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Classic Kaposi sarcoma in an HIV-negative Han Chinese man: a case report

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Abstract

Kaposi sarcoma (KS) is a multifocal angioproliferative tumor of endothelial origin. Despite nearly identical clinical and histopathologic presentations, KS is classified into four distinct varieties: classic/sporadic, AIDS-associated, African/endemic, and iatrogenic. All subtypes are invariably linked to human herpesvirus-8 (HHV-8) and show a male predilection. Classic Kaposi sarcoma is exceedingly rare in the Asian population and its incidence varies by region and ethnic group predominance. A study in the Xinjiang region of China found that only 1% of classic KS cases occurred in patients belonging to the Han Chinese ethnic group, which formulates 84% of the Taiwanese population. Therefore, classic KS is extremely rare in Taiwan, with very few reports describing the manifestations of disease in this population. We report a case of an immunocompetent 68-year-old HIV-negative Han Chinese man born and raised in Taiwan with classic Kaposi sarcoma on his trunk and extremities.

Keywords: classic Kaposi sarcoma; Han Chinese; HIV-negative; Taiwan

Introduction

Kaposi sarcoma (KS) is an angioproliferative spindle cell tumor of endothelial origin first described in 1872 by Moritz Kaposi [1-5]. Before 1981, KS was considered an uncommon disease in the United States, primarily affecting elderly men of Eastern European, Jewish, and Mediterranean descent. Today this is known as the classic variant, which follows an indolent course [1, 5-7]. Classic Kaposi sarcoma presents in the lower limbs and feet in 85-98% of patients [5, 7, 8], with

trunk involvement in 9-15% of patients [7, 8] and very rare involvement of the viscera, lymph nodes, and oral cavity [1, 5-7]. Classic Kaposi sarcoma is very rare in the Asian population. In the Xinjiang region of China, 87% of cases of classic KS occurred in patients in the Uyghur ethnic group and only 1% in the Han Chinese ethnic group, although each compose approximately 40% of the population in the region [7]. People in the Han Chinese ethnic group populate 84% of Taiwan [9]. Therefore, it is not surprising that classic KS is extremely rare in Taiwan, with very few reports describing the manifestations of disease in this population [6, 10].

Case Synopsis

A 68-year-old immunocompetent HIV-negative Han Chinese man born and raised in Taiwan presented with a six-month history of lesions on his trunk and upper extremities, and a five-year history of similar lesions on his lower extremities. He had a known history of non-insulin dependent diabetes mellitus, but was otherwise healthy.



Figure 1. Erythematous and violaceous papules, nodules, and plaques with lichenification on the bilateral feet and ankles.



Figure 2. Multiple erythematous to purpuric papules and plaques on the back.



Figure 3. Erythematous papules coalescing into plaques on the right upper arm.

Examination revealed multiple erythematous to violaceous plaques on his trunk and extremities, as well as lichenified purpuric papules, nodules, and plaques on his bilateral lower extremities. Additionally, he had painful bilateral lower extremity edema that reduced his mobility; he reported a ten-pound weight loss with associated lethargy over the past six months. A biopsy from his left upper back revealed a dermal infiltrate of atypical spindle cells with slit-like spaces and focal red blood cell extravasation. Histologically, the lesions were compatible with the characteristic plaque stage of Kaposi sarcoma. Immunohistochemical studies confirmed the lesion was HHV-8 positive and HIV screening was negative. A diagnosis of classic Kaposi sarcoma was made. Given the diffuse nature of his

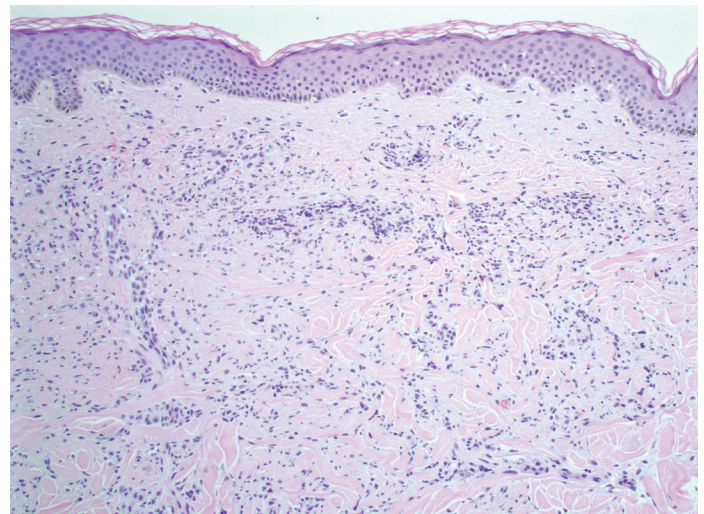


Figure 4. Punch biopsy of the left upper back shows dermal proliferation of atypical spindle cells and slit-like vascular spaces. There is focal red blood cell extravasation. (H&E, 100x)

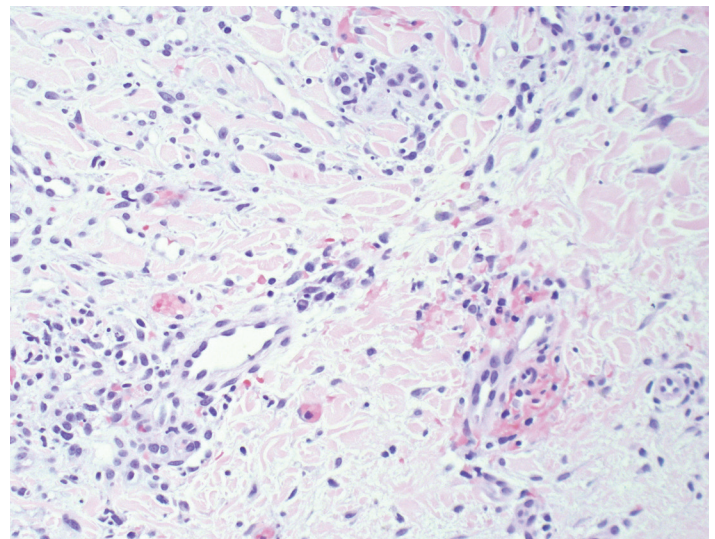


Figure 5. Biopsy shows prominent interlacing bundles of spindle cells, slit-like vascular spaces and extravasated red blood cells with scattered lymphocytes and plasma cells. (H&E, 200x).

lesions, he was treated with five rounds of systemic liposomal doxorubicin and paclitaxel, which led to flattening of the lesions, improvement in lesion color, and complete resolution of edema. A sixth and final round of chemotherapy was not administered owing to marked improvement in his lesions and unfavorable side effects including nausea, vomiting, and weight loss.

Case Discussion

Kaposi sarcoma (KS) is a multicentric neoplasm of endothelial origin characterized by proliferation of spindle cells, angiogenesis, and inflammation [1, 4]. Despite nearly identical histopathologic and clinical

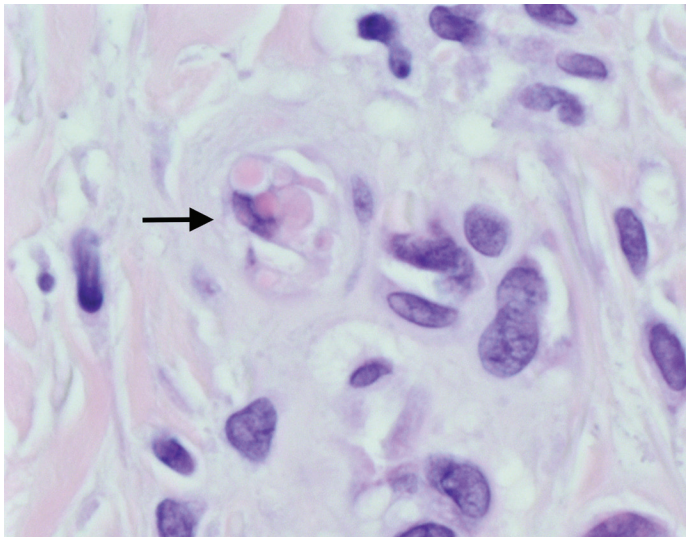


Figure 6. Biopsy shows two histiocytes with engulfed fragments of red blood cells (arrows), commonly referred to as intracytoplasmic hyaline globules. (H&E, 1000x, oil immersion).

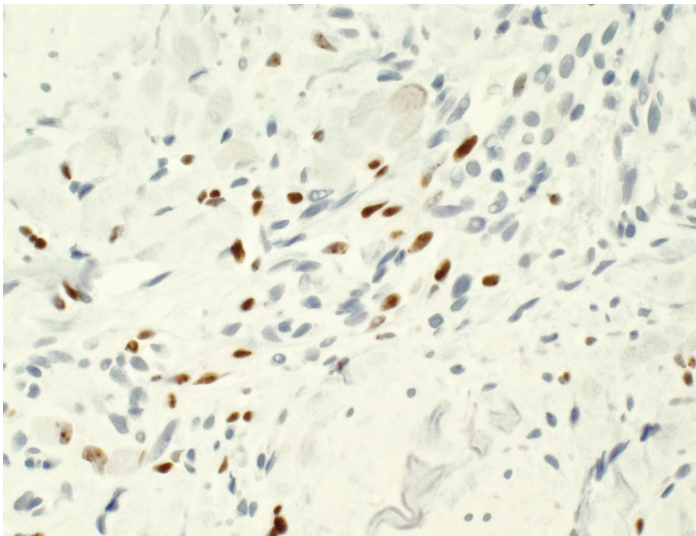


Figure 7. Human herpesvirus type 8 (HHV8) immunohistochemical stain demonstrates strong nuclear positivity in scattered spindle cells, 400x.

presentations, KS is divided into four distinct entities based on epidemiology, body site, and disease course: classic/sporadic, AIDS-associated, African/endemic, and iatrogenic [1-4]. Clinically, KS presents in the patch stage as irregularly shaped blue-red macules [1, 11]. These lesions evolve into plaques and nodules that enlarge into violaceous tumors [1]. These stages often coexist and may be associated with severe hyperkeratosis [1]. All subtypes are invariably linked to human herpesvirus-8 (HHV-8) and show a male predilection [7]. Histopathologic analysis in conjunction with immunohistochemical identification of HHV-8 is used to definitively diagnose KS.

Before 1981 in the United States, KS was considered an uncommon disease, primarily affecting elderly men of Eastern European, Jewish, and Mediterranean descent. Today this is known as the classic variant, which follows an indolent course [1, 5-7]. Classic KS presents in the lower limbs and feet in 85-98% of patients [5, 7, 8], with trunk involvement in 9-15% of patients [7, 8], and very rare involvement of the viscera, lymph nodes, and oral cavity [1, 5-7]. Furthermore, lower extremity edema is seen in 20-30% of patients with classic KS [1, 7, 12]. Although pain is the most common presenting symptom, approximately 50% of people are asymptomatic at presentation [8]. Notably, an increased risk of classic KS has been reported in patients with diabetes mellitus [13].

Classic KS treatment primarily involves slowing disease progression. Given its often indolent course, clinical observation may be preferred for asymptomatic patients with early-stage lesions [14]. Local chemotherapy, immunotherapy, and radiotherapy are effective in treating limited disease. Among localized therapies, a $\geq 50\%$ decrease in lesion size has been demonstrated in 62% of patients treated with intralesional vincristine, 50-90% treated with intralesional interferon- $\alpha 2$, and 56% treated with imiquimod [14]. Alitretinoin gel has demonstrated an overall response rate of 37% [15]. Radiotherapy has shown a complete response rate in 60-93% [14]. Additionally, surgical excision is limited to small, nodular lesions and has been associated with Koebner phenomenon [1, 14]. Systemic chemotherapies are reserved for disseminated and aggressive disease. Pegylated liposomal doxorubicin is frequently used as first-line therapy and has shown a $\geq 50\%$ decrease in lesion size in 71-100% of cases [14, 16]. For other commonly used systemic therapies, a $\geq 50\%$ reduction in lesion size has been documented in 58%-90% of patients for vinca-alkaloids, 74%-76% for etoposide, 93%-100% for taxanes, and 100% for gemcitabine [14].

The close association between HHV-8 and KS was first identified in 1994 using representational difference analysis. The major route of transmission is exposure to HHV-8-infected saliva in endemic areas, and sexual activity in non-endemic areas [17]. Human herpesvirus-8 prevalence varies between geographic

regions with the rates greater than 50% in sub-Saharan Africa, 20-30% in some Mediterranean countries, and less than 10% in most of Europe, the United States, and Asia [18]. Although the pathogenesis of Kaposi sarcoma remains unclear, HHV-8 infection has been found to be necessary but insufficient for the development of KS, likely requiring some degree of host immune dysfunction [11]. Human herpesvirus-8 induces an atypical differentiation of infected endothelial cells and promotes an endothelial-mesenchymal transition that increases invasiveness via cellular metalloproteinase MTT1-MMP [19]. Human herpesvirus-8 infected cells secrete pro-angiogenic cytokines such as VEGFR3 [19]. Kaposi sarcoma lesions often develop in sites of trauma or in individuals with chronic inflammation, such as AIDS patients. These findings suggest that activation of inflammatory pathways or repair mechanisms increases the risk of KS tumor development in HHV-8-infected individuals. Thus, it appears that HHV-8 not only promotes inflammation by releasing inflammatory cytokines such as vIL6, but also benefits from inflammatory environments [19].

The histopathologic findings of Kaposi sarcoma vary by clinical stage [11]. The characteristic histopathologic features of KS appear in the plaque stage and include proliferation of vascular channels composed of collagen and reticulin fibers appearing as clefts between increased spindle cells. Extravasated red blood cells and hemosiderin-laden macrophages are often present, giving KS lesions their characteristic erythematous to violaceous hue [1, 11]. Clusters of variably sized eosinophilic hyaline globules may be seen within spindle cells and macrophages in an intracytoplasmic location or may be seen extracellularly. The plaque stage normally involves most of the dermis, exhibiting the same histologic features as the nodular stage [1]. A chronic inflammatory infiltrate, including lymphocytes, plasma cells, and dendritic cells, is often present in variable amounts [1, 11].

Immunohistochemistry of lesional cells in Kaposi sarcoma reveals expression of vascular, lymphatic, and mesenchymal markers. Lymphatic markers include D2-40, LYVE-1, Prox-1, and VEGFR3 [11, 20]. Endothelial markers include factor VIII-related antigen, CD31 (PECAM-1), and CD34, with factor

CD34 present in the more advanced-stage lesions of KS [11]. Mesenchymal markers include vimentin and PDGFR α [20]. HHV-8 immunohistochemical stain is the most diagnostically sensitive and specific marker for KS diagnosis and targets a latency associated nuclear antigen-1 (LANA-1), which is a key HHV-8 gene product essential for maintaining episomal viral DNA during latent infection and for regulating cell division [1, 11, 21].

Conclusion

Although classic Kaposi sarcoma remains exceedingly rare in the Asian population, our report suggests that KS should still be considered in the differential diagnosis of HIV-negative Asian patients.

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