Discordant HHV8 Detection in a Young HIV-Negative Patient with Kaposi’s Sarcoma and Sarcoidosis

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Human herpesvirus 8 (HHV8), which has been suggested as the causal agent of Kaposi’s sarcoma (KS), has also been implicated in the pathogenesis of sarcoidosis. We describe a patient affected concomitantly by sarcoidosis and KS. HHV8 sequences were detected with PCR only on KS lesions, whereas sarcoid tissues did not harbor HHV8 DNA. Immune dysfunction related to sarcoidosis may have facilitated the oncogenic role of HHV8 and the development of KS.

Human herpesvirus 8 (HHV8), also called “Kaposi’s sarcoma herpes virus,” was first discovered by molecular isolation in Kaposi’s sarcoma (KS) lesions [1] in 1994. Since then, basic research has been targeted at determination of the viral oncogenic potential. HHV8 sequences have been observed in all forms of KS, irrespective of the HIV status of the patients [2]. The viral sequences have been detected in almost all cases of primary effusion lymphoma, a rare neoplasm involving serous cavities, and in 100% of cases of Castleman’s multicentric disease [3]. Besides being the causative agent of KS and of the above-mentioned lymphoproliferative syndrome, HHV8 has been implicated in the pathogenesis of several diseases, including multiple myeloma and Waldenstrom’s macroglobulinemia, and nonneoplastic conditions such as sarcoidosis.

We describe a 33-year-old Italian HIV-seronegative woman affected by concomitant sarcoidosis and aggressive KS. The patient was referred to our institution in March 1998 because of a recent diagnosis of cutaneous and lymph-nodal KS.

Seven years earlier, she had been affected by sarcoidosis histologically proven by cervical lymph-node biopsy; hence she had been treated with a steroid (Prednisone, 50 mg/d for 45 d) with complete recovery from the disease. During the last 3 months, the patient’s clinical status had been severely compromised by fever, weight loss, the appearance of nodular skin lesions, and systemic lymphadenopathy.

Histological examination of cervical lymph node had shown typical features of KS. Staging procedures were performed, including chest X-ray, abdominal computed tomography, gastroscopy, whole-body gallium-tallium scan with chest single positron-emission tomography, bone marrow biopsy, and biopsy of the right tonsil and of an inguinal lymph node. On completion of the above procedures, stage IVB (according to the New York University staging system) KS, with mediastinal and abdominal lymph-nodal, cutaneous, and pharyngeal involvement, and concomitant lymph-nodal sarcoidosis were diagnosed. In particular, on histological examination, the inguinal lymph node was involved by nodular KS and sarcoid granulomas (figure 1). KS affected a part of the lymph-nodal parenchyma and consisted of criss-cross–patterned neoplastic spindle cells and vascular channels separated by slit-like spaces containing erythrocytes. This was a typical KS lesion, with moderate nuclear pleomorphism and few mitotic figures. Hemosiderin deposits, lymphoplasmacytic aggregates, and dilated vessels were evident at the periphery of the nodule.

Immunohistochemical studies showed appropriate positive staining of neoplastic cells for CD34 (figure 2), vimentin, and factor VIII–related antigen. Noncaseating sarcoid granulomas

Figure 1. Coexistent nodal localizations of Kaposi’s sarcoma (KS) (right) and sarcoid granuloma (left). KS and a well-demarcated sarcoid granuloma, with some epithelioid cells, were separated by patrimonial lymphoid cells.
were scattered throughout the node. They were discrete and strikingly uniform in size and shape and were composed of epithelioid cells, with abundant cytoplasm and oval nuclei, often containing a small central nucleolus, and rare giant cells of the Langhans type. The molecular analysis (PCR KS330-233 bam) performed on the same lymph-nodal sample was positive for HHV8 DNA on KS lesions but was negative on the sarcoïd tissue (HHV8 DNA was not amplified in this site). Serology (immunofluorescence and Western blot) showed antibodies to lytic and latent HHV8 antigens. Hematochemical values and T and B cell subsets were all normal. The angiotensin-converting–enzyme level was 1.5 times higher than normal.

Because of the aggressive course of KS, the patient was treated with antiblastic polychemotherapy, with 9 cycles of a regimen including liposomal Daunorubicin (40 mg/m²) plus Bleomycin (10 mg/m²) plus Vindesine (2 mg/m²). When the treatment was finished, the patient’s clinical status had improved dramatically. Clinical restaging procedures evidenced complete remission of KS. Three months later, the patient returned for observation. Laboratory values showed cholestasis and liver impairment (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, 1.5 times above normal), and revealed thrombocytopenia (platelets, 61,000/mm³). Abdomen CT scan showed splenomegaly with multiple hypodense splenic areolae, but no lymph-nodal relapse was detected. Gallium-tallium spleen scans gave positive results for both radionuclides, which indicated the occurrence of a splenic disease other than KS. For this reason, laparotomy procedures with diagnostic and therapeutic splenectomy were performed.

Macroscopically, the spleen was enlarged (3 times normal volume) and showed numerous small nodules. Histologic examination showed splenic granulomatosis of the sarcoïd type, whereas minimal KS involvement was detected only on abdominal lymph node. HHV8 DNA was not detected on the splenic tissue by PCR. In the following months, the patient recovered fully and no relapse of KS was observed.

To our knowledge, only a few cases of concomitant KS and sarcoïdosis have been described [4, 5]. Sarcoïdosis is a multistystem granulomatous disease of unknown cause. More than 90% of patients affected by sarcoïdosis have lung or intrathoracic lymph-nodal involvement [6]. Hepatosplenic sarcoïdosis occurs in 2%–6% of cases [7]. Pathogenesis of sarcoïdosis is found on antigen-driven cell-mediated immune response, which leads to a cytokine cascade and to formation of sarcoïd granulomas. Several chemical agents, bacteria (mycobacteria, streptococci, Propionibacterium acnes, Borrelia burgdorferi, Mycoplasma species, Nocardia species, and Chlamydia pneumonias), herpesviruses (HHV1-2, HHV3, and HHV4), and other viruses [8, 9] have been suggested as possible causal agents of sarcoïdosis, but no definitive causal relationship has been confirmed.

In a recent study, De Alberti et al. [10] found HHV8 DNA sequences with nested PCR on a wide range of sarcoïd tissues; the overall prevalence of the viral sequences proved to be significantly higher in the sarcoïd samples than in the nonsarcoïd controls (38 of 39 sarcoïd samples vs. 6 of 113 controls, \( P < .0001 \)). In particular, HHV8 sequences were detected on 26 of 27 sarcoïd lymph-nodal biopsies. These results have not been confirmed by other groups that have applied nested PCR to check for HHV8 sequences on sarcoïd tissue specimens—mediastinal lymph-nodal or muscle samples [11], skin and peripheral blood mononuclear cells [12], or other unspecified tissue samples [13]. In these series, viral DNA was not detected in any of the biopsy samples. To our knowledge, there are no data regarding the presence of HHV8 DNA in tissues of patients affected by concomitant KS and sarcoïdosis. Our results show that HHV8 DNA sequences can be detected on KS lesions, as expected, but not in coexisting lymph-nodal or concomitant splenic sarcoïdosis. The lack of HHV8 DNA sequences in histologically proven sarcoïd tissue does not support an association between HHV8 and sarcoïdosis.

Data from seroepidemiologic studies for HHV8 antibodies have shown a high prevalence rate in Mediterranean areas; in particular, in the Italian population, seroepidemiologic data in healthy blood donors suggest that HHV8 infection is widespread [14] and correlates with the high incidence of classic KS (0.27/100,000 women), 2–3 times higher than in other western countries [15]. However, the classic form of KS is relatively indolent and occurs more frequently with skin involvement and rare visceral localization in otherwise elderly people. Aggressive KS with visceral disease has been reported mainly in immunocompromised patients. Sarcoïdosis is known to induce marked disregulation of cellular immune function, with anergy and T helper lymphocytopenia. Moreover, recent data suggest that sarcoïdosis appears to be associated with a significantly increased risk of KS.
increased risk of cancer in affected organs [16]. Furthermore, >50 cases of KS in patients treated with corticosteroid have been described: in the largest group, the time span from the treatment start to the occurrence of KS lesions has ranged from 2 to 36 months (mean, 13.7 months) [17]. In these cases, visceral involvement is rare (10%), but the course is unpredictable. Recent in vitro studies have indicated that hydrocortisone can directly activate the HHV8 lytic cycle in infected cells, thus further supporting the assumption that HHV8 is activated in corticosteroid-treated immunocompromised patients [18]. We suppose that, in our patient, underlying sarcoidosis determined severe disregulation of immune function. Immunosuppression may have facilitated the development of KS through the oncogenic transformation mediated by HHV8 and may have influenced the clinical behavior of KS.

Acknowledgment

We thank Daniela Furlan for expert assistance in the preparation of the manuscript.

References