Correspondence

Serum viral interleukin-6 in AIDS-related multicentric Castleman disease

Viral interleukin-6 (vIL-6) encoded by Kaposi sarcoma (KS)–associated herpesvirus (KSHV) has been detected in 3 acquired immunodeficiency syndrome (AIDS)-related disorders: KS, primary effusion lymphoma, and multicentric Castleman disease (MCD). Similar to its human counterpart, vIL-6 supports the growth and survival of certain mouse and human cell lines in vitro. When expressed in mice, recombinant vIL-6 induced marked lymph-node plasmacytosis similar to morphology in the plasmacytosis noted in the plasma-cell variant of human MCD. MCD is a lymphoproliferative disorder featuring systemic manifestations of inflammation and B-cell hyperreactivity. Virtually all HIV-positive cases of MCD and nearly 50% of HIV-negative cases are infected with KSHV, and all KSHV-positive MCD tissues were found to express vIL-6. In contrast to localized Castleman disease that typically remits after surgical removal of the localized mass, the multicentric form, occurring in a small percentage of patients, behaves more aggressively and is frequently fatal. Immunohistochemical studies demonstrated abundant human IL-6 (hIL-6) expression in the germinal centers of MCD lymph nodes, and there is evidence for a pathogenetic role of hIL-6 in MCD. KSHV vIL-6 is expressed by immunoblastic cells present among the mantle zone of MCD. The expression of vIL-6 in MCD lesions and the functional similarities of cellular and vIL-6 raised the possibility that vIL-6 may also play a role in the pathogenesis of MCD. But the role of vIL-6, if any, in MCD or other KSHV-associated disorders has not been fully examined. As a step toward further understanding a potential pathogenetic role of vIL-6, we measured circulating vIL-6 levels in an HIV-positive patient at the onset of MCD.

A 40-year-old HIV-positive homosexual man presented with a sore throat, nonproductive cough, night sweats, fever, diarrhea, marked fatigue, and weight loss in June 1999. The patient had received highly active antiretroviral therapy (HAART) since July 1996; January 1997; 150 mg × 2/d), stavudine (d4T; 40 mg × 2/d), and nelfinavir (NFV; 2250 mg × 1/d). HIV-RNA load had been stable at less than 1200 copies/mL since 1996. CD4+ T-cell counts had remained over 300 cells/μm3. On physical examination, the patient had lymphadenopathy, abdominal distention with hepatosplenomegaly, abdominal tenderness, and skin rash, but no evidence of KS. Oral administration of prednisone (30 mg/d) was started, to relieve systemic symptoms. A cervical lymph-node biopsy displayed the typical features of mixed plasma cell/hyaline vascular type of MCD: concentric layers of small lymphocytes surrounding the germinal centers and plasma cell infiltration in the interfollicular areas (Figure 1A-B). KSHV infection in the patient was confirmed by immunohistochemical detection of KSHV–latency-associated nuclear antigen (KSHV-LANA) in a lymph-node biopsy specimen (Figure 1C). A vIL-6–specific monoclonal antibody detected vIL-6 expression in the same specimen by immunohistochemistry (Figure 1D). The KSHV-LANA–positive and vIL-6–positive cells, similar in frequency, localized predominantly to the mantle zone of the lymph node. By contrast, expression of hIL-6, which has previously been detected in the germinal centers of certain MCD cases, was not detectable by immunohistochemistry in this lymph node (data not shown). Due to a dramatic improvement of systemic symptoms, prednisone was tapered after 10 days, and administration of the antiretroviral agent foscarin (7g × 2/day) started, followed by splenectomy in September 1999. Fifteen months later, the patient continued to be well, in remission, on occasional maintenance chemotherapy.

Serum vIL-6 was initially detected at 4756 pg/mL (Figure 2). But vIL-6 decreased to undetectable (less than 300 pg/mL) levels over the next 10 days and subsequently remained undetectable. By contrast, serum levels of hIL-6 fluctuated at low levels (range, < 1.0-10.8 pg/mL) throughout this period. The HIV-RNA load presented marked changes during this period. For approximately 3 years prior to the onset of MCD, the HIV-RNA load in this patient had remained at less than 1200 copies/mL. After MCD was diagnosed, the HIV-RNA load peaked at 146 460 copies/mL, followed by a rapid decrease to 792 copies/mL on day 21 of treatment (Figure 2). Of note, the patient continued to receive the same therapy with effective suppression of HIV-RNA levels up to the present. The patient was well for 8 months prior to the onset of MCD in August 1999. In 1997, the patient had received lamivudine (3TC; 150 mg × 2/d) and nelfinavir (NFV; 2250 mg × 1/d). HIV-RNA load had been stable at less than 1200 copies/mL since 1996. CD4+ T-cell counts had remained over 300 cells/μm3. On physical examination, the patient had lymphadenopathy, abdominal distention with hepatosplenomegaly, abdominal tenderness, and skin rash, but no evidence of KS. Oral administration of prednisone (30 mg/d) was started, to relieve systemic symptoms. A cervical lymph-node biopsy displayed the typical features of mixed plasma cell/hyaline vascular type of MCD: concentric layers of small lymphocytes surrounding the germinal centers and plasma cell infiltration in the interfollicular areas (Figure 1A-B). KSHV infection in the patient was confirmed by immunohistochemical detection of KSHV–latency-associated nuclear antigen (KSHV-LANA) in a lymph-node biopsy specimen (Figure 1C). A vIL-6–specific monoclonal antibody detected vIL-6 expression in the same specimen by immunohistochemistry (Figure 1D). The KSHV-LANA–positive and vIL-6–positive cells, similar in frequency, localized predominantly to the mantle zone of the lymph node. By contrast, expression of hIL-6, which has previously been detected in the germinal centers of certain MCD cases, was not detectable by immunohistochemistry in this lymph node (data not shown). Due to a dramatic improvement of systemic symptoms, prednisone was tapered after 10 days, and administration of the antiretroviral agent foscarin (7g × 2/day) started, followed by splenectomy in September 1999. Fifteen months later, the patient continued to be well, in remission, on occasional maintenance chemotherapy.

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Figure 1. Microscopic morphology of representative lymph node sections and immunohistochemical detection of KSHV infection. (A) Small hyalinized germinal center surrounded by concentric layers of small lymphocytes (hematoxylin and eosin stain; × 100). (B) Interfollicular sheets of plasma cells are shown (hematoxylin and eosin stain; × 1000). (C) KSHV-LANA antigen detection in the lymph node mantle zone visualized by immunohistochemical staining with monoclonal antibody (∼200). The inset shows the characteristic speckled nuclear pattern (∼1000). (D) vIL-6 detection in immunoblastic cells in the lymph node mantle zone (∼1000). The insets show specific cytoplasmic staining (∼1000).
same antiretroviral drug regimen he had received during the previous 3 years. Thus vIL-6 and HIV-RNA serum levels displayed parallel decreases over a 20-day period of observation following initiation of steroid treatment for MCD (Rho = .9; P = .005, Spearman test).

The widespread use of HAART has led to a substantial decrease in the incidence of KS,7 perhaps due to KS cell growth stimulation by certain HIV-derived proteins,8 but the impact of HAART on AIDS-related B-cell disorders is unclear.7 In this patient, it is unlikely that either the increase or the decrease in HIV-RNA load is attributable to HAART because the antiretroviral regimen had not changed. Rather, it is more likely that factors derived from or induced by MCD lesions, including vIL-6, may have activated HIV replication in this patient. Although the pathogenesis of MCD is likely complex, the remarkable association between circulating vIL-6 levels and MCD status shown here, combined with previous information on the biologic activities of this virkone, further support a role of vIL-6 in the pathogenesis of AIDS-MCD.

Yoshiyasu Aoki, Giovanna Tosato
Medicine Branch
National Cancer Institute
National Institutes of Health
Bethesda, MD

Terry W. Fonville
Department of Medicine
St Vincent’s Hospital and Medical Center
New York, NY

Stefania Pittaluga
Hematopathology Section
National Cancer Institute
National Institutes of Health
Bethesda, MD

References

To the editor:

Development of a myeloproliferative disorder in a patient with monoclonal gammopathy of undetermined significance secreting immunoglobulin of the M class and treated with thalidomide and anti-CD20 monoclonal antibody

A recent letter by Tefferi and Elliott1 reported the development of a myeloproliferative reaction and thrombocytosis after thalidomide administration in myelofibrosis with myeloid metaplasia. Thalidomide is being used currently with promising results, in the treatment of refractory multiple myeloma,2 other plasmacytic dyscrasias,3 and myelofibrosis.4 The reported results of the ongoing therapeutic trials with thalidomide are preliminary. Therefore, the side effects of this drug are not entirely known.

In this letter we present a patient with a monoclonal gammopathy of undetermined significance secreting IgM (IgM-MGUS) who underwent treatment with thalidomide followed by a monoclonal antibody against the CD20 antigen (anti-CD20, mabthera) and developed thrombocytosis along with features of bone marrow dysplasia with excess of blasts.

During a routine examination, an asymptomatic 72-year-old man was found to have a mild anemia (Hb concentration of 12.5 g/dL) with white blood cell (WBC) count of 7.2 × 10^9/L, normal differential, and platelet (PLT) count of 232 × 10^9/L. No evidence of blood loss or nutritional deficiency was found (normal iron, ferritin, folate, and vitamin B12 levels). Bone-marrow smear and trephine biopsy were normal. Biochemistry and immunology tests revealed only a small (480 mg/dL) IgM monoclonal compound present in the serum without proteinuria. Computed tomography (CT) scans of the chest and abdomen did not reveal any abnormality. He was then diagnosed as having an IgM-MGUS, and in the context of a therapeutic trial conducted in another hospital, he was administered 200 mg thalidomide daily, but this regimen was stopped after 20 days because of constipation, dizziness, and edema of the lower extremities. After thalidomide, his Hb concentration was 11.3 g/dL and his WBC count, 4 × 10^9/L, with normal differential and PLT count of 497 × 10^9/L. Treatment continued as scheduled by their protocol with 4 courses of 375 mg/m^2 anti-CD20
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