AIDS, Multicentric Castleman’s Disease, and Plasmablastic Leukemia: Report of a Long-Term Survival


Abstract
Plasmablastic leukemia (PL) as a complication of human herpes virus 8 (HHV8)-associated Castleman’s disease is marked by a rapid and fatal outcome. In patients with AIDS, survival of 7 to 14 days after diagnosis has been reported. Prompt splenectomy and chemotherapy might lead to a significant survival benefit. Here we report a case of long-term survival in a patient with AIDS and multicentric Castleman’s disease (MCD) complicated by PL.

Introduction
Human herpes virus 8 (HHV8) or Kaposi’s sarcoma-associated herpesvirus (KSHV) is causally related to Kaposi’s sarcoma and multicentric Castleman’s disease (MCD). It has recently been reported that HIV-positive patients with KSHV/HHV8-dependent MCD show a 15-fold higher incidence of non-Hodgkin’s lymphoma (NHL) compared to non-affected HIV-positive populations, e.g. plasmablastic NHL [1]. After infection of naive B cells by HHV8 as an initial event during the development of these tumors, cellular and viral IL-6 might stimulate these cells to differentiate into plasmablasts [3]. In fact, in MCD, HHV8 seems to be specifically associated with monotypic (IGλ) but polyclonal HHV8-positive plasmablasts which occur as isolated cells in the mantle zone of B-cell follicles and may form microlymphoma or frank plasmablastic lymphoma. The latter is believed to most likely represent the expansion of plasmablastic microlymphoma from MCD lesions and progression toward aggressive NHL [1, 2], probably triggered by a second oncogenic event. This might imply that MCD and NHL form two stages of the same disease entity.

Disregulated production of human interleukin 6 (hIL-6) and viral IL-6 (vIL-6) in HHV8-infected cells is not only considered a major trigger for disease progression in MCD and NHL. Additionally, clinical symptoms, e.g. systemic inflammatory response syndrome (SIRS), seem to be dependent on IL-6 blood levels [4].

While the overall median survival of patients with HIV, MCD, and NHL has been reported to be approximately 1 month [1], plasmablastic NHL is often marked by a leukemic phase and an even more rapid fatal outcome. To our knowledge, no HIV-positive patient with MCD and PL survived more than 2 weeks despite highly active antiretroviral therapy (HAART).

Here we report a case of long-term survival in an AIDS patient with MCD and plasmablastic leukemia (PL).

Case Report
A 41-year-old male presented with a 3-month history of fever up to 41 °C, chills, weight loss, and general malaise. HIV infection had been diagnosed and antiviral treatment had been started with a triple combination therapy containing two nucleoside reverse transcriptase inhibitors and one boosted protease inhibitor (3TC, d4T and lopinavir/ritonavir) 1 year prior to admission. Additionally, he had received liposomal doxorubicin every 3 weeks (cumulative dose of approximately 500 mg on admission) for extensive cutaneous Kaposi’s sarcoma.

On examination, the patient was feverish and slightly confused. His blood pressure was 110/65 mmHg, pulse rate 88/min, and his body temperature 39.5 °C. His lungs and heart appeared normal. An abdominal examination revealed an enlarged spleen. The patient’s right leg was massively swollen; the upper thigh, groin, scrotum, and lower abdomen were covered by a large, indurated Kaposi’s sarcoma. Smaller sarcoma lesions, up to 5 cm in size, were scattered over the whole integument. Cervical and axillary lymph nodes were enlarged, soft and painless. On admission, the viral load was < 50 cp/ml, CD4+ T-lymphocyte count 43/µl (9%), leukocyte count 3.6 T/µl with lymphocytopenia (19.6%), otherwise unremarkable, Hb 6.0 g/dl, erythrocyte count 2 M/µl, reticulocytes 33/1,000 E, platelet count 91 T/µl, C-reactive protein (CRP) 14.5 mg/dl (< 1 mg/dl), IL-6 23 pg/ml (< 5.4 pg/ml) and HHV8-IgG 1:128 (Figure 1). The viral load had dropped from > 400,000 cp/ml to < 50 cp/ml within three months after the initia-
Infection 32 · 2004 · No. 5 © URBAN & VOGEL

S. Horster et al. AIDS, Castleman’s Disease and Leukemia

...tion of antiviral treatment and remained below detection limit throughout the described time frame. The CD4+ T-lymphocyte count was 60/µl when antiviral treatment was first initiated and fluctuated between 43/µl (9%) and 112/µl (7%) throughout the described time frame. Other laboratory parameters were within normal range. Extensive investigations gave no evidence for any infectious focus. Within 3 weeks, the patient’s condition deteriorated; the size of the spleen increased from 15 to 21 cm and platelets dropped to 7 T/µl despite substitution and therapeutic attempts with steroids and immunoglobulins. An emergency splenectomy was performed and a 2.5 kg spleen was removed (Figure 2). Histology of the spleen revealed plasma cell type Castleman’s disease (CD); analysis showed the typical diffuse infiltration with mature plasmablastic cells and immature plasmablastoid cells, which stained positive for HHV8-specific latency-associated nuclear antibodies (LANA). Plasma cell type CD usually has a multicentric appearance [3], in contrast to non-virus-associated localized CD. Along with constitutional symptoms and laboratory abnormalities at presentation, our patient’s initial disease was classified as multicentric plasma cell type CD. Liposomal doxorubicin, etoposide, and bleomycin (3 cycles every 3 weeks) were subsequently administered. 20 days after the splenectomy, the patient was discharged in an improved condition with a platelet count of 135 T/µl and leukocytes of 4.7 T/µl. 2 weeks later, he was re-admitted with fever, chills, leukocytosis of 66 T/µl and LDH of 724 U/l. 47% of peripheral blood mononuclear cells (PBMC) showed monophenotypic plasmablastic phenotype (CD19+, CD45+, λ+) (Figure 3). IgH-CDR3 PCR of these cells revealed two monoclonal cell populations on a polyclonal background. Assuming transformation of CD into aggressive plasmablastic B-NHL, chemotherapy with a modified cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine sulfate) and prednisone (CHOP) regimen including liposomal doxorubicin (six cycles every 3 weeks) was initiated. Two cycles resulted in complete cytologic remission. After six cycles, therapy was discontinued for 5 weeks before the patient presented again with a leukemic relapse, i.e. 1% of PBMC showing monophenotypic plasmablastic phenotype. We resumed chemotherapy with the above-mentioned modified CHOP regimen (two cycles) and then changed to IMVP16 (etoposide, ifosfamide, and methotrexate; six cycles every 3 weeks). Maintenance therapy with oral etoposide (100 mg/d for 2 days, every 2 weeks; since October every 3 weeks only) and liposomal doxorubicin iv (every three weeks) was subsequently started. A previous attempt for maintenance therapy with oral thalidomide as a suppressor of IL-6 production was stopped due to the deterioration of a pre-existing peripheral polyneuropathy. 28 months after diagnosis of PL, the patient remains in complete cytological and clinical remission and has taken up his former work.

Discussion

MCD is characterized by lymphadenopathy with angiofollicular hyperplasia and tissue infiltration by plasma cells. So far, there is no standard therapeutic regimen recommended for HIV-positive patients with this disease. Oksenhendler