Classic Kaposi’s Sarcoma Associated with Human Herpesvirus 8 Infection in a 13-Year-Old Male: A Case Report


INTRODUCTION

Classic KS, 2 a clinical form not related to HIV infection, iatrogenic immunosuppression, or African-endemic KS, was first described by Moriz Kaposi in 1872 as a malignant vascular proliferation involving the dermis of the lower extremities. Affecting predominantly elderly men of Mediterranean, Eastern European, and Jewish heritages, the disease often runs a protracted course with gradual proximal progression (1). Its preponderance in certain populations suggests a genetic predisposition. Recently, HHV-8 has been identified in classic KS lesions (reviewed in Ref. 2), suggesting that this virus is a cause of the tumor (3–12).

Classic KS is extremely rare in pediatric population, despite ~5% of children reportedly exposed to HHV-8 (13). Therefore, physicians are not familiar with the disease in young patients. Here we report an HIV-seronegative 13-year-old male with classic KS associated with HHV-8 infection to facilitate the diagnosis and treatment of this entity in children. Furthermore, a brief review of the relevant literature is provided.

SUBJECT AND METHODS

Case Presentation. This 13-year-old boy was first seen in February 1998 for recurrent epistaxis and found to have normal coagulation studies. Ten months later, he developed the sudden-onset of petechiae, a purpuric lesion on the tip of his nose and purpuric patches on the frontal aspects of his lower extremities (Fig. 1). Otherwise, he had no complaints, and his physical examination was normal. His WBC count was 2.7 × 10^9/mm^3 (with 34% neutrophils, 2% bands, 45% lymphocytes, 14% monocytes, and 3% eosinophils), hemoglobin concentration 13.8 g%, mean corpuscular volume 83 fl, and platelet count 4000/mm^3. His direct Coombs test was positive. His bone marrow examination showed increased megakaryocytes, consistent with consumptive thrombocytopenia. The thrombocytopenia resolved after an i.v. infusion of Rh(D) immunoglobulin (human anti-D polyclonal antibodies, WinRho-SDF, 40 µg/kg) and prednisone (60 mg/day × 1 week, followed by 30 mg/day × 2 weeks). However, his purpuric lesions persisted. Furthermore, he developed intermittent dependent edema in the left lower extremity.

The patient was of Sicilian decent. He was born in the United States and never traveled outside the country. He was Tanner stage 2, had never been sexually active, and had no known risk factors for HIV infection. His family history was entirely unremarkable.

In May 1999, he had recurrent petechiae and thrombocytopenia (platelet count 4000/mm^3), which were treated with prednisone (60 mg/day × 1 week). During the steroid course, he developed multiple cutaneous vascular lesions in the groins, more prominent on the left (Fig. 1, inset). The arterial pulse and the perfusion in the lower extremities were intact.

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2 The abbreviations used are: KS, Kaposi’s sarcoma; HHV-8, human herpesvirus 8; IVIgG, i.v. IgG; MRA, magnetic resonance angiography; PBMC, peripheral blood mononuclear cell; HTLV, human T-cell lymphoma leukemia virus.
MRA showed a normal-appearing venous system in the lower extremities and pelvis but remarkable small vessel proliferation affecting the cutaneous and s.c. tissues of the thighs and calves, more prominent on the left (Fig. 2). The lower extremity arterial duplex scan showed no occlusion. The abdominal and pelvic computed tomography scans showed extensive periaortic, mesenteric, and retroperitoneal adenopathy, as well as small hypodense hepatic lesions. The chest computed tomography scan, bone scan, and bone marrow were all unremarkable.

The prednisone was stopped, and he had skin biopsies that showed KS (Fig. 3). HHV-8 DNA was detected in the skin specimen by PCR (Fig. 4). The sequence of the amplified DNA was homologous to the prototype HHV-8-KS330/BAM (Fig. 5; Refs. 2, 3, 8). Moreover, his HHV-8 strain belongs to the A subgroup (Table 1), the type commonly associated with Mediterranean classic KS (11, 12).

His serum HHV-8 IgG antibody titer was ≥1:640. Serological assays for HIV antibodies and PBMC cultures and PCR assays for all of the known primate lentiviruses including HIV-I, HIV-II, HTLV-I, and HTLV-II sequences in his PBMCs and skin were all negative.

His serum immunoglobulin levels were normal. His absolute lymphocyte count was 1,092/mm³, with 15% CD19 (B cell), 72% CD3 (mature T cell), 40% CD4 (helper cell), 23% CD8 (suppressor cell), and 12% CD56/16 (natural killer cell). The in vitro lymphocyte proliferation assay showed a normal response to phytohemagglutinin, candida, and tetanus and a slightly decreased response to pokeweed. Over a 1-month period, the lesions progressed off prednisone. Thus, he was treated with daily IFN-α (Roferon-A, 2-million units i.m.) and twice monthly IVIgG (0.5 g/kg). Within 1 month, he had regression of the groin lesions and resolution of the cytopenia. The cutaneous lesions on the distal lower extremities remained unchanged.

The IFN dose was gradually increased to 9-million units/day over a 2-month period. However, because of the development of neutropenia, the dose was subsequently reduced to 9-million units 3 times/week. Six months later, the dose was additionally reduced to 3-million units 3 times/week. One year later, the groin lesions remained improved, and the cutaneous lesions were unchanged on the same reduced dose of IFN. Furthermore, his liver lesions and lymphadenopathy were stable.

**PCR Assay and Southern Blot.** DNA was extracted from the formalin-fixed, paraffin-embedded skin tissue of the patient and analyzed for HHV-8 DNA via PCR assay and Southern blot hybridization as described (10, 14, 15). The amplified HHV-8 DNA was also cloned and sequenced (10, 14). DNA was also extracted from his PBMCs and analyzed with nine separate PCR assays capable of detecting all known primate lentivirus sequences (including HIV-I M, HIV-X, HIV-IIa, HIV-IIb, SIV-chimpanzee, SIV-sooty mangabey, SIV-African green monkey, and SIV-macaque; Refs. 15, 16). The
PBMC DNA was analyzed for HTLV-I and HTLV-II DNA via PCR assays as described (17).

**ELISA Assay.** His plasma was analyzed for HIV-I and HIV-II antibodies using a commercial ELISA assay (Abbott Laboratories, Chicago, IL), as well as for HIV RNA via RNA-PCR using a commercial assay (Roche Molecular Diagnostics, Nutley, NJ), an in-house assay, and a commercial branch chain assay (Chiron, San Francisco, CA; Ref. 15). His plasma was tested for HTLV-I and HTLV-II antibodies using a commercially available ELISA assay (Abbott Laboratories; Ref. 16).

**DISCUSSION**

Classic KS is a malignant vascular proliferation that involves the skin and deep tissues. It typically presents in the distal lower extremities as bluish-reddish macules, papules, or nodules. Over years the disease spreads proximally, with angiogenic lesions coalescing to form plaques and tumors, which may erode, ulcerate, or fungate. The vascular proliferation can impair lymphatic drainage resulting in painful edema, especially in the groins and lower extremities. Lesions may also develop in the oral cavity, gastrointestinal tract, lymph nodes, liver, lungs, kidneys, and spleen (18–20).

HHV-8 has been identified in almost all of the classic KS lesions as well as in PBMCs in ≈70% of patients (3–12). Moreover, serological studies indicate that HHV-8 infection is increased in populations at risk for classic KS, and it precedes the disease onset (21). Epidemiological data suggest that the virus is sexually transmitted, including through the saliva (22, 23). With homology to sequences found in the transforming viruses Epstein-Barr virus and herpes virus saimiri, HHV-8 is classified in the Gammaherpesvirinae subfamily (2).

It is not yet known whether HHV-8 directly produces classic KS, especially because several cytokines may contribute to its development (reviewed in Ref. 24). The occurrence of other malignancies in up to one-third of patients suggests an impaired immunosurveillance (25–29).

Classic KS rarely occurs in children, and only nine patients, with variable natural histories and outcomes, have been reported since 1960 (reviewed in Refs. 29–33). The patient described herein, an HIV-negative adolescent male of Sicilian descent, is presented with severe thrombocytopenia and purpuric lesions on his lower extremities (Fig. 1A), mimicking immune thrombocytopenic purpura. The lesion on the tip of his nose (Fig. 1B) and progression on prednisone alerted to the possibility of classic KS, an extremely rare disease in an immunocompetent adolescent. The diagnosis was established by the characteristic findings on skin biopsy (Fig. 3) and HHV-8 detection by PCR (Fig. 4) and sequences (Fig. 5). Comparison of the HHV-8 open reading frame 26-specific bases from the patient to those of three HHV-8 subgroups indicates that his strain belongs to the A subgroup, which is associated with Mediterranean classic KS (Table 1; Refs. 11, 12).

Prednisone exacerbated his disease. However, the lesions were present before the treatment and therefore were not iatrogenic. Moreover, his disease cannot be classified as epidemic (i.e., HIV-related) or African-endemic. Thus, his condition best fits the classic form of KS.

His lesions (Fig. 1), although characteristic of classic KS,

![Fig. 2 MRA of the lower extremities.](image-url)

A, coronal spin echo T1 weighted image of the groins and upper thighs; B, axial fast spin echo T2 weighted image of the groins and upper thighs; C, coronal spin echo T1 weighted image of the legs. Bilateral vascular proliferation with a network of small vessels infiltrating the cutaneous and s.c. tissues of the groins, thighs, and legs more prominent on the left side are seen (∆ and black arrowheads).
may mimic the manifestations of vascular insufficiency, benign vascular proliferation, histiocytoma, pigmented or intradermal nevi, secondary syphilis, sarcoidosis, papular urticaria, urticaria pigmentosa, and other types of sarcoma or melanoma. However, the evolution from a macular stage and the characteristic color and multifocal distribution strongly suggest classic KS (18–20). Moreover, the presence of lesions on the tip of the nose and on the toes is unusual in other conditions.

The pathological differential diagnosis of KS is reviewed in Ref. 20. However, proliferations of spindle cells, jagged endothelial-lined and sinusoidal vascular channels, an inflammatory infiltrate, extravasated erythrocytes (Fig. 3), and the presence of HHV-8 DNA (Figs. 4 and 5), altogether indicate classic KS (3–12, 18–20).

His MRA showed a network of small vessels infiltrating the cutaneous and s.c. tissues of the lower extremities (Fig. 2). Such rapid vascular proliferation, to our knowledge, has not been described previously. His lymphadenopathy and liver le-

Fig. 3 Section of a classic KS lesion on the left lower extremity. A, increased vascularity extending from dermis into s.c. tissue is evident. Prominent small round vessels and irregular slit-like areas (arrow) of vascular proliferation with lymphoid infiltration are also seen. In addition, there are large, dilated, irregular vascular spaces with infolding papillae extending into the s.c. region (arrowheads). B, dilated, irregular vessel lined with attenuated endothelium (short arrow) and jagged sinusoidal channels with perivascular spindle cells (long arrow) are evident. C, collection of spindle cells with nuclear atypia (arrow) and occasional erythrocytes are seen. D, inflammatory infiltrate of plasma cells and siderophages (arrow) adjacent to a dilated vascular space with attenuated endothelium is seen.

Fig. 4 Autoradiograph of Southern blot of DNA samples amplified by PCR, using HHV-8-specific oligonucleotide primers and then hybridized with HHV-8-specific oligonucleotides as described (10). Lane 1 (negative control) contains primer without added DNA; Lane 2 (negative control) contains DNA from normal skin; Lanes 3–5 (patient) are replicates containing 1 μg of DNA from the patient’s skin sample; Lanes 6–9 (positive control) contain 1, 10, 100, and 1000 copies, respectively, of HHV-8 DNA diluted in normal human DNA.
sions suggest either independent lesions or systemic metastases. Furthermore, his leukopenia, thrombocytopenia, and positive Coombs test suggested immuno-mediated cytopenia (31, 32, 34–37).

The patient had no clinical or laboratory evidence of immune deficiency and was previously healthy. His disease progressed on prednisone, indicating that the short-term immunosuppressive therapy worsened his classic KS, as has been reported previously (37–39).

The treatment of classic KS depends on the site of lesions and clinical status of the disease. Observation may be appropriate for asymptomatic individuals with little progression over a long period. Patients with lesions in limited areas are often treated with radiation therapy (26, 40).

The antiviral, antineoplastic, and immune-modulating effects of IFN prompted its use in classic KS clinical trials. Studies demonstrate that IFN-α (1–6 million units, 3–6 times/week for ≥6 months) results in ~80% objective response, with remission lasting 4–84 months (41, 42).

IVIg was effective in an adult with prednisone- and azathioprine-induced KS not responsive to withdrawal of immunosuppressive therapy. Within 1 month of treatment (0.4 g IVIgG/kg/day for 5 days), his lesions almost completely resolved (43). The patient described herein reported clinical improvement after almost every IVIG treatment.

In summary, this report emphasizes the importance of recognizing the purpuric lesions of classic KS and the tendency of the disease to progress on immunosuppressive therapy. The described therapeutic approach was both effective and well tolerated.

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