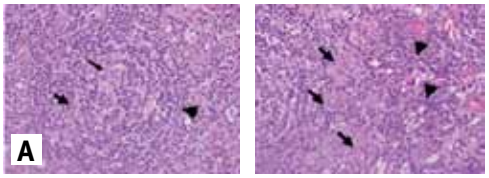
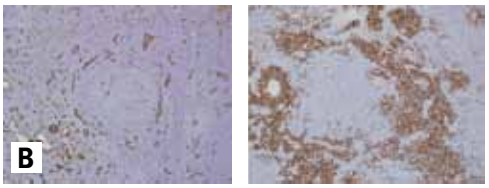


Figure 2. [A] On the left, lymphoid follicle containing blood vessels (thin arrow) and a penetrating venule (thick arrow). The mantle zone shows lymphocytes arranged in concentric rings (arrowhead). On the right, the inter-follicular area is rich in blood vessels (arrows) and plasma cells (arrowheads). Part of a follicle is present in the left part of the figure. (Hematoxylin & eosin. x400)



[B] Right axillary lymph node pathology: on the left, Factor VIII immune-staining highlights the rich vasculature around the follicle. On the right, dense aggregates of plasma cells are present around the follicles and are immune-stained by CD138 (immunoperoxidase stains x100)

deteriorated further and adult respiratory distress syndrome developed. At this stage, with imminent respiratory failure, he was admitted to the intensive care unit (ICU).

Upon admission to the ICU invasive ventilation was initiated and the patient's respiratory state was stabilized. The differential diagnosis at that time included hemophagocytic syndrome (HLH, hemophagocytic lympho-histiocytosis). This diagnosis, however, was not considered final and did not lead to an HLH-specific therapy, mainly because HLH criteria were only borderline for diagnosis and, in fact, some were abating. In that regard, ferritin level, which was initially 1181 ng/ml, decreased to 900 ng/ml; levels above 3000 ng/ml are more HLH-specific [1]. Blood count results were only borderline lower than the cutoff limit used for diagnosis. Finally, an alternative diagnosis that was consistent with the entire clinical and laboratory picture was determined by the final lymph node pathologic result which showed a variant of Castleman's disease, with some plasmoblastic features demonstrating a very high burden of HHV-8 virions within the lymph node [Figure 2].

The patient was immediately started on high dose steroid and rituximab therapy.

During his stay in the ICU, the patient was treated with the following combination: rituximab as treatment for Castleman's disease, gancyclovir as an anti-viral anti-HHV-8 agent, wide-spectrum antibiotics for both gram-positive and negative bacteria, and amphotericin as an antifungal agent.

Due to acute kidney injury and despite low blood pressure, use of continuous venous-venous hemodialysis was initiated. During the following days, a profound liver injury developed: blood total bilirubin exceeded 48 mg/dl. Ultrasonography refuted intra- or extrahepatic bile duct obstruction, and CT scan ruled out portal and hepatic vein thrombosis. In the subsequent days numerous blood products were infused due to profound thrombocytopenia, and severe hepatic and renal failure. The patient died 28 days after hospitalization.

COMMENT

The patient died due to an aggressive lymphoproliferative disease with borderline characteristics of hemophagocytic syndrome against a background of an infection with HHV-8. The following cause and effect scheme is suggested: Chronic infection by HHV-8 is an established causative agent for Kaposi sarcoma [2], some variants of lymphoma [3] and variants of Castleman's disease [3]. The relevant pathophysiology involves cytokine dysregulation by the presence of virions and subsequent proliferation of B lymphocytes infected by HHV-8. Accordingly, rituximab, a monoclonal antibody targeting B lymphocytes, was demonstrated to be effective, among other effects, in reducing the lymphadenopathy burden associated with diffuse Castleman's disease. Castleman's disease is characterized by diffuse lymphadenopathy (with angiofollicular hyperplasia within affected lymph nodes), hepatosplenomegaly and constitutional symptoms including fever, fatigue and weight loss. The coexistence of Castleman's disease and Kaposi sarcoma occurs in up to 82% of Kaposi sarcoma patients [2]. The pace of disease development in multicentric Castleman's disease is variable, and a rapidly progressive form that can lead to death within weeks was found to be more common in

HIV-infected patients [4]. The presence of both Kaposi's sarcoma and HHV8+ multicentric Castleman's disease in an HIV-negative patient is quite rare and suggests the presence of an underlying immune deficiency [5] which was not previously recognized in our patient.

CONCLUSION

Investigation of the FUO patient might transform from the urgent to the emergent. The present case signifies the possible hemophagocytic syndrome as a catastrophic event, culminating both infectious and malignant pathologies, even when not all diagnostic criteria are fulfilled.

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