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Concurrent HIV viral blips during two episodes of multicentric Castleman disease in an adult on antiretroviral therapy: Implication for HIV persistence

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ABSTRACT

Human herpesvirus-8 (HHV8)-associated multicentric Castleman disease (HHV8-MCD) is a rare non-malignant lymphoproliferative disorder most commonly observed in PLWH. Herein, we describe an HIV-infected adult male from Cameroon with relapsing HHV8-MCD (HIV+MCD). The patient developed constitutional symptoms, diffuse lymphadenopathy, thrombocytopenia and autoimmune hemolytic anemia. Excisional lymph node biopsy findings were consistent with HHV8-MCD. He was successfully treated with corticosteroids and rituximab. One year later, he developed relapsing disease and was successfully treated again with rituximab. Interestingly, HIV viral load blips correlate with MCD flares, suggesting that low-level viremia is linked with T-cell clonal expansion and/or inflammation, rather than a lack of effective antiretroviral therapy. Rituximab either alone or in combination with chemotherapy for aggressive disease is the standard of care, with approximately 95% of treated patients achieving complete remission. Despite highly effective therapy, HIV+MCD often presents with a relapsing and remitting disease course and carries an increased risk for the development of HHV8-associated lymphoma.

Introduction

Castleman disease encompasses a group of rare disorders with heterogeneous clinical presentations, treatments and outcomes. There are two known histopathologic variants - the hyaline vascular and the plasmacytic subtypes – both of which can present as either unicentric or multicentric disease (UCD and MCD, respectively). MCD can be divided into (1) human herpesvirus-8 (HHV8)-associated MCD (HHV8-MCD), (2) idiopathic MCD (iMCD), and (3) polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD [1].

HHV8-MCD is increasingly common in persons living with HIV (PLWH) and is not associated with CD4 count or adherence to antiretroviral therapy (ART) [2,3]. This plasmacytic variant of MCD is linked to HHV8, in combination with cytokine dysregulation [4]. HHV8 replicates within lymph node plasmablasts and induces a cytokine storm mediated by transcription of several viral genes homologous to cellular genes involved in inflammatory pathways including a viral homolog of human IL-6 (vIL-6), which stimulate proliferation of germinal center cells [1].

The worldwide frequency of HIV-associated HHV8-MCD (HIV+MCD) is generally unknown but appears to be increasing in the ART era, however potentially confounded by case-identification bias [3]. Affected patients are typically in their fifth or sixth decades of life without gender predominance [5]. Non-Caucasian ethnicity, in particular Black African, may be a risk factor for the development of disease [3]. Herein, we report a case of a 38-year-old black male living with HIV from Cameroon with relapsing HIV+MCD, whose HIV viral load mirrored the course of relapsing MCD.

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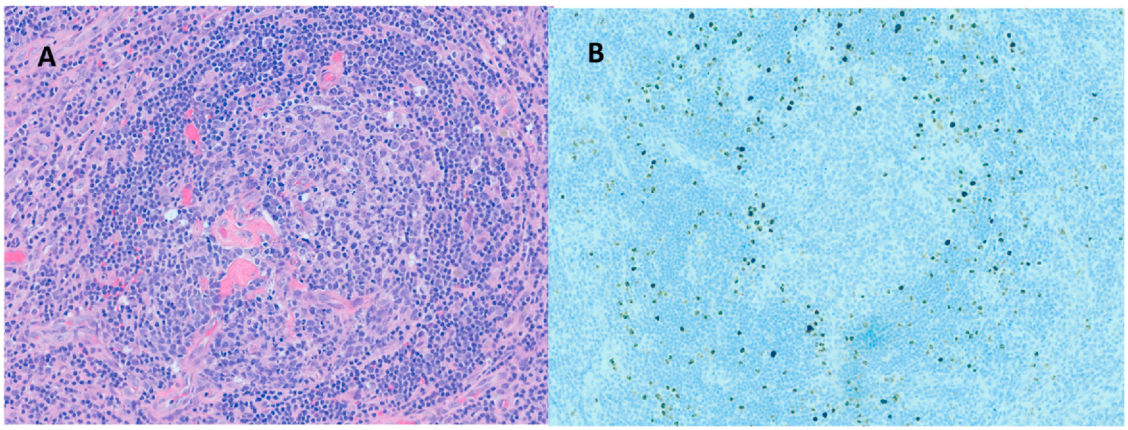

Fig. 1. Axillary lymph node biopsy. Medium power photomicrographs showing (A) hyaline vascular changes in a follicle with mantle cell hyperplasia and (B) HHV-8 positivity in mantle cells and in the periphery of the follicle.

The case

A 38-year-old male from Cameroon presented to McGill University Health Centre, Chronic Viral Illness Service, seeking HIV medical care. The patient was diagnosed with HIV-1 infection nine years prior and was adherent to a lamivudine/tenofovir-disoproxil fumarate/efavirenz single tablet. His CD4 count was 441 cells/uL (16%, CD4/CD8 ratio 0.4) and plasma HIV viral load was 35 copies/mL. Initial blood work revealed an autoimmune hemolytic anemia (AIHA) with a hemoglobin of 76 g/L, reticulocyte count of 6%, haptoglobin of < 0.06 g/L, and a positive direct Coombs test. Leukocyte count was 6.4 × 10^9/L and platelet count was 189 × 10^9/L. Liver enzymes and creatinine were within normal range. The patient was treated for AIHA with prednisone 100 mg (1 mg/kg) PO daily, folic acid 5 mg PO daily, and received trimethoprim-sulfamethoxazole one double strength tablet three times per week for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis as the expected treatment duration was two to three weeks followed by a taper over the following weeks.

Four weeks later, the patient presented to the emergency department with a one-week history of fatigue, dry cough and fever, with a maximum temperature of 39.4 degrees Celsius. Cardiac and respiratory examinations were unremarkable. Bilateral lymphadenopathies were palpable in the occipital, cervical, axillary and inguinal regions. There was evidence of splenomegaly. No skin or oral mucosal lesions were observed. Laboratory investigations revealed a low platelet count at 90 × 10^9/L and an elevated ALT at 216 U/L. Inflammatory markers included an elevated lactate dehydrogenase (LDH) of 336 U/L, a C-reactive protein (CRP) of 182 mg/L and a ferritin of 910.5 ug/L. HIV viral load increased from 35 to 197 copies/mL. Serology was negative for acute toxoplasmosis, hepatitis B, hepatitis C, syphilis, cytomegalovirus, histoplasmosis, and HTLV I/II. A Positron Emission Tomography (PET) scan showed symmetrical hypermetabolic lymphadenopathies on both sides of the diaphragm associated with hypermetabolic splenomegaly, compatible with lymphoproliferative disease. An excisional right axillary lymph node biopsy showed marked polyclonal plasmacytosis, focal hyaline vascular change in follicles and mantle cell hyperplasia (Fig. 1A) with HHV-8 positivity (Fig. 1B), mainly in mantle cells. No clonal B-cell or T-cell rearrangements were identified with molecular studies. These findings are consistent with HHV8-associated multicentric Castleman disease.

Bone marrow biopsy demonstrated mild reactive plasmacytosis with no evidence of bone marrow involvement. The patient was treated with dexamethasone 20 mg intravenously and rituximab 375 mg/m^2 intravenously per week for four weeks. Positivity of HHV-8 PCR in peripheral blood (non-quantitative) became negative after therapy. By this time, the patient had returned to his usual state of health.

One year later, the patient developed periorbital swelling, a pruritic urticarial rash over the torso and fever, with recurrence of cervical and inguinal lymphadenopathies. Compared to eleven months prior, CRP was 126 mg/L from 0.8 mg/L and D-dimer was 4 ng/mL from 2.09 ng/mL. Ferritin was 1252 mcg/L from 374.4 mcg/L two months prior. IgG was elevated at 33.7 g/L (IgA and IgM within normal limits), albumin was low at 34 g/L, LDH was elevated at 333 U/L, and transaminases were elevated with an AST of 84 U/L and an ALT of 122 U/L. HIV viral load increased from 30 to a peak of 367 copies/mL and CD4 count was 444 cells/uL (29%, CD4/CD8 ratio 0.7) from 784 cells/uL (28%, CD4/CD8 ratio 0.6). HHV-8 PCR in blood was positive. Relapsing MCD was treated with prednisone 25 mg orally daily for five days followed by dexamethasone 20 mg intravenously and rituximab 375 mg/m^2 intravenously per week for four weeks. He responded well to treatment, with resolution of fever, adenopathy and HHV-8 peripheral blood PCR positivity. He is currently asymptomatic and in disease remission at his baseline functional status.

Discussion

HIV-associated HHV8-MCD (HIV+MCD) is a rare nonmalignant lymphoproliferative disorder with increased frequency among PLWH. Most cases are described among Caucasian individuals. One study found an increased incidence (per 10,000 patient years of follow-up) for non-Caucasian individuals. This could be related to higher HHV8 seroprevalence in these populations [3]. Clinical manifestations of HIV+MCD include fever and lymphadenopathy in nearly all patients. Splenomegaly, hepatomegaly, and respiratory symptoms/signs occur in most patients [6]. Presentation can range from mild to rapidly progressive disease leading to uncontrolled edema and anasarca. Laboratory features of disease include inflammatory or hemolytic anemia, leukocytosis, thrombocytosis or thrombocytopenia (ITP), elevated CRP, D-dimer, fibrinogen, ferritin and LDH, with hypergammaglobulinemia, and hypoalbuminemia, driven by excessive IL-6 [6].

Rituximab remains the standard of care with approximately 95% of rituximab-treated patients achieving complete remission, when used alone or in combination with chemotherapy e.g. etopiside for aggressive disease [7,8]. Rituximab, an anti-CD20 monoclonal antibody, is effective through its anti-cytokine effect and its depletion of B-cells – the primary reservoirs for HHV-8 – similar to EBV [7]. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, aimed at dampening the overwhelming inflammatory response / cytokine storm implicated in disease pathogenesis, has recently shown moderate efficacy against HHV-8 [9].

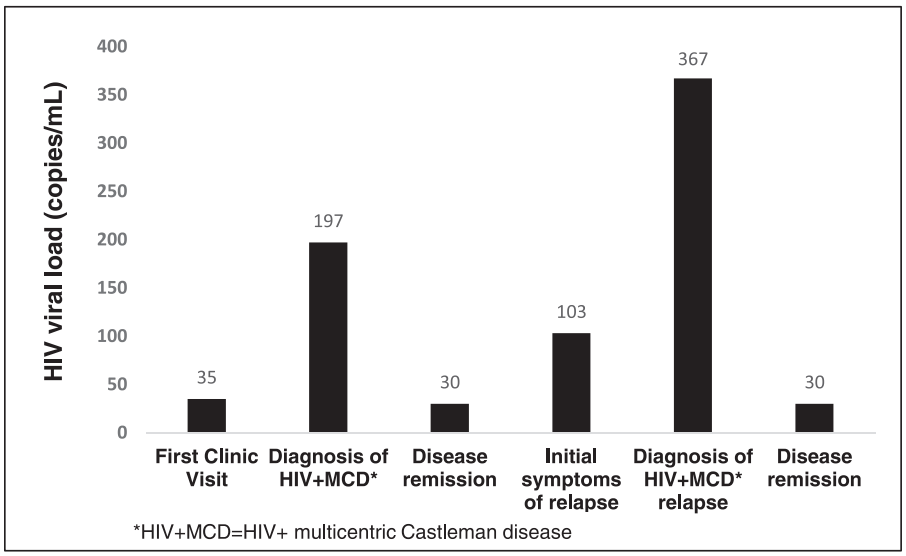

Fig. 2. HIV viral load (copies/mL) at first clinic visit, onset of HIV+multicentric Castleman disease (HIV+MCD) symptoms, HIV+MCD diagnosis, and HIV+MCD disease remission.

Patients with MCD often experience relapsing and remitting disease which can progress to lymphoma. In a study of 46 HIV+MCD patients treated with rituximab, with a median time to follow up of 4.2 years, 8/46 (17%) patients had a first relapse, with a median time to relapse of two years. All recurrences were confirmed histologically. All were successfully re-treated with rituximab alone or rituximab with chemotherapy and in remission at the time of publication. The two and five-year progression-free survival rates for all patients were 85% and 61%, respectively [10]. Pria et al [7]. followed 84 patients with HIV+MCD for a longer median follow-up time of seven years. Eighty out of eighty-four patients (95%) achieved a first remission with either rituximab or rituximab and etopiside. Eighteen out of eighty patients (21%) had biopsy-proven relapsing disease; four of these patients (22%) had concurrent HHV8-associated diffuse large B-cell lymphoma and one patient had concurrent primary effusion lymphoma, extracavity type. Five percent of patients experienced four relapses and 3.5% experienced five relapses [7].

Predicting relapse remains difficult. A detectable HHV8 viral load during remission has been associated with relapse [11]. HHV-8 viremia, age, adherence to ART, HIV viral load, lymphocyte subset counts, and the addition of etopiside chemotherapy for high risk patients, do not predict relapse [7].

HIV is characterized by immune dysregulation which in part persists despite ART [12]. Castleman disease is also thought to be a disorder of immune dysregulation with impaired B and T cell functioning and frequent development of autoimmune disorders [13]. Our patient developed AIHA heralding his presentation of MCD. Although we were unable to measure IL-6 levels, IL-6 induced hyper production can lead to lymphoproliferation and plasma cell differentiation. In addition, cooperation between HHV-8 and EBV, another gammaherpesvirus, can have synergistic effects on tumorigenesis HHV-8 [14].

The temporal association between the two flares of MCD and HIV viral load blips is shown in Fig. 2. This suggests that these blips are linked to T-cell clonal expansion and inflammation rather than a lack of ART potency or adherence. CD8+T cell activation has been shown to increase with disease flares in three patients with IL-6 blockade refractory iMCD [15]. CD8 elevation in persons with well-controlled HIV infection on ART is associated with an increased risk of inflammatory non-AIDS-related clinical events independent of CD4 T-cell recovery [16]. The propensity to develop “blips” is also influenced by the site in the genome where HIV provirus is integrated, with proviruses integrated into non-coding or transcriptionally-repressed regions being less likely to reactivate. HIV proviruses integrated into DNA sites situated much further than accessible chromatin are also less likely to re-activate [17]. Further research is required to understand the role of T-cell clonal expansion and autoantibody production in the pathogenesis of HIV+MCD, in addition to the role of synergy between HHV8, HIV and other viral pathogens.

CRediT authorship contribution statement

Ilyse Darwish: Design, acquisition of data, analysis, interpretation, drafting article, revising article, final approval. **Cecilia Costiniuk**: Analysis/interpretation of data, drafting article, revision of article, final approval. **Nadine Kronfli**: Acquisition of data, analysis and interpretation of data, revising article, final approval. **David Haegert**: Analysis/interpretation of data, figure generation, final review and approval. **Jean-Pierre Routy**: Conception and design, data acquisition, interpretation, critical revision, final approval.

Consent

Consent was provided by the patient to publish this case report.

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Conflict of Interest Statement

ID – no conflicts of interest to declare. CC – no conflicts of interest to declare. NK has received research funding from Gilead Sciences, advisory fees from Gilead Sciences, ViiV Healthcare, Merck and Abbvie, and speaker fees from Gilead Sciences and Merck. DH – no conflicts of interest to declare. JPR – no conflicts of interest to declare.

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