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CASE REPORT

Vinblastine, rituximab and HAART, treatment of an HIV-positive patient with multicentric Castleman's disease

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ABSTRACT

An HIV-positive man from Somalia presented with severe malaise, weight loss, relapsing fever, lymphadenopathy and splenomegaly. An FDG-PET-scan-guided lymph node biopsy revealed the characteristic histological features of the plasma cell variant of Castleman's disease. A high HHV-8 viral load was detected in the serum (7980 copies/ml). Treatment with HAART, rituximab and vinblastine resulted in a full and rapid recovery and lowered HHV-8 viral load to undetectable levels.

KEYWORDS

Castleman's disease, HAART, HHV-8, rituximab, vinblastine

INTRODUCTION

A well-known benign lymphoproliferative disease (LPD) is infectious mononucleosis, induced by the Epstein-Barr virus (EBV) of the γ-herpes family. Another γ-herpes virus is human herpes virus 8 (HHV-8), one of the causes of a much rarer LPD, known as multicentric Castleman's disease (MCD). Both viruses have also been linked to lymphoproliferative disease and lymphoma. Especially immunocompromised hosts such as post-transplantation and HIV-positive patients are susceptible to uncontrolled infection with these viruses and their associated diseases;[1,2] however, MCD also occurs in HIV-negative patients.

Here we describe the case of an HIV-positive man from Somalia with MCD who responded well to treatment with HAART, rituximab and vinblastine. In addition we will give a brief review of the literature. The unicentric hyaline vascular, the unicentric plasma cell and the not otherwise specified variant occur in a different population and are rarely or not related to HHV-8. This case report concerns only the HHV-8-associated multicentric plasma cell and plasmablastic variants.

CASE

A 49-year-old man from Somalia had been HIV-positive since 2004. Because he had always been asymptomatic, and his CD4 count had never dropped below 400 cells/mm^3, antiretroviral therapy had not been initiated.

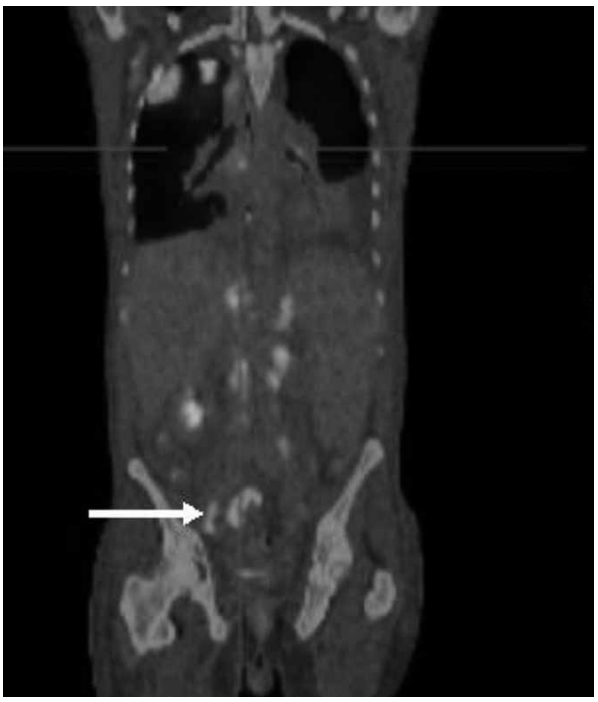
The patient presented with a solitary enlarged lymph node in the neck and marked hepatosplenomegaly. Laboratory examination revealed a normocytic anaemia (haemoglobin 3.7 mmol/l) and a declining CD4 count (290/mm^3).

The differential diagnosis included (opportunistic) infections such as tuberculosis but also malignant lymphoma. A computed tomography (CT) scan of the neck, chest and abdomen revealed pleural effusion, extensive lymphadenopathy and hepatosplenomegaly, but no pulmonary infiltrates or tumours. The Mantoux test proved negative and a biopsy of an enlarged lymph node in the neck displayed no signs of lymphoma, tuberculosis or other opportunistic infection. A bone marrow aspirate revealed an increased number of polyclonal plasma cells, but no signs of other pathology.

Within five weeks the patient's condition deteriorated with a non-productive cough, relapsing fever and severe weight loss (10 kg). The laboratory results revealed a Coombs-positive normocytic anaemia (haemoglobin 4.9 mmol/l), without clinical haemolysis. Also, an elevated C-reactive protein was detected (186 mg/ml). Lactate dehydrogenase was not increased with 204 U/l.

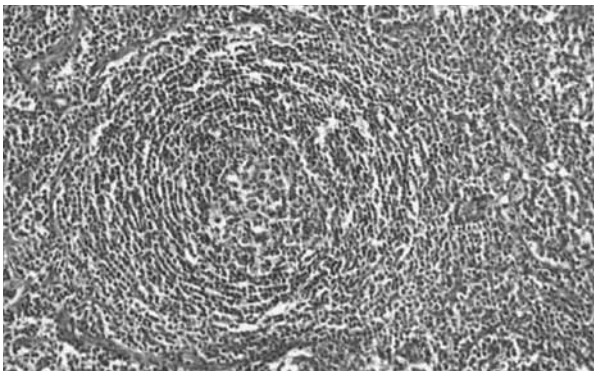
Cytology of the pleural effusion revealed unspecific reactive cells. A second biopsy of an axillary lymph node displayed follicular hyperplasia only. An FDG-PET-scan revealed FDG-PET positive lesions, among which the right axillary lymph nodes (possibly an effect of the second biopsy), and lymph nodes in the right inguinal region (*figure 1A*).
The FDG-PET positive inguinal lymph node was extracted. It showed the characteristic features of the plasma cell variant of Castleman's disease, with hyperplastic follicles surrounded by a concentric mantle of plasma cells (*figure 1B*). The serum load of HHV-8 was 7980 copies/ml. Serum IL-6 was 28 pg/ml (in other HIV-positive MCD patients, IL-6 levels above 4500 pg/ml have been reported).[3]

Figure 1A. *Pet scan*



The PET-scan revealed several hot-spots. The arrow demarks the location of the lymph node that displayed the characteristic features of Castleman's disease.

Figure 1B. *A lymphoid follicle surrounded by a concentric mantle of plasma cells, as seen in the plasma cell variant of Castleman's disease*



Treatment with antiretroviral therapy was started together with a regime containing both vinblastine (6 mg/m^2 three times, once every other week) and rituximab (375 mg/m^2, four times weekly). Within two weeks, after the start of therapy, the patient started to recover; he regained 10 kg of weight and his temperature normalised. Four months after treatment, the HHV-8 viral load was undetectable (<150 copies/ml).

EPIDEMIOLOGY

While the exact epidemiology remains unknown, HHV-8-associated MCD is rare. Despite its relation to immunodeficiency, several studies demonstrate a low CD4 count to be only a minor risk factor.[4,5]

CLINICAL PRESENTATION

Patients generally present with waxing and waning systemic symptoms, such as malaise, fever, weight loss, lymphadenopathy, hepatosplenomegaly and skin rash. HHV-8 is related to Kaposi sarcoma, which frequently occur in MCD patients. Rarely MCD patients present with pemphigus. Cytopenias, raised lactate dehydrogenase and C-reactive protein, as well as increased liver enzymes and hypergamma-globulinaemia are generally found.[6,7] Often, autoimmune anaemia is observed. Bone marrow examination may reveal significant plasmocytosis. Seldom, patients present with a haemophagocytic syndrome.

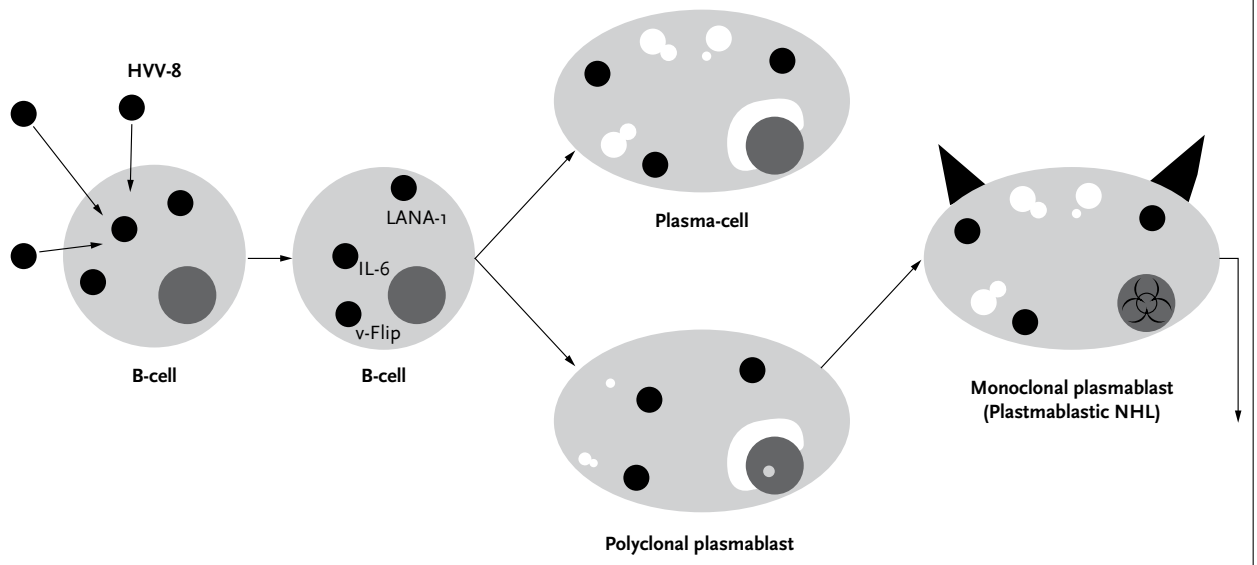
HUMAN HERPES VIRUS 8

The aetiology of plasma cell and plasmablastic MCD involves HHV-8.[8] The virus resides in B-cells, endothelial and epithelial cells, and produces a protein strongly analogous to interleukin 6 (IL-6). When a high dose of IL-6 is infused in mice, plasmocytosis, an expansion of B-cells and organomegaly develop.[9] HHV-8 produces other proteins: v-FLIP, which has antiapoptotic properties and LANA-1, which makes B-cells skip vital steps in the differentiation towards plasma cells.[10,11]

PROGNOSIS

Even though the B-cell proliferation is initially polyclonal, the clinical course of MCD is severe with a high mortality. Most patients eventually die of a SIRS-like syndrome with multi-organ failure.[6,7,12] Chronic proliferation and deviant differentiation of B-cells eventually induce monoclonal plasmablastic non-Hodgkin lymphoma (*figure 2*).

Figure 2. *HHV-8 infects B-cells. Pirating the cell's replication mechanism, it produces several proteins among which IL-6, v-Flip and LANA-1. IL-6 stimulates B-cell proliferation and differentiation into plasma cells. V-Flip and LANA-1 may induce aberrant deviation into plasmablasts, which might eventually lead to the development of a non-Hodgkin lymphoma*



Non-Hodgkin lymphoma has been reported to occur in an estimated 20% of HHV-8-associated MCD patients.[13]

TREATMENT

Evidence is based on small series and case reports; therefore, no standard therapy is defined. Few clinical results on HHV-8-targeting antiviral therapy have been published, but ganciclovir and cidofovir seem to inhibit HHV-8 replication both *in vitro* and *in vivo*.[14,15] Also splenectomy may improve clinical condition and blood count transiently, and could be considered an adjunct to systemic treatment.[11] Recently a case report described complete and lasting remission in an HIV-negative MCD patient after splenectomy without any systemic therapy.[16] Mortality rates among HIV-positive MCD patients were higher in the pre-HAART era than in the HAART era.[5] In a small series of immunodeficient HIV-positive MCD patients, initiation of HAART therapy initially worsened symptoms, possibly related to an immune reconstitution syndrome.[17]

Due to the aggressive nature of MCD and the high risk of subsequent non-Hodgkin lymphoma, chemotherapy is indicated. Moreover, vinblastine and etoposide are known to effectively suppress symptoms.[12,18] When such treatment is stopped, however, MCD generally relapses rapidly. More-toxic CHOP chemotherapy may be effective as well, also in the long run.[19] It must be noted that such intensive chemotherapy is often poorly tolerated by these very ill patients.

Another approach is the use of rituximab, a monoclonal antibody, directed against the CD20 protein on B-cells and plasmablasts. By inducing antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis, rituximab effectively eliminates almost the entire B-cell population.[20]

The two largest studies (n=21 and n=24) on rituximab in the treatment of HIV-positive, HHV-8-associated MCD patients showed promising results in lowering HHV-8 viral load,[21] with disease-free survival rates of 71% after one year in the first study[22] and 95% after two years in the second study.[21] A small number of patients died of progressive MCD, an effect possibly attributable to sudden increases in HHV-8 viral load shortly after administration. Also mild exacerbations of Kaposi sarcoma were reported in both trials during treatment. These results have not been compared in a clinical trial with mild or intensive chemotherapy; however, the results in pretreated patients seem to be better than the results of chemotherapy alone.

The mechanism underlying the beneficial effect of rituximab possibly relates to a reservoir function of B-cells and plasmablasts, essential for the survival and proliferation of HHV-8. What contradicts this is that not all plasmablasts express CD20 and that HHV-8 is also known to reside in epithelial and endothelial cells.

DISCUSSION

Bone marrow or lymph nodes will not always display signs characteristic of MCD. In this case, an FDG-PET scan helped out and ultimately revealed a lymph node of diagnostic value.

When comparing the different treatment modalities available to HHV-8-associated MCD in HIV patients, anti(retro)viral therapy, splenectomy, chemotherapy and/or immunotherapy may be used. The case for chemotherapy is clear, however, intensive chemotherapy is often too toxic for the patient's generally poor clinical condition. Moreover, relatively mild chemotherapy alone induces acceptable response rates and seems to control symptoms. The results of immunotherapy with rituximab are impressive: monotherapy induces long-lasting response after relapse on chemotherapy. The combination of rituximab with mild chemotherapy seems to be effective as a first-line therapy. Because this combination is a relatively nontoxic treatment with favourable results, it seems to be a reasonable first choice.

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