Eruptive Kaposi Sarcoma: An Unusual Presentation in an HIV-Negative Patient

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Kaposi sarcoma (KS) is an angioproliferative disease associated with human herpesvirus 8 (HHV-8) infection. Four clinical variants have been described, all unified by common histopathologic features. We report a case of KS in an elderly Italian man with an unusual clinical presentation characterized by a relatively rapid onset of lesions and an unexplained low CD4 lymphocyte count. We review KS, including the 4 recognized variants, the central histopathologic findings, and various treatment options. In addition, we briefly discuss causes of CD4 lymphocytopenia, including a cursory overview of idiopathic CD4 lymphocytopenia (ICL).

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Case Report

A 77-year-old man of Italian descent presented with multiple, nontender, nonpruritic lesions on the arms, legs, and feet of 2 months' duration. The lesions initially appeared on the feet and spread to the thighs. He experienced concurrent swelling of the bilateral legs and was previously hospitalized for suspected cellulitis. A review of systems was otherwise unremarkable.

His medical history included gastroesophageal reflux disease and Lyme disease. Medications included lansoprazole and aspirin.

Physical examination revealed multiple, nontender, red to purple nodules and plaques on the arms, sacrum, and bilateral lower extremities, as well as thick verrucous plaques on the bilateral plantar and dorsal feet (Figure 1). Pitting edema (2+; somewhat deeper pit [4 mm]; disappears in 10–15 seconds) of the bilateral lower extremities also was observed. No lymphadenopathy or hepatosplenomegaly was appreciated.

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Punch biopsies were obtained from the left lower leg and back. Histopathologic examination demonstrated a dermal proliferation of spindle cells and slitlike vascular spaces with substantial red blood cell extravasation and hemosiderin deposition. Diffuse and nodular inflammatory infiltrates, consisting predominantly of lymphocytes and scattered plasma cells, also were observed (Figure 2). Given the histopathologic appearance of Kaposi sarcoma (KS), a human herpesvirus 8 (HHV-8) immunohistochemical stain (latent nuclear antigen−1 [LNA-1]) was performed and revealed strong positivity of the spindle endothelial cells lining the vascular spaces (Figure 3).

Laboratory evaluation yielded the following results: hemoglobin, 12.7 g/dL (reference range, 14.0−17.5 g/dL); hematocrit, 35.9% (reference range, 41%−50%); absolute CD4 lymphocyte count, 419 and 368 cells/mm^3 (2 values, 1 week apart) (reference range; 490–1740 cells/mm^3); serum urea nitrogen, 26 mg/dL (reference range, 8−23 mg/dL); creatinine, 1.69 mg/dL (reference range, 0.6−1.2 mg/dL); erythrocyte sedimentation rate, 29 mm/h (reference range, 0−20 mm/h); antinuclear antibody titer, negative; protein electrophoresis, within reference range; human immunodeficiency virus (HIV) 1 and 2 enzyme immunoassay, nonreactive (2 screenings, 6 weeks apart); human T-lymphotropic virus 1 and 2 Western blot analysis, indeterminate (1 of 11 viral bands reactive); HHV-8 antibody, positive; HHV-6 IgG titer, 1:160 (reference, <1:10); HHV-6 IgM titer, negative; IL-6, 6.59 pg/mL (reference range, 0.31−5.00 pg/mL); *Ehrlichia chaffeensis* antibodies (IgG, IgM), negative; Lyme antibody screen, positive; and Lyme disease Western blot analysis, negative.

A chest radiograph and computed tomography of the chest, abdomen, and pelvis were unremarkable. Initial therapy for the patient included cryotherapy to various newer lesions as well as imiquimod cream 5% under occlusion 5 days a week to 1 lesion on the thigh.

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Comment

Clinical Variants—When KS was initially described in the late 1870s, it was referred to as idiopathic pigmented sarcomas of the skin. Pulmonary and gastrointestinal tract lesions also were found on autopsy.[1] Since then, 4 clinical variants have been described, each sharing common histopathologic features[1,2]: (1) classic (Mediterranean) KS; (2) endemic (African) KS, including a lymphadenopathic subtype; (3) iatrogenic KS in immunocompromised patients; and (4) AIDS-related (epidemic) KS.

The classic form of KS typically occurs in elderly males of Mediterranean and Ashkenazi descent.[1,2] Clinically, classic KS is characterized by slowly growing, red, violaceous, or blue-black macules and patches that coalesce and may evolve into plaques and nodules. Primary lesions usually are distributed on the distal lower extremities, favoring the toes or soles of the feet. Classic KS usually is slowly progressive, with lesions enlarging and new lesions appearing over 10 to 15 years. Venous stasis and lymphedema of the involved lower extremity are frequent complications. In long-standing cases, systemic lesions can develop along the gastrointestinal tract, in lymph nodes, and in other organs.

Endemic (African) KS has a male preponderance with a younger age of onset compared to classic KS (peak age of onset, 35−39 years in men and 25−39 years in women).[2] It is now the most common tumor in central Africa, occurring in both HIV-negative and HIV-positive patients.[1] The lymphadenopathic subtype is a rapidly progressive form of endemic KS that usually is seen in children younger than 10 years and may be fatal within 12 months of onset.[2]

Iatrogenic KS characteristically is observed in individuals who have undergone organ transplants and require long-term immunosuppressive therapy.[1] A variable geographic incidence of 0.5% to 5.3% has been reported among organ transplant recipients. The renal transplant population is most commonly affected, with rare occurrences seen in the setting of heart, liver, and lung transplants.[2] An increased risk for iatrogenic KS based on gender (males) and ethnic background (namely Italian or Mediterranean descent, as seen in classic KS) also has been found. Iatrogenic KS usually is aggressive with involvement of the lymph nodes, mucosa, and viscera. The median time from transplant to diagnosis is approximately 29 to 31 months.[1]

A particularly aggressive (considered to be the most aggressive of the subtypes) and often fatal course, especially among homosexual men with AIDS, is noted in patients with AIDS-related (epidemic) KS.[1] Although its incidence has declined since the early 1980s, likely attributable in part to the advent of antiretroviral therapies, this variant of KS is still the most common AIDS-related neoplasm observed in the United States.

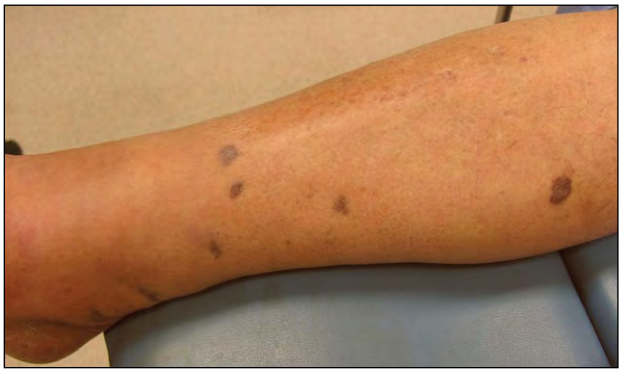

Figure 1. Purple nodules and plaques on the left leg.

Human Herpesvirus—In 1994, Chang et al[3] isolated the DNA of HHV-8 from the lesions of a patient with AIDS. Infection by HHV-8 (also known as KS-associated herpesvirus) is required for the development of KS, though not all patients infected with HHV-8 develop clinical disease.[2,4] Human herpesvirus 8 belongs to the Gammaherpesvirinae subfamily along with Epstein-Barr virus, which has similarly been implicated in certain human neoplasms, including lymphoproliferative disorders.[1] Human herpesvirus 8 has been detected in more than 95% of KS lesions, with no bias for any one of the KS clinical variants. It also is the etiologic factor in multicentric Castleman disease and primary effusion lymphoma.[2]

Pathogenesis—The development of KS is a multifactorial process. Genetic and geographic factors as well as immunocompromised states (eg, organ transplant, HIV) have been reported to influence the host's development of KS following HHV-8 infection. The virus ultimately promotes the proliferation of spindle endothelial cells in the formation of KS lesions.[4] Whether these cells are of vascular or lymphatic origin may be disputed; however, current evidence suggests that HHV-8 induces the expression of lymphatic markers on vascular endothelium and vascular endothelial markers on lymphatic endothelium.[4,5]

In a review published in 2006, Ganem[4] proposed that while the term *sarcoma* implies a neoplastic process, the nature of KS is more accurately described as a vascular proliferative response to infection. To support this argument, he noted that the clinical lesions often appear in multiple locations simultaneously without a primary lesion; also, the lesions may remain stable for extended periods and even regress with improvement in host immune status.[4]

The viral pathogenesis of KS has been the subject of intense scrutiny, and more recent investigations

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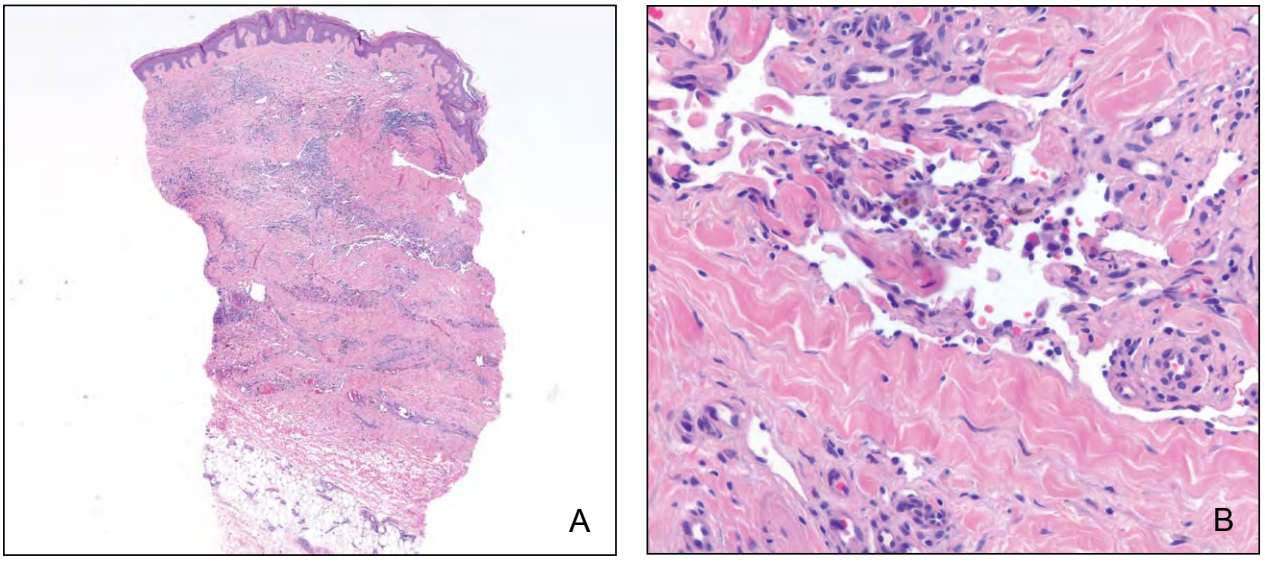

Figure 2. Punch biopsy from the left leg demonstrating a dermal proliferation of spindle cells and slitlike vascular spaces with substantial red blood cell extravasation and hemosiderin deposition (A and B)(H&E; original magnifications ×4 and ×40, respectively).

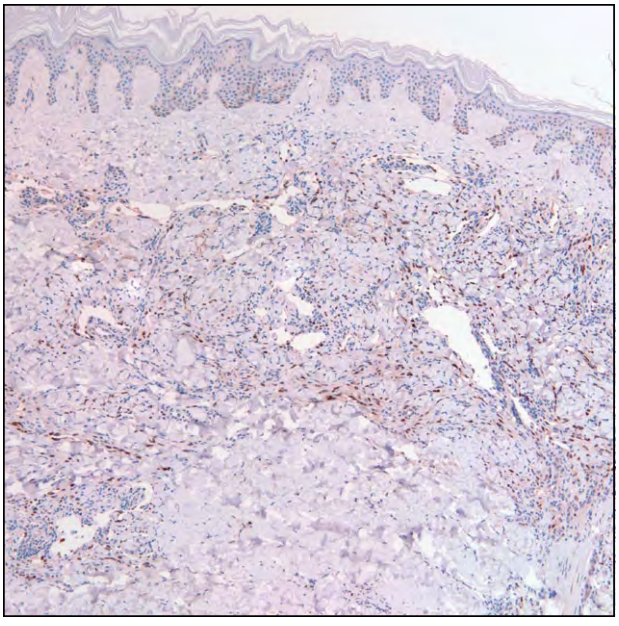

Figure 3. Latent nuclear antigen–1 staining of spindle endothelial cells (original magnification ×4).

have provided great insights into the etiology of KS. Human herpesvirus 8 produces several proteins that are homologous to human oncoproteins and cell-cycle regulatory proteins.[1,4] Latent nuclear antigen−1 inhibits transcriptional activity mediated by the protein p53 and the tumor suppressor pathway associated with the retinoblastoma protein.[5,6] Other proteins and chemokines expressed during latency have been found to drive cell proliferation, block apoptosis and enable immune evasion, and promote angiogenesis.[5,7,8] Viral IL-6, encoded by the HHV-8 genome, promotes the growth of infected spindle cells in KS lesions in an autocrine fashion and the growth and proliferation of surrounding cells via paracrine stimulation.[7,8] It also induces the growth and proliferation of lymphoma cells in primary effusion lymphoma and promotes angiogenesis by inducing the production of vascular endothelial growth factor (VEGF).[7]

Histopathology—Immunohistochemical staining for LNA-1 is both highly specific and sensitive for the detection of HHV-8−infected spindle cells within KS lesions.[9,10] Latent nuclear antigen–1 is expressed constitutively by all virally infected cells.[11] Therefore, the development of a monoclonal antibody against LNA-1 has made it possible to reliably distinguish KS from other spindle cell and angioproliferative tumors, such as spindle cell hemangioma, cutaneous angiosarcoma, dermatofibrosarcoma protuberans, pyogenic granuloma, and spindle cell melanoma, among others.[10-12] The reduced potential for false positives from the amplification of incidental viral DNA of infected circulating passenger lymphocytes confers a distinct advantage over polymerase chain reaction analysis.[10,12]

The histopathologic appearance of KS varies by lesion stage.[13] The patch stage is characterized by more vascular spaces in the dermis lined by swollen, focally hyperchromatic endothelial cells. The vessels usually are surrounded by an admixture of lymphocytes, plasma cells, and focal hemosiderin deposition. In the plaque stage, the vascular proliferation is more obvious and extends into the deeper dermis. The vasculature is characterized by lumina with variable calibers lined by plump endothelial cells that still remain single layered. Normal adnexal structures and

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preexisting blood vessels commonly protrude into newly formed blood vessels (promontory sign). Also apparent are eosinophilic spindle cells found around the dermal vessels. The nodular stage consists of a well-defined dermal nodule composed of spindle cells and slitlike vascular spaces (without an endothelial lining) occupied by red blood cells. As previously mentioned, immunohistochemical testing for LNA-1 of HHV-8 has been shown to be a useful marker of KS and other HHV-8–associated disorders.[9,10] Other more common and less specific markers include CD31 and CD34.[13]

Diagnosing Our Patient—Our patient shares many features of classic KS: the clinical distribution of his lesions, late age of disease onset, and Mediterranean ethnicity. However, the evolution of his disease was rather uncharacteristic, following an eruptive course with many lesions developing within only a few months. It is likely that his low CD4 lymphocyte count was related to the eruptive course of his illness, as observed with the depression in CD4 lymphocyte counts in iatrogenic and AIDS-related KS.

The etiology of our patient's immunosuppression was elusive. He was not on any immunosuppressive therapy and was negative for HIV. Substantial decreases in the CD4 lymphocyte population are most commonly associated with HIV but also may be explained by other infections (ie, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, human T-lymphotropic virus 1 and 2, fungi, mycobacteria), immunosuppressive medications (ie, corticosteroids, chemotherapy agents), autoimmune diseases (ie, Sjögren disease, systemic lupus erythematosus), and hematologic malignancies (ie, lymphoma, mycosis fungoides, myelodysplastic syndrome).[14]

In 1992, the Centers for Disease Control and Prevention defined criteria for idiopathic CD4 lymphocytopenia (ICL), a rare condition characterized by a severe decrease in CD4 lymphocytes and susceptibility to opportunistic infections.[15] The condition also has been classified a severe unexplained HIV-seronegative immunosuppression. A diagnosis of ICL requires patients to have a depressed circulating CD4 lymphocyte count of fewer than 300 cells/μL or less than 20% of the total lymphocyte count on at least 2 separate occasions, no less than 6 weeks apart, as well as laboratory evidence of HIV seronegativity (HIV-1 and HIV-2) and the absence of any defined immunodeficiency disorders or medications that characteristically lower CD4 lymphocyte counts.[15]

Idiopathic CD4 lymphocytopenia may originate from a reduced production of T cell precursors in the bone marrow. Additionally, Walker and Warnatz[14] reported a slightly decreased CD4:CD8 ratio and normal B-cell counts. Susceptibility to HHV-8 also is noted in patients with ICL as well as numerous infectious agents including other viruses, atypical mycobacteria, fungi, and *Toxoplasma*. It is important to note that low CD4 lymphocyte counts also may be related to age, sex, and even smoking.

Although our patient demonstrated low CD4 lymphocyte counts, his values were not low enough to meet the minimal criteria defined by the Centers for Disease Control and Prevention for a diagnosis of ICL. In addition, a cursory serologic evaluation was not suggestive of autoimmune disease or active involvement of specific infectious agents, though more extensive testing is warranted to further exclude these potential etiologies. Further serial CD4 lymphocyte counts in our patient would potentially allow for a proper diagnosis of ICL.

Treatment—The treatment of KS is dependent on the particular variant as well as lesion morphology and extent of disease. Classic KS may require only observation if lesions are asymptomatic and not progressive.[1] Solitary lesions of KS may respond to simple surgical excision, cryotherapy, topical alitretinoin, intralesional interferon alfa-2b, or imiquimod cream 5%.[1,16-18] Multiple localized lesions may respond well to radiation therapy. In more extensive or refractory cases, chemotherapy alone or in conjunction with radiation therapy may be employed. Historically, agents used included vincristine, bleomycin sulfate, doxorubicin hydrochloride, and dacarbazine. More recently, liposomal encapsulated anthracyclines and paclitaxel have replaced the traditional therapies.[19]

Endemic (African) KS may require more aggressive therapy with chemotherapy and/or radiation. Iatrogenic KS usually responds to discontinuation or reduction of the immunosuppressants used in organ transplant recipients, which may not be possible without risking rejection of the graft. In such scenarios, additional chemotherapeutic agents and/or local radiation therapy may be used.[1]

One goal in the treatment of AIDS-related KS is to improve the immune system and increase circulating CD4 lymphocytes. Hence, highly active antiretroviral therapy has become a key component in the treatment of this particular variant of KS.[20] Local radiation treatment also may be used, and for extensive refractory cases typically observed in patients with this variant of KS, interferon alfa and systemic cytotoxic agents often are required, including liposomal anthracyclines, paclitaxel, Vinca alkaloids, and bleomycin sulfate.[1] Other more experimental systemic therapies may include VEGF inhibitors; all-*trans* retinoic acid, which inhibits IL-6 production and angiogenesis; and thalidomide.

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Future investigative treatment strategies may focus on the use of specific biologic agents, such as antibodies. Nakahara et al[21] demonstrated a reduction in VEGF in patients with rheumatoid arthritis treated with a monoclonal antibody against the IL-6 receptor. Nishimoto et al[22] observed improvement in symptoms using a humanized anti−IL-6 receptor monoclonal antibody (tocilizumab) in patients with multicentric Castleman disease, a condition characterized by the dysregulated production of IL-6. More recently, Ahmed et al[23] demonstrated rapid improvement in patients with cutaneous Castleman disease using a chimeric murine anti−human IL-6 antibody.

Conclusion

Kaposi sarcoma is a disorder governed by the angiogenic effects of HHV-8. It may be categorized based on factors such as ethnic background, geographic location, and immune status. The most serious cases involve immunosuppression, specifically related to either AIDS or organ transplantation. Further investigational studies are necessary to elucidate the pathogenic mechanisms involved and hopefully discover more effective and better-tolerated therapies.

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