Multicentric Castleman's disease and HIV

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Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder found with a higher frequency in HIV-seropositive patients. Human herpes virus 8 is found in virtually all cases of HIV-associated MCD. The majority of cases of MCD in patients with HIV are also associated with Kaposi's sarcoma. The dysregulated production of human IL-6 is thought to be an important factor in the pathogenesis of MCD. HIV-seropositive individuals with MCD have a significantly greater risk of developing non-Hodgkin lymphomas than their HIV-seronegative counterparts. MCD occurring in HIV patients has been associated with a poor prognosis. With newer therapy regimens, it is hoped that the prospects of HIV-infected patients with MCD will improve.

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder. It is found with a higher frequency in patients with HIV infection and is associated with systemic symptoms and a poor prognosis. We present the case of a 43-year-old man with HIV receiving antiretroviral therapy. A week prior to admission, he developed symptoms of fever, myalgias, and malaise. He had extensive lymphadenopathy, and a lymph node biopsy revealed human herpes virus 8 (HHV-8) MCD. MCD is discussed in the setting of HIV infection.

CASE PRESENTATION

A 43-year-old man was first diagnosed with HIV 1 year before presentation. He had been compliant with his antiretroviral therapy. One week before admission, his therapy was changed, as he had become resistant to efavirenz, emtricitabine, and tenofovir, as demonstrated by a viral load plateau. The patient subsequently developed a diffuse rash and fevers up to 100.6°F, initially thought to be drug related. He continued, however, to complain of fevers associated with diffuse myalgias and malaise. On exam, his heart rate was 112 beats/minute and his blood pressure was 99/56 mm Hg. Marked lymphadenopathy was noted in the cervical chains and axillary and inguinal areas bilaterally. The spleen tip was also palpable. Two small Kaposi's sarcoma lesions (biopsy proven) were present on the right lower extremity and seemed to be fading.

Laboratory evaluations revealed a hematocrit of 21%, an HIV viral load of 444 copies/mL, and a CD4 count of 193 cells/mm³. Notably, the patient's HHV-8 titer was >10,000,000

copies/mL. Other relevant laboratory results included an IL-6 > 29.7 pg/mL (normal value < 17.4), positive results on hepatitis B core antibody and hepatitis surface antibody tests, and negative results on hepatitis B surface antigen and hepatitis B viral DNA tests.

On biopsy, the bone marrow was normal with trilineage maturation. A lymph node biopsy revealed pathologic findings consistent with MCD. There were numerous follicles, some of which had penetrating small vessels (*Figure 1a*). Lymphocytes in the mantle zone were arranged in concentric circles (so called "onion skinning"). There was prominent interfollicular vascular proliferation with a pronounced plasma cell infiltrate. The plasma cells expressed IgM and were polytypic by flow cytometric analysis and immunohistochemistry stains. Large cells with vesicular nuclei, prominent nucleoli, and amphophilic cytoplasm (plasmablasts) were present in the mantle layer and interfollicular areas. Focal clusters of these plasmablasts encroached on the germinal centers, forming so-called microlymphomas (*Figure 1b*). HHV-8 was detected in the plasmablasts by in situ hybridization (*Figure 1c*). A test for Epstein Barr virus-encoded small RNA (EBER) was negative. The lesion was considered to be HHV-8-associated MCD with microfoci of large cell lymphoma (microlymphomas).

The patient underwent six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP21) with growth factor support and continues to do well clinically. After two cycles of R-CHOP21 (Day 1: intravenous rituximab 375 mg/m², intravenous cyclophosphamide 750 mg/m², a 24-hour intravenous infusion of doxorubicin 50 mg/m², and intravenous vincristine 1.4 mg/m², with oral prednisone 100 mg on Days 1–5), the patient had a complete clinical regression of all previous mentioned lymphadenopathy. An interim positron emission tomography (PET) scan showed resolution of extensive hypermetabolic activity involving multiple nodal stations above and below the diaphragm. All

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Figure 1. Lymph node biopsy results showing features of Castleman's disease. **(a)** A germinal center with a penetrating blood vessel. H&E $\times 200$. **(b)** Collection of plasmablasts encroaching on the germinal center, forming a "microlymphoma." GC indicates germinal center; PB, plasmablasts. H&E $\times 500$. **(c)** HHV-8 staining in plasmablasts surrounding the germinal center. In situ hybridization $\times 20$.

previously pathologic lymph nodes were normal in size. A PET scan done after completion of chemotherapy showed no residual disease. The patient continues retroviral therapy, and his HIV load is now undetectable. He is also being treated with abacavir/lamivudine for hepatitis B. A follow-up HHV-8 DNA by polymerase chain reaction was <1000 copies/mL. An IL-6 level was not repeated.

DISCUSSION

MCD is a rare, aggressive lymphoproliferative disorder that has a poor prognosis usually requiring systemic chemotherapy (1–4). MCD is commonly associated with HHV-8, an oncogenic herpesvirus, and is most often seen in immunosuppressed individuals infected by HIV type 1 (5). The pathologic features of MCD strongly suggest a chronic antigen stimulation response, and HHV-8 has been found in virtually all cases of HIV-related MCD (6). The presentation is usually nonspecific, resulting in an extensive differential diagnosis that often results in a delay of the diagnosis. The diagnosis is established on the clinical presentation of a lymphoproliferative disorder with evidence of multisystem involvement and the classic histopathology on a lymph node biopsy as described in the case presentation. Those with MCD may develop lesions described previously as microlymphomas composed of plasmablasts. The plasmablasts typically reveal lambda light chain restriction but do not harbor somatic mutations in the rearranged immunoglobulin genes. With disease progression, frank plasmablastic lymphomas may develop (7, 8). It is interesting that these lymphomas are monoclonal, although the immunoglobulin genes remain unmutated (8). Compared with HIV-infected patients without MCD, those with MCD have a 15-fold increased risk of non-Hodgkin lymphomas, with the most common subtype of MCD being HHV-8–positive plasmablastic lymphoma.

It has long been recognized that the features of MCD strongly suggest a secondary antigen proliferation response. It has been hypothesized that an infectious agent could be the triggering antigen for the introduction of a pathological process via abnormal IL-6 production, unregulated by a defective immune

system (9, 10). The IL-6 level in our case was elevated. HIV itself is highly replicated in lymphoid tissue and could play a role in the persistent B-cell activation (11). The IL-6 signaling pathway may play an important role in driving HHV-8-infected naive B cells to differentiate into plasmablasts (12). HHV-8 encodes for viral IL-6, an IL-6 homologue that has many of the biological activities of human IL-6 (13). Furthermore, elevated levels of IL-6 correlate with clinical symptoms and HHV-8 viral load (10, 12).

While the survival of patients with HIV and coexistent MCD and non-Hodgkin lymphoma is generally poor, with a median survival of 48 months (14, 15), there are exceptions. Researchers have documented success in treating patients with HIV-associated MCD with antivirals (16) and in treating AIDS-related lymphoma patients with highly active antiretroviral therapy, rituximab, and chemotherapy (17). Hopefully, the prospects of HIV-infected patients with HHV-8–associated MCD and plasmablastic lymphoma will also improve.

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