

BRIEF REPORT

A Relapsing Inflammatory Syndrome and Active Human Herpesvirus 8 Infection

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SUMMARY

We describe an immunocompetent 61-year-old woman who was negative for human immunodeficiency virus and who had recurrent human herpesvirus 8 (HHV-8) infection associated with a relapsing systemic inflammatory syndrome characterized by fever, lymphadenopathy, splenomegaly, edema, arthrosynovitis, and rash. Kaposi's sarcoma developed 10 months after the initial clinical presentation. A correlation was documented between the recurrent clinical manifestations and the HHV-8 load in plasma and peripheral-blood mononuclear cells. Histologic examination of an enlarged lymph node heavily infected with HHV-8 revealed an atypical lymphoproliferative disorder characterized by paracortical hyperplasia and collapsed primary and secondary follicles.

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HUMAN HERPESVIRUS 8 (HHV-8), ALSO KNOWN AS KAPOSI'S SARCOMA (KS)—associated herpesvirus, is a member of the subfamily Gammaherpesvirinae and is etiologically linked to KS,¹ primary effusion lymphoma (body-cavity-based B-cell lymphoma),² and the plasmablastic form of multicentric Castlemann's disease.³ Nonspecific signs and symptoms, such as fever, arthralgia, splenomegaly, lymphadenopathy, diarrhea, and fatigue, have been reported both in immunocompromised patients^{4,5} and in otherwise healthy subjects^{6,7} in association with HHV-8 antibody seroconversion. However, the clinical manifestations of primary or reactivated HHV-8 infection continue to be updated. The levels of HHV-8 DNA in plasma and peripheral-blood mononuclear cells have been associated with the risk of KS^{8,9} as well as with the activity and exacerbation of HHV-8-associated multicentric Castlemann's disease.¹⁰

We describe a previously healthy woman who was negative for human immunodeficiency virus (HIV) and who had recurrent episodes of active HHV-8 infection, in whom a relapsing systemic inflammatory syndrome, characterized by fever, lymphadenopathy, edema, arthrosynovitis, and erythematous rash, preceded and accompanied the development of KS. A correlation was observed between the clinical manifestations and the levels of HHV-8 replication.

CASE REPORT

In February 2000, a 61-year-old woman was referred to our hospital with a one-year history of low-grade fever, lymphadenopathy, splenomegaly, arthralgia, edema, and rash involving the face and limbs. Her medical history was unremarkable. In February 1999

she had been hospitalized elsewhere. On that occasion, laboratory studies showed mild anemia, an elevated erythrocyte sedimentation rate (34 mm per hour; normal range, 2 to 15), and elevated levels of C-reactive protein (63 mg per liter; normal range, 2 to 6), lactate dehydrogenase (751 U per liter; normal range, 210 to 425), and beta₂-microglobulin (6.6 mg per liter; normal, less than 3.0). To rule out a lymphoproliferative disorder, the patient underwent an axillary-lymph-node biopsy, which was described as showing "nonspecific inflammatory changes," and a bone marrow core biopsy, the results of which were reported to be normal. She was treated with antibiotics, acetaminophen, and nonsteroidal antiinflammatory drugs, with minimal benefit. In November 1999, multiple cutaneous nodules with normal overlying skin, Raynaud's phenomenon, and diffuse severe arthrosynovitis developed. A biopsy of a skin nodule was diagnostic of KS. No specific treatment was instituted.

At the time of admission to our hospital, in March 2000, the patient appeared fatigued but not in acute distress. Her body temperature was 37.5°C. A few lymph nodes, each less than 2 cm in diameter, were palpable in the cervical, axillary, and inguinal regions. Severe arthrosynovitis of the hands, wrists, elbows, and knees was present. A nonpitting edema and a nonpruritic, nonpalpable, erythematous rash that involved the face and limbs and blanched on diascopy, as well as multiple cutaneous nodules with normal overlying skin, were present (Fig. 1). The spleen was palpable. The findings on physical examination were otherwise normal. Routine laboratory examination showed mild anemia and leukopenia with a normal differential count, increased levels of lactate dehydrogenase and C-reactive protein, and an increased erythrocyte sedimentation rate. Tests for rheumatoid factor, antinuclear antibodies, anti-DNA antibodies, and antibodies against extractable nuclear antigens were negative, as were direct and indirect Coombs' tests. The results of the immunologic studies are summarized in Table 1. Findings on examination of a skin-nodule biopsy specimen were diagnostic of hypodermic KS.

Because of the rapid appearance and progression of the skin lesions, the patient was treated with liposomal daunorubicin (40 mg per square meter of body-surface area intravenously) for two months, with improvement of the edema, arthritis, and rash and disappearance of the fever and skin nodules. In June 2000, however, the patient was readmitted for recurrence of fever (temperature, up to

39°C), fatigue, diffuse arthrosynovitis, edema, and rash. Total-body computed tomography showed cervical, axillary, thoracic, and abdominal lymphadenopathy accompanied by marked splenomegaly (longitudinal diameter of the spleen, 17 cm). Examination of an excised axillary lymph node was negative for lymphoma or KS but showed features consistent with the presence of an atypical immunoproliferative disorder. In view of the recurrence of symptoms and the detection of HHV-8 DNA in plasma and lymph-node tissue, antiviral therapy with foscarnet sodium (180 mg per kilogram of body weight, given intravenously) was begun and was followed by an initial improvement in the patient's condition, but it was discontinued because of worsening renal function and fever.

In September 2000, 17 typical KS skin lesions appeared on the patient's left arm; they were associated with recurrence of edema and an erythematous rash on the face and legs, as well as diffuse arthrosynovitis. The patient was again treated with liposomal daunorubicin, with progressive improvement and regression of sarcoma nodules. In February 2001, the patient once again reported arthralgias, leg and face edema, diffuse rash, and the reappearance of multiple KS skin lesions. Her symptoms worsened over a three-week period, and a high-grade fever developed. Given the reappearance of HHV-8 viremia, the patient was treated with cidofovir (5 mg per kilogram, given intravenously every other week for five months), resulting in the disappearance of all clinical signs and symptoms and a concomitant sustained virologic response. The patient had no symptoms for six months after the termination of therapy, at which time a small KS lesion accompanied by local lymphedema appeared on her left ankle. Three months later, inguinal lymphadenopathy developed. A lymph-node biopsy showed localized KS.

METHODS

IMMUNOLOGIC STUDIES

In vitro proliferation assays for recall antigens were performed according to published protocols.¹¹ The natural killer cell activity was assessed by means of a standard chromium-51-release assay.

SAMPLE PREPARATION AND QUANTIFICATION OF HHV-8 DNA

DNA was extracted from plasma, peripheral-blood mononuclear cells, or tissue samples according to the phenol-chloroform protocol. The levels of

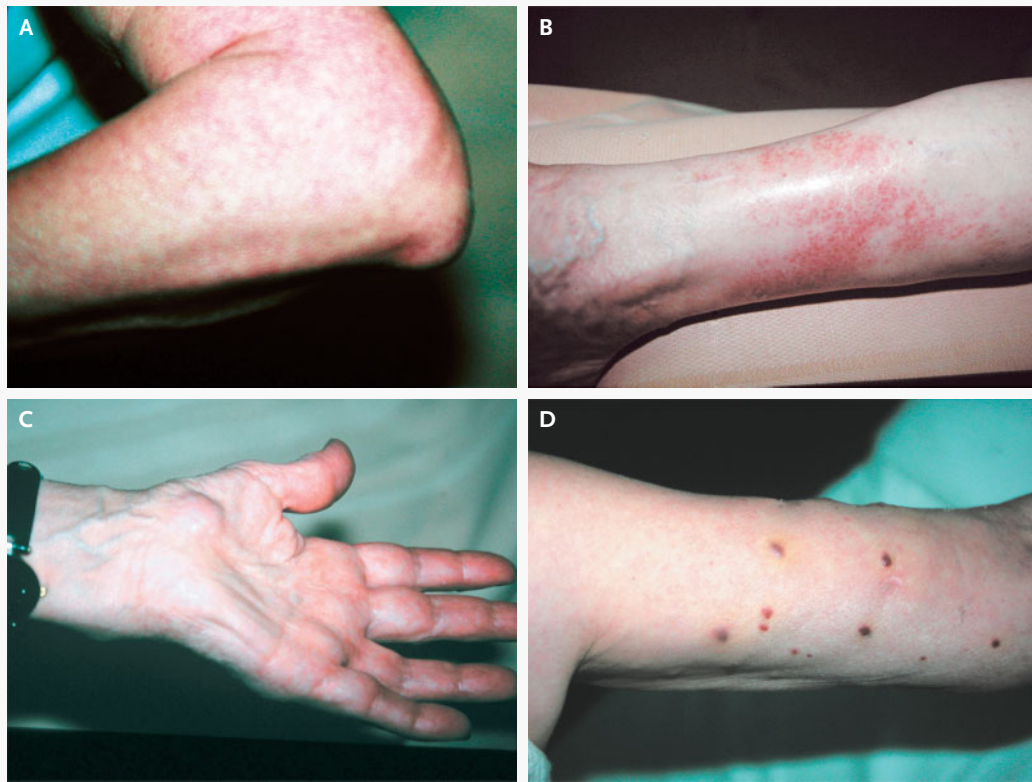


Figure 1. Clinical Signs and Symptoms.

When first admitted to our institution, the patient had a low-grade fever; diffuse lymphadenopathy; nonpitting edema; severe arthrosynovitis of the hands, wrists, knees, and elbows (Panel A); and a nonpruritic, erythematous rash involving the face and limbs (Panel B). Four months before admission, the patient had had multiple cutaneous nodules with normal overlying skin on her trunk, legs, and left hand (Panel C); seven months later, 17 typical KS nodules appeared on her left arm (Panel D).

HHV-8 DNA were determined by a quantitative, calibrated, real-time polymerase-chain-reaction (PCR) assay, as described previously.¹² This assay is based on the use of a specific synthetic calibrator molecule, which allows one to adjust for the difference in the recovery of nucleic acids during extraction and to identify PCR artifacts. The limit of detection was 10 genome equivalents of HHV-8 DNA per milliliter of plasma.

SEROLOGIC ASSAYS

To detect antibodies against lytic and latent antigens of HHV-8, we used immunofluorescence assays based on the HHV-8–positive BCBL-1 cell line and the BCP-1 cell line, respectively, as described previously.^{7,13,14}

HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

We used sequential sections of formalin-fixed, paraffin-embedded lymph-node tissue that were 3 μ m thick. Monoclonal antibodies or antiserum against CD3 and CD21 (Ylem), CD20, and κ and λ immunoglobulin chains (Dako) and antibody against HHV-8 interleukin-6 (Advanced Biotechnologies) were used according to the manufacturers' instructions or as described previously.¹⁵ The antibody against HHV-8 interleukin-6 specifically recognizes viral interleukin-6 and does not cross-react with human interleukin-6. Paraffin-embedded sections of the lymph node were also tested for Epstein-Barr virus (EBV) by means of in situ hybridization with a fluorescein isothiocyanate–labeled probe specific for EBER-1, an EBV-encoded RNA tran-

Table 1. Immunologic Characteristics of the Patient on First Admission.

Characteristic	Patient's Value	Normal Value
Serum IgG (g/liter)	17.0	8.40–16.6
Serum IgM (g/liter)	1.09	0.48–2.20
Serum IgA (g/liter)	1.01	0.90–3.95
CD4+ T lymphocytes		
% of mononuclear cells	64	32–60
Cells/mm ³	840	
CD8+ T lymphocytes		
% of mononuclear cells	23	16–40
Cells/mm ³	301	
B lymphocytes (CD19+) (% of mononuclear cells)	4	3–17
Natural killer cells (CD16+) (% of mononuclear cells)	4	4–22
CD4+:CD8+ ratio	2.7	1.3–2.5
Tests		
In vitro cell proliferation (stimulation index)		
Cytomegalovirus antigens	4.5	Reactive if >3.0
Candida antigens	4.9	Reactive if >3.0
Tuberculin purified protein derivative	10.9	Reactive if >3.0
Natural killer cell activity, measured by specific lysis of K562 target cells	Similar to values for 3 age- and sex-matched controls tested in parallel	
Delayed hypersensitivity*	Not anergic	
HIV-1 and HIV-2†	Negative	
Human T-lymphotropic viruses 1 and 2†	Negative	

* A cell-mediated immunity multitest (Pasteur Merieux) was used.

† Enzyme-linked immunosorbent assays, Western blotting, and the polymerase chain reaction were used. The tests were performed at admission, month 7, and month 12.

script (Dako). Sections from normal lymph nodes with mild plasmacytosis were obtained from two age-matched patients and used as negative controls.

MEASUREMENT OF HUMAN INTERLEUKIN-6 AND INTERLEUKIN-10 LEVELS

Levels of human interleukin-6 and interleukin-10 were measured in sequential plasma samples by means of an enzyme-linked immunosorbent assay (ELISA) (R&D Systems), according to the manufacturer's instructions. Plasma levels of human interleukin-6 and interleukin-10 were considered normal if they were lower than 10 pg per milliliter and 8 pg per milliliter, respectively.¹⁶

RESULTS

VIROLOGIC AND SEROLOGIC FINDINGS

At the time of the first admission to our institution, the patient had a high viral load (4.2×10^7 genome

equivalents of HHV-8 DNA per 10^6 cells) in the excised KS lesion; the levels were lower in peripheral-blood mononuclear cells and plasma (850 genome equivalents per 10^6 cells and 164 genome equivalents per milliliter of plasma, respectively). Treatment with liposomal daunorubicin was followed by clinical improvement associated with rapid abatement of the viremia (Fig. 2). In June 2000, the patient had a recurrence of viremia and a clinical relapse, accompanied by massive and diffuse lymphadenopathy; PCR analysis revealed a very high HHV-8 DNA load in an enlarged lymph node (3.7×10^6 genome equivalents per 10^6 cells). The patient was treated for a short time with foscarnet sodium monotherapy, which resulted in a virologic and clinical improvement. During follow-up, the patient had two more peaks of viremia associated with clinical relapse. In March 2001, cidofovir monotherapy was begun; it resulted in clinical and virologic remission (Fig. 2). Eventually, before the patient was lost to follow-up, reactivation of plasma viremia was

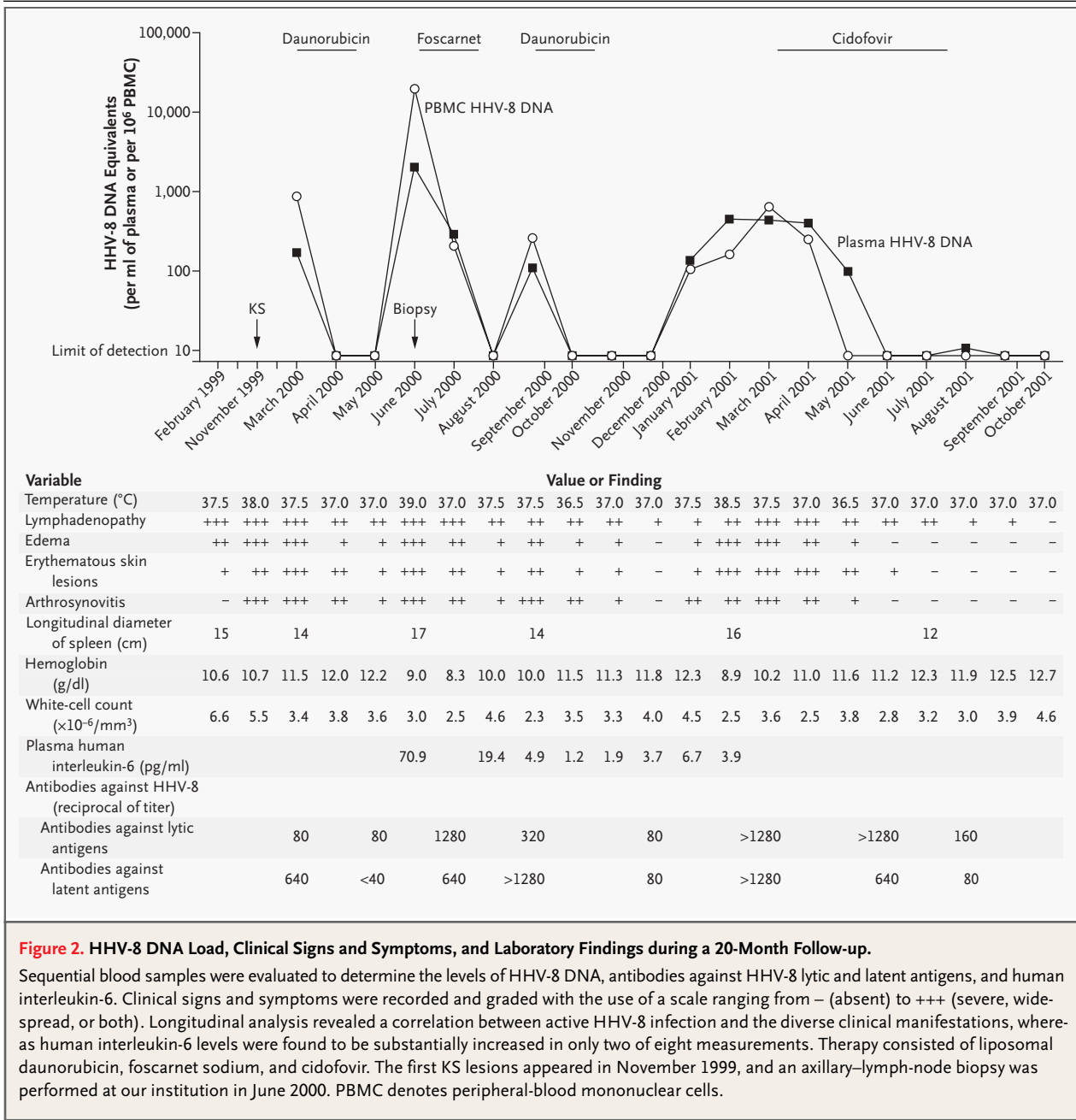


Figure 2. HHV-8 DNA Load, Clinical Signs and Symptoms, and Laboratory Findings during a 20-Month Follow-up.

Sequential blood samples were evaluated to determine the levels of HHV-8 DNA, antibodies against HHV-8 lytic and latent antigens, and human interleukin-6. Clinical signs and symptoms were recorded and graded with the use of a scale ranging from - (absent) to +++ (severe, widespread, or both). Longitudinal analysis revealed a correlation between active HHV-8 infection and the diverse clinical manifestations, whereas human interleukin-6 levels were found to be substantially increased in only two of eight measurements. Therapy consisted of liposomal daunorubicin, foscarnet sodium, and cidofovir. The first KS lesions appeared in November 1999, and an axillary-lymph-node biopsy was performed at our institution in June 2000. PBMC denotes peripheral-blood mononuclear cells.

confirmed, with the reappearance of a KS lesion and, shortly thereafter, the development of KS in a lymph node (64 and 254 genome equivalents per milliliter of plasma, respectively).

As summarized in Figure 2, longitudinal analysis over a period of 20 months demonstrated a remarkable correlation between active HHV-8 infection and the diverse clinical manifestations, including fever,

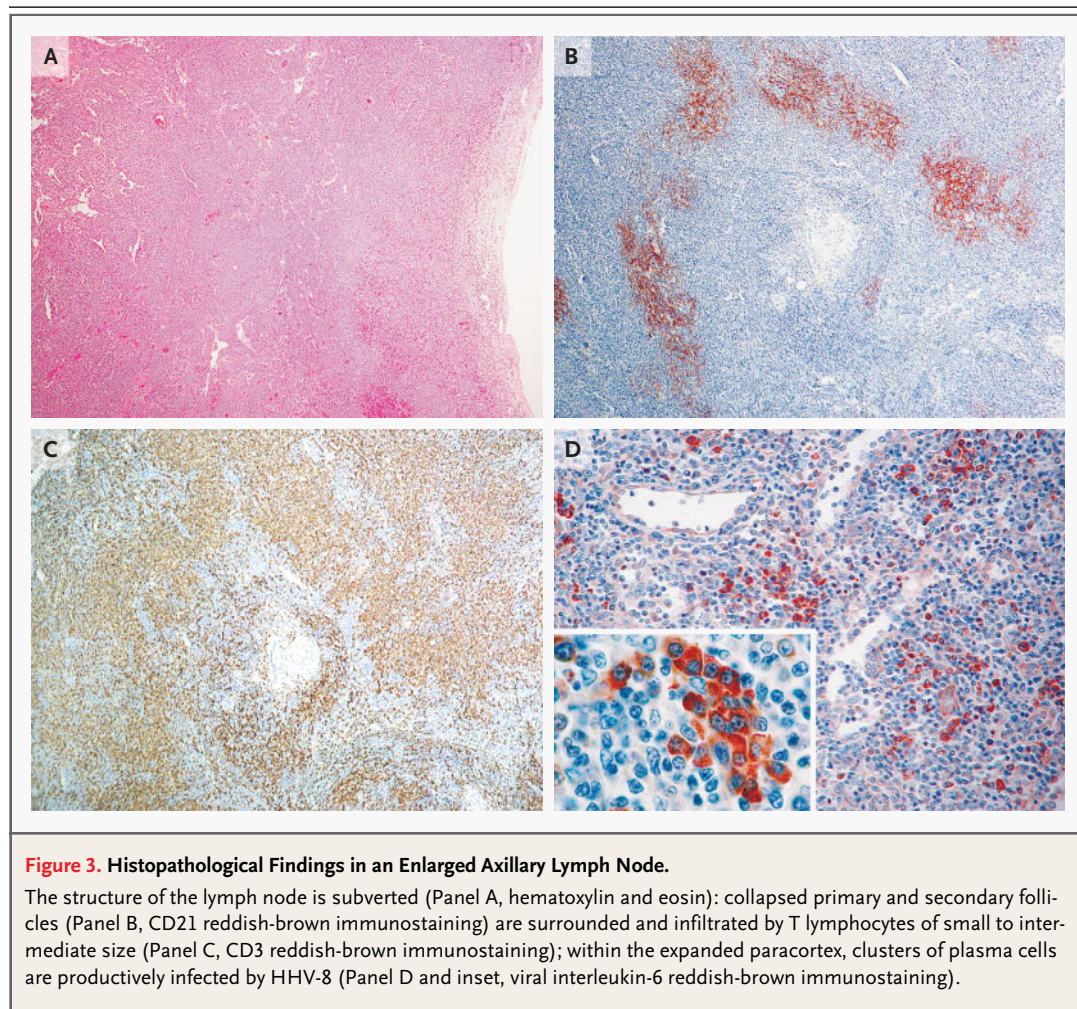
arthrosynovitis, diffuse lymphadenopathy, edema, and rash. Sequential serum samples were positive for IgG antibodies against both lytic and latent HHV-8 antigens (Fig. 2), suggesting that the clinical findings at the time of the first admission to our hospital were unlikely to be due to primary HHV-8 infection. A correlation was seen between increases in both the level of viremia and antibody titers.

No serum sample collected before admission to our institution was available for testing, and therefore we cannot rule out the possibility that the previous symptoms were associated with HHV-8 seroconversion. Extensive immunologic studies showed no evidence of primary or acquired immunodeficiency (Table 1). During follow-up, plasma levels of human interleukin-6 were substantially elevated on only two occasions (Fig. 2), whereas interleukin-10 levels were always within the normal range (data not shown).

HISTOLOGIC FEATURES OF LYMPH NODES

An axillary lymph node removed during the first relapse was moderately enlarged (diameter, 2 cm) and showed substantial effacement of the architecture by a lymphoid infiltrate, which had a predom-

inantly diffuse and focally vaguely nodular pattern of growth (Fig. 3) and comprised small lymphocytes, large lymphoid cells (many with the appearance of immunoblasts), scattered eosinophils, and polyclonal plasma cells, as indicated by immunostaining for immunoglobulin light chains. There was an intense proliferation of postcapillary venules lined by high endothelium. Many of the sinuses were dilated. Lymphoid follicles were difficult to discern, and germinal centers were absent. There was no evidence of necrosis or hyalinized vessels, and mitotic activity was moderate. About 10 percent of plasma cells in the paracortical or interfollicular region were strongly positive for HHV-8 interleukin-6 (Fig. 3D). EBV-encoded RNA transcripts were not detected. No foci of KS were identifiable. Reexamination of the axillary lymph node that had been



excised approximately one year earlier showed similar characteristics, despite the fact that the architecture was more conserved.

DISCUSSION

We describe a relapsing syndrome characterized by fever, lymphadenopathy, splenomegaly, edema, arthrosynovitis, and erythematous rash accompanied by leukopenia and anemia of chronic inflammatory disease in an HIV-negative, immunocompetent woman who had recurrent episodes of HHV-8 reactivation. Over a 20-month period of follow-up, we documented four recurrences of the same signs and symptoms, which closely correlated with the course and extent of HHV-8 replication. In accordance with descriptions of KS and multicentric Castleman's disease in the literature,^{9,10,17} exacerbations were always accompanied by spikes of viremia, whereas improvements after therapeutic interventions were consistently associated with an abatement of the viral load. Of particular interest was the finding that antiviral therapy with foscarnet or cidofovir led not only to the suppression of HHV-8 viremia, but also to the concomitant disappearance of both the KS nodules and the other clinical manifestations.

KS is extremely rare in women in the absence of concomitant HIV infection or other causes of immunosuppression. In our patient, however, an extensive search for infection with immunosuppressive retroviruses was unsuccessful, and no clinical or immunologic signs of immune dysfunction were observed.

The extensive lymph-node and splenic involvement suggested the presence of an underlying lymphoma or multicentric Castleman's disease, but both diagnoses were ruled out on the basis of histopathological analysis of two lymph nodes excised at different times. Indeed, the morphologic changes were consistent with the presence of an atypical immunoproliferative disorder characterized by reactive, nonspecific paracortical hyperplasia, which can occur in response to viral infections¹⁸ but to our knowledge has not previously been described in a patient with HHV-8 infection.

As far as Castleman's disease is concerned, the

morphologic features of our patient did not satisfy the criteria for either the hyaline vascular or the plasma-cell type of that disorder.¹⁹ Regarding the former, follicles were not prominent, germinal centers were hardly discernible, and the hyaline vascular changes that characterize this entity were absent; regarding the plasma-cell variant, the number of plasma cells present in the excised lymph nodes was limited, and such cells were not arranged in the form of solid sheets. Moreover, we did not detect increased levels of both human interleukin-6 and interleukin-10, as are found during the active phases of HHV-8-associated multicentric Castleman's disease.^{10,20-22}

Polyclonal plasma cells in the patient's lymph node were productively infected by HHV-8, as revealed by intense immunostaining for viral interleukin-6.^{15,23} This finding, together with the massive viral load in lymph-node-derived mononuclear cells and the presence of splenomegaly and diffuse lymphadenopathy, suggests that secondary lymphoid organs were important reservoirs for viral replication and that viral interleukin-6 may have played a role in some of the systemic manifestations in our patient.

The availability of molecular diagnostic techniques has permitted the association of HHV-8 infection with diseases or syndromes the causes of which were previously unknown.^{2-6,24,25} Although HHV-8 is apparently less prevalent in the general population than are other human herpesviruses, the assessment of serum antibody titers and even of cell-associated viral DNA may not provide clinically significant information, since this approach does not distinguish between latent and active infection. Only the integration of these data with measurement of the HHV-8 viral load in plasma and biologic fluids by means of reliable quantitative methods allows the accurate diagnosis of an active infection and thus makes it possible to establish an etiologic link.

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