MULTICENTRIC CASTLEMAN'S DISEASE IN 2 PATIENTS WITH HIV INFECTION, UNRESPONSIVE TO ANTIVIRAL THERAPY

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Key-words: Castleman's disease, HIV infection, Herpes virus type 8

ABSTRACT

Two HIV infected patients with multicentric Castleman's disease (MCD) and Kaposi's sarcoma are reported. Both died despite combination antiretroviral therapy including protease inhibitors.

INTRODUCTION

Angiofollicular Lymph Node Hyperplasia, better known as Castleman's disease (C.D.), is a rare and atypical lymphproliferative disorder, of unknown origin. Since the first description by Castleman in 1954, two histologic types have been recognized, the "hyaline vascular" (HV) and the "plasma cell" (PC) variants and a wide variety of clinical syndromes have been described (1).

Among HIV-infected patients, the multicentric form of Castleman's disease (MCD) has always been reported with the histopathological features of the PC variant, or a mixed HV/PC type. HIV-associated MCD presents with similar multisystemic manifestations to those in non HIV-infected patients, but is characterised by a strong association with Kaposi's sarcoma (KS) and usually a poor prognosis (2).

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The newly identified human herpes virus type 8 (HHV-8) is now strongly suspected to represent a transmissible causal agent of MCD, as well as of Kaposi's sarcoma (KS) and of a particular subgroup of non-Hodgkin's lymphoma. HIV infection probably has a synergetic action in this pathogenesis (3-4).

These findings suggest that anti-retroviral and/or anti-herpes treatments may positively alter the course of HHV-8-related diseases.

We report the fatal outcome of two HIV-infected patients with MCD; both of them were treated with combination anti-retroviral therapy and the second one also with foscarnet.

CASE 1

A 39-year-old white Belgian homosexual man was admitted in August 1996 with fever, night sweats, fatigue and dry cough of one-week duration. HIV infection had been diagnosed eight months earlier, because of several KS skin lesions. At that time, he had a CD4 lymphocyte count of 109/mm3. He was initially treated with zidovudine. Three months later, lamivudine and nevirapine were added.

On admission, physical examination revealed fever (39°C), serious pallor, disseminated asymmetric, firm and mobile lymph nodes (1-2 cm) and KS lesions on arms and legs. Laboratory data showed: a hemoglobin of 6,4 g/dl, a white blood cell count of 5200/mm^3, a platelet count of 150000/mm^3, a CD4 lymphocyte count of 180/mm^3 and a viral load of >750000 copies/ml. A computerised tomography of chest and abdomen revealed multiple mediastinal, hilar and para-aortic lymphadenopathies, a limited peritoneal effusion, but no hepatosplenomegaly. No opportunistic infection could be demonstrated.

A biopsy of a supraclavicular lymph node showed a widely expanded interfollicular area (fig. 1) containing

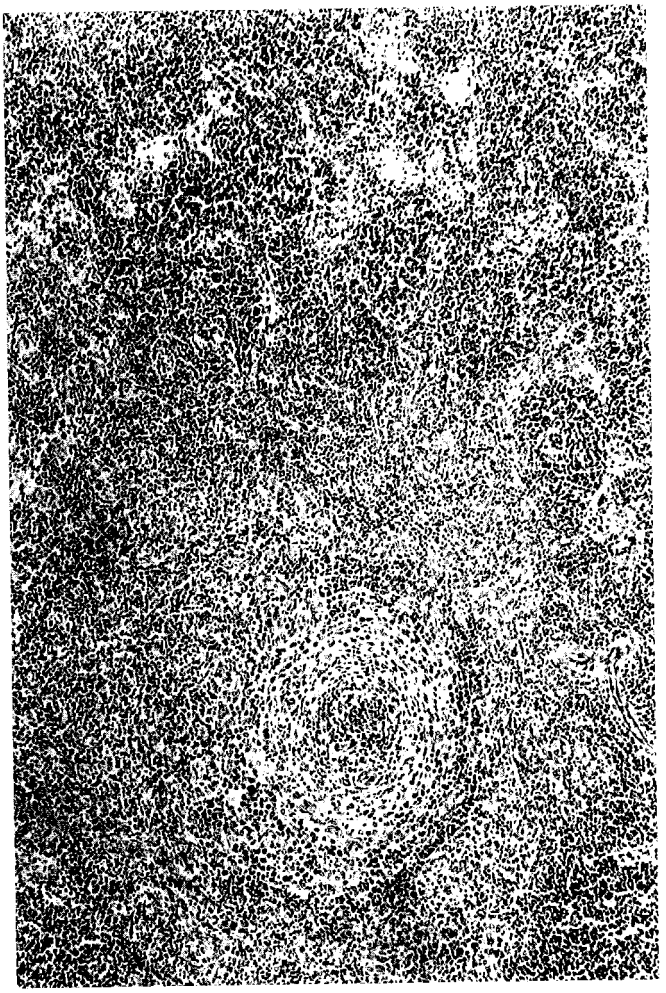

Figure 1 — Case 1: lymph node with an involution of the follicles and an expanded interfollicular area containing numerous blood vessels (Haematoxylin and eosin, X 73)

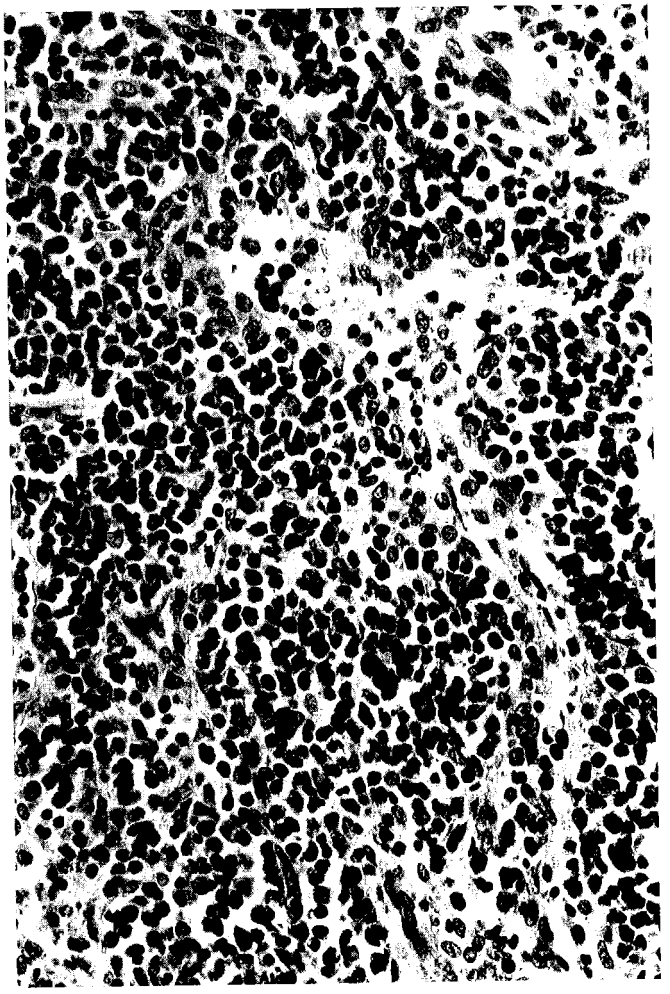

Figure 2 — Case 1: a plasmocytosis of the interfollicular area of the lymph node (Haematoxilin and eosin, X 290)

a lot of plasma cells (fig. 2). The interfollicular area displayed a vascular proliferation with endothelial cell hyperplasia and fibrous thickening of the vessel walls. The number of follicles was clearly decreased and the few remaining follicles had involuted germinal centers with a concentric arrangement of follicular dendritic cells. Some follicles contained a penetrating hyalinized blood vessel.

High doses of prednisone(1-2 mg/kg) were given and his symptoms disappeared within 2-3 days, with an impressive decrease of the number and size of the lymph nodes. At the end of August, indinavir was added.

He was readmitted with fever, anemia, large polyadenopathies, subacute dyspnea, hepatosplenomegaly and ascites. Again, a microbiological work up did not show any opportunistic infection. Despite high doses of prednisone and broad-spectrum antibiotics, he died 4 days later with symptoms and signs of multiple organ failure.

The patient died of respiratory insufficiency. The autopsy showed lung oedema, organising pneumonitis as well as KS of the tongue and small foci of KS in lymph nodes. Histologically, the lymph nodes were characterised by a lymphoid depletion and an absence of follicles. The lymph nodes were mainly populated with plasma cells, lymphocytes and to a lesser extend histiocytes and interdigitating reticulum cells. There was a marked atrophy of the white pulp of the spleen.

CASE 2

A 39-year-old African heterosexual man, with HIV disease and no history of opportunistic infection, was admitted in December 1996 with fever, dry cough and

intense weakness of three weeks' duration. On physical examination the patient had a temperature of 39.7°, a mild pallor, a diffuse maculo-papular rash, a palpable liver (3 cm below the costal margin) and a discrete splenomegaly. Laboratory data confirmed a moderate anemia and an elevation of inflammatory proteins. Although no opportunistic infection could be demonstrated, his condition initially improved with broad-spectrum antibiotic therapy. He was readmitted two weeks later with similar symptoms. Physical examination then revealed a very large splenomegaly (7 cm below the costal margin) and multiple enlarged lymph nodes.

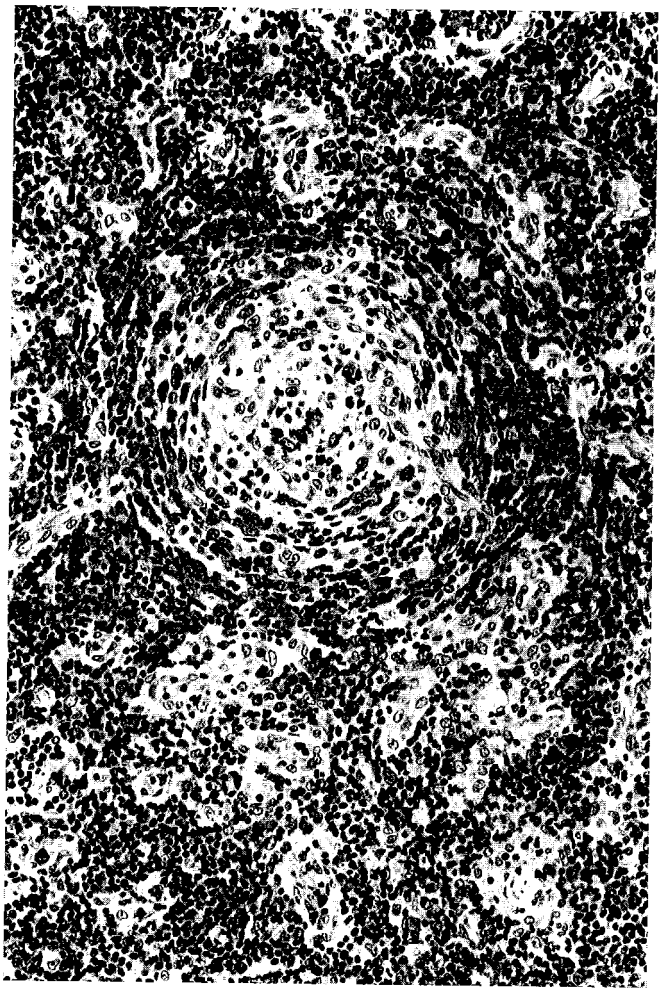

Figure 3 — Case 2: lymph node with follicles reminescent of Castleman's disease. In the hyalinized germinal centre there is a concentric arrangement of the follicular dendritic cells. Note the pentrating hyalinized vessel (Haemotoxylin and eosin, X 183)

The histology of a cervical lymph node was characterised by atrophic follicles with hyalinized germinal centers (fig 3) and an expanded interfollicular area with prominent plasmocytosis and proliferation of blood vessels. In addition, a moderate number of eosinophils was present.

Systemic symptoms disappeared within a few days during chemotherapy including cyclophosphamide, vincristine and prednisone (CVP). In February 1997, the CD4 lymphocyte count was 705/mm^3, but because of the high viral load (2.225.000 copies/ml), antiretroviral therapy, consisting of lamivudine, stavudine and ritonavir, was initiated.

In the following months, the patient remained free of symptoms and in June 1997, after seven courses of CVP, the antimitotic treatment was interrupted. At that time, he had a CD4 lymphocyte count of 261/mm^3 and a viral load of 7728 copies/ml. Ritonavir was stopped because of abdominal discomfort and replaced by indinavir. The patient was authorised to go to Africa for 2 months, for a family visit.

In November 1997 he was readmitted with fever, abdominal pain and splenomegaly; cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy (as used in high-grade Non Hodgkin Lymphoma) was started and 6 courses were given till March 1998. During this period the patient experienced regular exacerbations of the systemic symptoms, which required several hospitalisations.

Because of these recurrences despite the antimitotic treatment, foscarnet was given in March 1998. As there was no clinical improvement after 2 weeks, this treatment was stopped.

In spite of a good immunological status (CD4 lymphocyte count of 582/mm^3 and an undetectable viral load), the patient's condition worsened progressively and he developed severe pancytopenia. A bone biopsy demonstrated a hypercellular bone marrow with hyperplasia of dysplastic megakaryocytes and a moderate dysgranulopoiesis. There was plasmocytosis and a moderate increase in reticulin fibres. A palliative splenic irradiation could not prevent hematological aggravation and the patient died in April 1998 from multiple organ failure.

At autopsy, multiple foci of KS were present in both lungs. The morphologic alterations in lungs, liver and kidneys were consistent with multi-organ failure. The lymph nodes of the mediastinum and abdomen exhibited lymphocyte depletion, histologically characterised by a total absence of follicles, a severely decreased number of lymphocytes and fibrosis. The spleen was devoid of white pulp.

DISCUSSION

MCD in HIV-infected patients is a distinct and aggressive illness, usually with a rapid fatal outcome; the first reported cases died within 6 months of the diagnosis (5-7). In the largest published series the median survival with chemotherapy was 14 months, in contrast with 30 months in non HIV-infected patients (2).

Optimal treatment is not well defined; splenectomy in case of thrombocytopenia usually brings transient relief of symptoms. Corticosteroid and chemotherapy in various combinations have proven to prolong survival. a-Interferon is another therapeutic option. However, discontinuation of treatment for more than 2-3 weeks usually results in the re-emergence of clinical symptoms and the inflammatory syndrome (as observed in our two cases). Fatal outcome is caused by multiple organ failure, progressive KS, infectious complications, or malignant transformation into non-Hodgkin's lymphoma (2).

A striking feature of HIV-associated MCD is the strong association with KS. Our first patient presented with obvious clinical KS, but the pulmonary KS lesions of the second patient were only diagnosed during autopsy. Epidemiological studies and biologic plausibility suggest the recently recognised gamma herpes virus HHV-8 as a causal agent of KS. Sequences of this virus have been detected in nearly all KS lesions (HIV-related or not) (8), as well as in the circulating B-lymphocytes of +50% of KS patients (9); moreover detection of HHV-8 in B-lymphocytes of HIV-infected patients without KS is strongly predictive of subsequent progression to KS (9). Antibodies against HHV-8 are present in >80% of KS patients and seroconversion always occurs before clinical appearance of KS (10).

HHV-8 infection has been documented in a rare B-cell primary effusion (body cavity-based) lymphoma (11). Sequences of HHV-8 DNA have also been detected in 100% of tumour tissues of MCD patients (12), as well as in circulating B-lymphocytes of some of them (13). An association has also been demonstrated between the clinical exacerbations of MCD and high HHV-8 DNA load in peripheral blood mononuclear cells (PBMCs) of 3 HIV-infected patients (14).

An intense production of interleukin-6 (IL-6) has been documented in the hyperplastic MCD lymph nodes, possibly explaining the multisystemic symptoms (15); this cytokine deregulation is now presumed to be triggered by an antigenic stimulation by HHV-8, probably in association with HIV itself (3).

If a herpes virus is the causal agent of MCD, and HIV synergistically promotes the development of the disease, antiviral therapeutic approaches are reasonable. As very little information is available about the efficacy of antiviral treatments in MCD, parallels drawn from results of KS studies are helpful. Clinical improvement has been reported in KS patients treated with antiretroviral combinations (16). In addition, clearance of HHV-8 DNA from PBMCs of KS patients has been reported with the use of a protease inhibitor (PI), and some direct antiviral effect on HHV-8 has been suggested (17). However, onset of a severe MCD could not be prevented in one HIV-infected patient, despite a combined treatment including protease inhibitors; HHV-8 DNA was repeatedly detected in the patient's PBMCs, while HIV RNA in plasma remained negative even during clinical exacerbations (18). In our two patients, high HIV RNA plasma loads were present concomitant with the clinical onset of MCD. Both patients were given combination antiretroviral treatment including a protease inhibitor. Unfortunately, the first patient died 2-3 weeks later. The second patient had remission of symptoms for 10 months with antimitotic and antiretroviral treatments. However, although efficient in controlling HIV replication, the antiretroviral therapy could not prevent exacerbations of MCD and the fatal outcome. The suggested inhibition of HHV-8 protease by HIV protease inhibitors does not seem to be sufficient to control HHV-8 replication.

Blockage of HHV-8 replication by specific anti-herpes therapies could reduce the risk of developing HHV-8 related disorders. Retrospective studies showed that foscarnet or ganciclovir use was associated with significant reductions in the subsequent occurrence of KS (19). Long-term remissions of KS lesions eventually followed foscarnet therapy (20). In addition, a sustained response to therapy with foscarnet (associated with splenectomy and antiretroviral therapy) has recently been reported in a patient with HIV infection and MCD (21). However, HHV-8 DNA was not cleared in PBMCs of patients treated with foscarnet and/or ganciclovir (22-23). Our second patient did not improve clinically during foscarnet treatment, but this therapy was only initiated 1 year after the MCD diagnosis. It could be judicious to start anti-HHV-8 therapy as soon as possible following the HHV-8 infection. Foscarnet and ganciclovir have a marked anti-HHV-8 activity (24); but other anti-herpes virus agents may be more effective. Cidofovir (HPMPC) has also a long-lasting activity against HHV-8. Adefovir (PMEA), like foscarnet, inhibits both HIV and HHV-8, but with a much higher efficacy. This new molecule, still under clinical study, could represent an interesting approach for the treatment or prophylaxis of HHV-8 infections (24).

In conclusion, classic treatments of HIV-related MCD are only partially effective and cause significant adverse effects. Apparently, sustained control of HIV plasma load by combination antiretroviral treatment including protease inhibitors does not prevent the fatal evolution of the disease. New therapies aimed at inhibiting HHV-8 may be effective, but convincing results are still lacking. Further clinical investigations with antiviral drugs are needed. Early recognition of HHV-8-infection and early combined therapies with powerful antiretroviral and anti-HHV-8 agents may alter the course of this highly lethal disease.

SAMENVATTING

Twee patiënten met HIV infectie met een multicentrische ziekte van Castleman en Kaposi sarcoom worden beschreven. Beide patiënten overlijden ondanks een combinatie antiretrovirale therapie met o.a. protease inhibitoren.

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