An unusual series of patients with Kaposi sarcoma

Jiasen Wang, BA, Holly Reid, MD, Natasha Klimas, MD, and Misha Koshelev, MD, PhD
Houston, Texas

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INTRODUCTION

Kaposi sarcoma (KS) is a mesenchymal tumor characterized by angioproliferation in the setting of infection by human herpesvirus 8 (HHV-8), also known as KS—associated herpesvirus. The disease has several manifestations, the most common of which is a violaceous-to-dark brown macule, plaque, or nodule on the skin. Involvement of the gastrointestinal tract is less common, only affecting 10% of patients but is much more prevalent in the immunocompromised.[1] Involvement of visceral organs outside the gastrointestinal tract such as the lungs, liver, and bone is extremely rare in immunocompetent patients.

Clinically, most cases of KS fit into 1 of 5 reported subtypes: classical, African endemic, AIDS epidemic, iatrogenic, and nonepidemic. Very rarely do patients present who do not conform to 1 of the 5 subtypes. We present 3 such patients and discuss their fit in the current classification system.

Abbreviations used:

KS: Kaposi sarcoma
HHV-8: human herpesvirus 8

REPORT OF CASES

Case 1

A 54-year-old previously healthy Hispanic woman presented for evaluation of a growing asymptomatic lesion located on her back. Physical examination found a cluster of 6 dark, purple, dome-shaped papules over a light purple patch located on her left mid back (Fig 1, *A*).

A punch biopsy of the lesion found an atypical vascular proliferation with large, ectatic, irregularly shaped blood and lymphatic vessels dissecting through collagen and subcutaneous tissue with positive immunohistochemical staining for HHV-8. Laboratory workup found that she was HIV negative and immunocompetent. She was initiated on local interferon-α therapy but has been lost to follow-up.

Case 2

A 41-year-old white woman presented complaining of a mass on the left side of her neck that failed to resolve with antibiotics. Magnetic resonance imaging found a lobulated mass in the left side of the neck. A biopsy found a spindle cell neoplasm that was confirmed on pathology to be KS encapsulated within the lymph node. Laboratory workup found that the patient was HIV negative and immunocompetent. At the age of 57 she was found to have recurrence of KS in a right axillary lymph node.

At the age of 62 a routine computed tomography scan found lymphadenopathy in the bilateral axillae, the right hilum, and left supraclavicular regions. Axillary lymph node core biopsy result was HHV-8 positive and consistent with KS. CD4/CD8 ratio was 5.06. An HHV-8 count was 10,000, which decreased 3 months later to 129 on valganciclovir but increased again to 11,000 when she stopped the medication due to nausea.

Asymptomatic cutaneous lesions developed on her left arm and left thigh that were suspicious for KS. On physical examination there was a blue-purple, 1.0- × 1.0-cm, firm nodule on her left posterior upper arm and a 0.5- × 0.7-cm, violaceous papule on her left inner thigh. Biopsy found spindle-shaped

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Correspondence to: Misha Koshelev, MD, PhD, 6655 Travis St, Suite 980, Houston, TX 77030. E-mail: Misha.V.Koshelev@uth.tmc.edu.

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cells and atypical vascular proliferation supportive of KS and stained positive for HHV-8 (Fig 1, *B*).

Case 3

A 72-year-old white man with a history of metastatic melanoma after excision, lymph node dissection, and interferon therapy with no evidence of disease presented with a 3-month history of asymptomatic, purple nodules over his left arm. On examination, several 3- to 5-mm, red-purple nodules occurred in a linear distribution along his left arm. Biopsy result was consistent with KS with positive immunohistochemical staining for HHV-8. HIV serology was negative. No treatment was initiated.

Over the next 2 years, several new lesions appeared on the arms and left lower extremity with biopsies consistent with KS. He then underwent local radiation with resolution of the lesions. When additional lesions appeared, he was treated with alitretinoin gel with good response.

DISCUSSION

First identified in 1994, HHV-8 is present in more than 95% of KS.[2] The seroprevalence of HHV-8 varies depending on the population, ranging from 3% to 5% in North America to more than 70% in sub-Saharan Africa. Most of those infected with HHV-8 will never go on to have KS.[3] For example, in a study from the Mediterranean, the annual incidence of KS was only 0.03% in men and 0.01% in women seropositive for HHV-8.[4] However, in the setting of immunosuppression, KS runs rampant, and it emerges as the most common malignancy associated with AIDS. In fact, the association between KS and HHV-8 was only discovered after a spike in the incidence of KS following the AIDS epidemic, peaking in the late 1980s at an age-standardized incidence of 33.3 per 100,000 person-years in the United States—more than 20,000 times more frequent than in the general population.[5,6]

The first described subtype, classic KS, is predominantly seen in the Ashkenazi Jewish, Mediterranean, and Eastern European populations with approximately a 3:1 male/female ratio. Two thirds of patients present past the age of 50 with indolent pink to violet lesions on the lower extremities that may regress or coalesce into larger plaques. In most cases, classical KS has a good prognosis with no significant impact on survival.

African endemic KS, the most rapidly fatal subtype, is further classified into the subgroups of nodular, florid, infiltrative, and lymphadenopathic. There is a high incidence among sub-Saharan Africans of up to 10% annually, and this subtype may account for up to 9% of all cancers in the region. Extreme HHV-8 prevalence of greater than 90% in many endemic sub-Saharan regions such as Uganda provided the proper conditions for the highest incidence of KS before the AIDS epidemic (>6 per 1000 person-years).[7]

Iatrogenic KS secondary to treatment-induced immunosuppression typically presents similarly to classical KS. It is quite rare in the West, with an incidence of less than 1% overall but up to 4% in Eastern European countries. The risk of iatrogenic KS is correlated to the length of time on immunosuppressive therapy, with mean onset to lesions of 16 months.[8] Iatrogenic KS will generally resolve completely upon cessation of immunosuppressive therapy, but the benefits of discontinuing immunosuppressive therapy must be balanced against risks such as transplant rejection.

AIDS-related epidemic KS affects HIV patients that have $CD4^+$ T-cell counts less than 500 cells/mm^3. The lesions of epidemic KS can be disfiguringly found on the face and often involve the visceral organs including the gastrointestinal tract, bones, and lungs. Because of increased visceral involvement with epidemic KS, its prognosis is poor. However, the incidence and severity of epidemic KS has dramatically decreased from a standardized incidence ratio of 22,100 to 3,640 compared with the general population after the advent of antiretroviral therapy.[9]

Non-epidemic KS is a rare, recently identified subtype of KS found in HIV-negative men who engage in sex with other men.[10,11] This subtype has been hypothesized to be related to the high prevalence of HHV-8 in semen and prostate samples.[12]

Our patients do not clearly fit into any of the existing subtypes of KS. None have HIV, are taking immunosuppressive drugs, are from Africa, nor are engaging in high-risk sexual behavior. They share no risk factors outside the general population HHV-8 seroprevalence of 3% to 5% in North America. The prevalent themes of HHV-8 seropositivity and immunodeficiency seem prerequisite factors for the development of KS across all patients. Of course, varying degrees of immunosuppression and immunosenescence may be caused by factors outside of HIV and medication effects. Although we did not identify any form of immunocompromise in our patients, it cannot be completely ruled out.

Unusual locations of KS outside the common locations on the bony prominences of the lower extremities have been well established since the latter 20th century.[13] Although classic KS has been documented across the skin surface and visceral surfaces, this point has been less emphasized lately

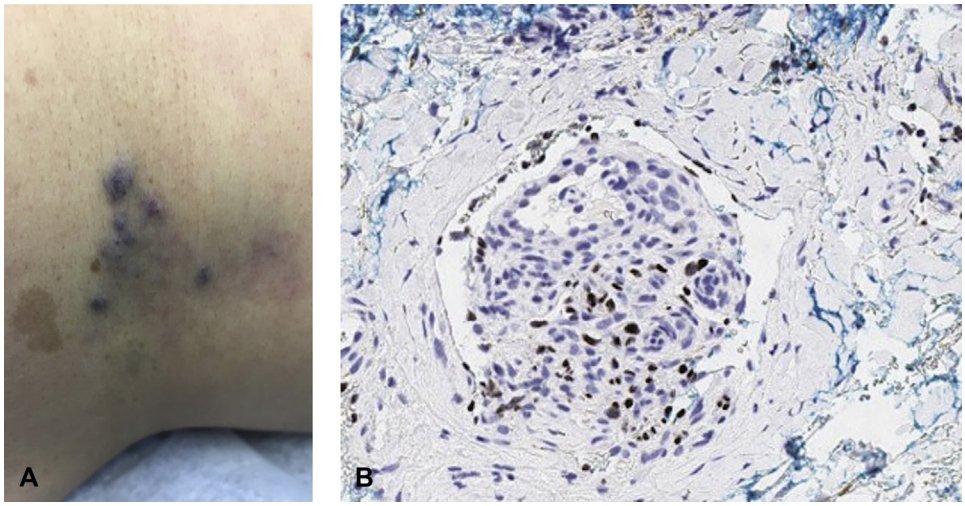

Fig 1. A, KS. A cluster of 6 dark, purple, dome-shaped papules over a light purple patch located on the left mid back. **B**, High-power view of HHV-8 immunohistochemistry highlighting blood and lymphatic endothelial cells.

in the literature. Perhaps the shortcomings of the current classification system, which relies on patient demographics and insufficiently accounts for all patients such as the 3 we presented, underscore the requirement for a revised classification system. One could, for example, propose a simplified classification system, consisting of 3 categories. Type I would encompass patients, such as our cases 1 and 3, and also include classic, nonepidemic, and many patients with iatrogenic KS. These would be patients who present with indolent, cutaneous lesions found predominantly, but not exclusively, below the umbilicus. Type II would encompass patients with African-endemic and AIDS-related epidemic KS, and would entail patients who present with aggressive disease with early visceral and lymphatic involvement, who are generally immunocompromised in some form or fashion. Finally, type III would encompass patients such as our case 2, who presented with disease that is not as aggressive as that of patients with type II KS nor as indolent as that of patients with type I KS. In the future, when more sensitive, quantitative measures of immunocompromise and immunosenescence are in general clinical use, a classification based on HHV-8 burden and quantitative immune response could be considered.

CONCLUSIONS

KS, an indolent vascular tumor, can present in myriad forms. Five clinical subtypes have been discussed in the literature, but not all lesions fit into 1 of the existing subtypes. In rare cases in which the patient does not have any risk factors for KS but the clinical presentation is suspicious, KS should still be considered in the differential diagnosis and ruled out with biopsy.

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