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OBSERVATION

Human Herpesvirus 8-Associated Inflammatory Cytokine Syndrome

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Human herpesvirus 8 (HHV8) is the etiological agent of Kaposi sarcoma (KS), primary effusion lymphoma, human immunodeficiency virus (HIV)-associated multicentric Castleman disease (MCD), and the recently described KS herpesvirus-associated inflammatory cytokine syndrome (KICS).¹⁻⁴

Report of a Case

A man in his 50s with HIV infection and under-going antiretroviral therapy with stable immunestatus developed a progressive KS in spite of pegylated-liposomal doxorubicin treatment (Figure). He presented with self-resolving episodes of high fever, respiratory distress, hemodynamic instability, pancytopenia, and acute-phase reactant elevation. Although these indications were initially interpreted as infectious processes, no microorganisms were isolated, and soon hemophagocytic lymphohistiocytosis (HLH) was demonstrated.



Figure. Kaposi Sarcoma Lesions. Erythematoviolaceous plaques involving the patient's legs.

By nested polymerase chain reaction analysis, HHV8 viremia peaks were evidenced to coincide with the successive episodes of pancytopenia, hypertriglyceridemia, hyperferritinemia, hepatosplenomegaly, elevation of CD25, and bone-marrow hemophagocytosis. Image tests and histopathologic findings excluded MCD; thus, the diagnosis of KICS was established. In light of the rapid disease progression, rituximab and valganciclovir were added to the therapeutic regimen achieving a good response, with no more HLH episodes. Patient remained in remission at 1-year follow-up.

Discussion

Just as with other herpesviruses, HHV8 has a latency phase and a lytic phase. During the lytic phase, the whole genomic machinery is deviated toward the production of viral proteins, including the codification of a viral interleukin (vIL).^{1,2,4} This vIL-6 and its homologous human IL-6 are believed to initiate a host's cytokine cascade, inducing a disproportionate inflammatory response in patients with HIV-related MCD.²⁻⁴ In 2010, Uldrick et al⁴ noted the existence of a group of 6 patients with HHV8 and HIV coinfection whose symptoms overlapped those of MCD but who did not present with the typical lymphadenopathies. However, IL-6 and HHV8 levels in the studied group were comparable to those of an MCD cohort and substantially higher than those in controls with HHV8 infection or KS alone. Consequently, they

described KICS as a separate entity with alleged similar etiopathogenesis to MCD and a high mortality rate (about 50%) (Box).

BOX. KICS Diagnostic Criteria^a

At least 2 clinical manifestations from at least 2 categories (1 A, B, and C) are required for a KICS diagnosis, together with each of the criteria in 2, 3, and 4.

1. Clinical Manifestations

A. Symptoms: fever, fatigue, cachexia, respiratory symptoms (including cough, dyspnea, airway hyperreactivity), gastrointestinal disturbance (including nausea, anorexia, abdominal discomfort, altered bowel habit), arthralgia and myalgia, altered mental state, neuropathy with or without pain.

B. Laboratory abnormalities: anemia, thrombocytopenia, hypoalbuminemia, hyponatremia.

C. Radiographic abnormalities: lymphadenopathy, splenomegaly, hepatomegaly, body cavity effusions.

2. Evidence of Systemic Inflammation

Elevated C-reactive protein levels.

3. Evidence OF HHV8 Lytic Activity

Elevated HHV8 viral load in peripheral blood mononuclear cells (≥ 100 copies/ 10^6 cells).

4. No Evidence of HHV8-Associated MCD

Exclusion of MCD requires pathologic assessment of lymph node, bone marrow, or spleen.

Abbreviations: HHV8, human herpesvirus 8; KICS, Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome; KSHV, Kaposi sarcoma-associated herpesvirus; MCD, multicentric Castlemann disease.

^aAs described by Polizzotto et al³ according to the clinical manifestations from the initial case series and from findings commonly seen in KSHV-MCD.

Furthermore, we have demonstrated the existence of HLH along with the exacerbation periods. Herpesviruses are known etiological agents of HLH, and there are several HHV8-related cases in the literature, not only in patients with HIV but also those with congenital immunodeficiency or transplant recipients.⁵ Fardet et al⁵ describe a series of 5 patients with HIV who experienced recurrent episodes of HLH coinciding with reactivations of their HHV8 infection. The clinical picture recounted by these authors resembles that of the present case and the one described as KICS. In our opinion, the existence of HLH could justify all KICS clinical manifestations. KICS, MCD, and HHV8-related recurrent HLH could be considered different manifestations of the same disease spectrum mediated by lytic reactivation of KS herpesvirus.⁶ The researchers characterize the condition by a systemic inflammatory response in addition to leuk syndrome features, with edema and pulmonary infiltrates leading to respiratory distress and eventual death.^{1,3,4}

We believe that KICS might be underdiagnosed, mistaken for septic shock in immunocompromised patients. There are no standard recommendations for its management,

though a parallel approach to MCD seems logical, trying to maintain the balance between immunosuppression and tumor control.¹ The refractory nature of KS is a constant, probably in relation to IL-6 promotion of spindle-cell proliferation. The combination of the anti-CD20 agent rituximab, targeting the B-cell viral reservoir,⁴ PLD directed to KS suppression, and the antiviral drug valganciclovir³ led to prolonged remission in the present case. New therapies such as tocilizumab or sirolimus may represent a future alternative.^{1,3} Dermatologists should be aware of HHV8-related diseases and suspect KICS when they find recalcitrant KS and febrile episodes of unknown origin. Early detection and treatment can substantially improve survival chances.

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