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Cutaneous HIV-associated Kaposi sarcoma: a potential setting for management by clinical observation

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Abstract

Kaposi sarcoma (KS) is a malignancy of viral etiology whose course ranges from cutaneous limited lesions to fulminant disease with multi-organ involvement. Four clinical variants of the disease exist: classic, endemic, iatrogenic, and epidemic. Iatrogenic and epidemic variants of Kaposi sarcoma develop in the setting of immune suppression. Transplant recipients who develop iatrogenic KS typically demonstrate improvement of lesions following de-escalation of immunosuppressive therapy. Similarly, HIV-infected patients who begin highly active antiretroviral therapy (HAART) experience immune reconstitution, which can induce KS regression. We describe two patients with varying clinical outcomes of cutaneous-limited HIV-associated KS after immune reconstitution with HAART. We propose that immune reconstitution with HAART, followed by clinical and radiographic surveillance for disease progression, may be an appropriate initial management strategy for limited cutaneous HIV-associated KS. In patients with more extensive disease at presentation or failure of HAART alone, antineoplastic therapy should be instituted.

Keywords: *acquired immunodeficiency syndrome, cutaneous, HAART, highly active anti-retroviral treatment, HIV, human immunodeficiency virus, immune, immunosuppression, Kaposi, KS, renal, transplant, sarcoma*

Introduction

Kaposi sarcoma (KS) was initially described by Moritz Kaposi at the University of Vienna in 1872. It is a virus-associated angioproliferative disorder of vascular

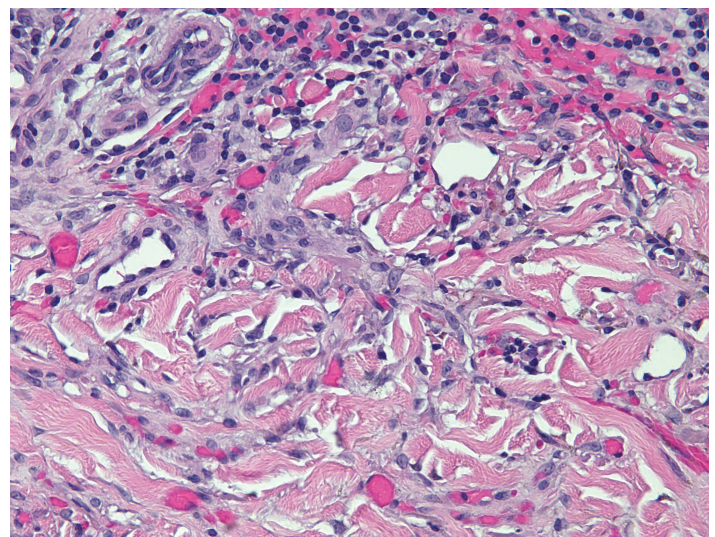
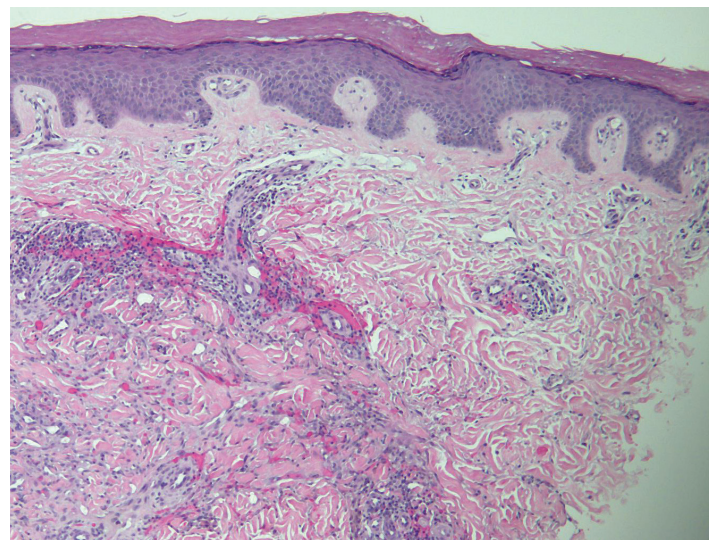


Figure 1. There is a proliferation of atypical appearing spindled cells forming blood filled slit-like spaces throughout the reticular dermis. Hemorrhage is also noted into the interstitial space. These atypical cells can be seen extending to both lateral margins. H&E, Top, 4x; Bottom, 40x.

endothelium with a multifactorial pathogenesis [1-8]. The sarcoma is multifocal and its course ranges

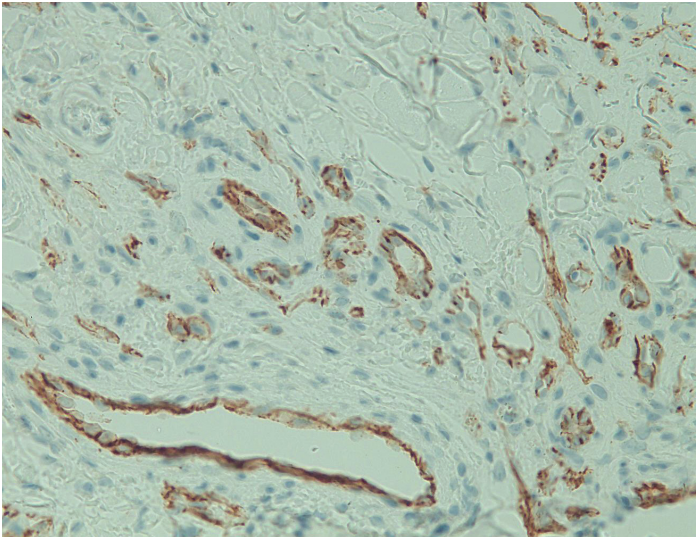


Figure 2. Immunohistochemical slides show positive staining of the vessels with CD31. 40x.

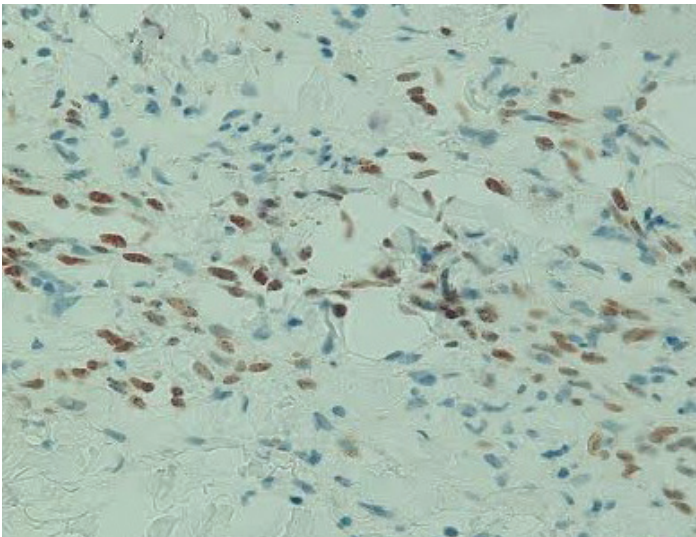


Figure 3. Immunohistochemical slides show positive staining of individual endothelial cells with HHV-8 latency-associated nuclear antigen (LANA). A, 10x; B, 40x.

from innocuous lesions confined to mucocutaneous tissues to fulminant disease with extensive visceral involvement leading to death [2, 4, 5].

Four clinical variants of the disease exist: classic, endemic, iatrogenic, and epidemic [2-6]. Each variant is associated with a different patient population, site predilection, clinical course and prognosis [4]. Classic KS is a mild variant that historically affects the lower extremities of elderly Mediterranean men [3, 4]. Endemic KS affects children and young adults in sub-Saharan Africa who are HIV-seronegative [4]. In the 1970s, the iatrogenic form of KS was described in organ transplant patients receiving

immunosuppressant treatment [2].

Epidemic KS, also termed acquired immunodeficiency syndrome-associated KS (AIDS-KS), emerged in 1981 and is currently the most common and most aggressive form [4]. Infection with human herpesvirus-8 (HHV-8), also termed Kaposi sarcoma-associated herpesvirus (KSHV), appears to be a necessary factor in the development of all variants of clinical disease [2-5, 9-11]. Genetic, immunologic, and environmental factors all contribute to the potential for malignant transformation following infection [2].

Immune suppression is the prominent and common feature of the iatrogenic and epidemic variants of Kaposi sarcoma. Two patients with limited cutaneous HIV-associated KS with varying clinical outcomes in response to immune reconstitution with highly active antiretroviral therapy (HAART) are described. The strategy of HAART therapy coupled with clinical and radiographic surveillance for disease progression as a primary means of treatment for limited cutaneous KS is also discussed.

Case Synopsis

Patient 1

In 2013, a 52-year-old man was referred by his primary care physician for painful, pruritic lesions of his left ankle of four months duration. He was afebrile and did not have any associated symptoms (chills or night sweats) or weight loss. In 1998, he was diagnosed with HIV, which was well controlled on HAART (abacavir-lamivudine, fosamprenavir) since that time, with a most recent CD4 count of 603 and an undetectable viral load.

Physical examination revealed two lesions of the left medial ankle, both approximately two centimeters in diameter. The lesions were flat, smooth, and vascular appearing with poorly demarcated borders. There were no oral lesions and no palpable lymphadenopathy.

Microscopic examination of a lesional biopsy revealed a proliferation of atypical appearing spindle cells forming blood-filled slit-like spaces throughout the reticular dermis. Immunohistochemical studies showed positive staining for CD31 and HHV-8

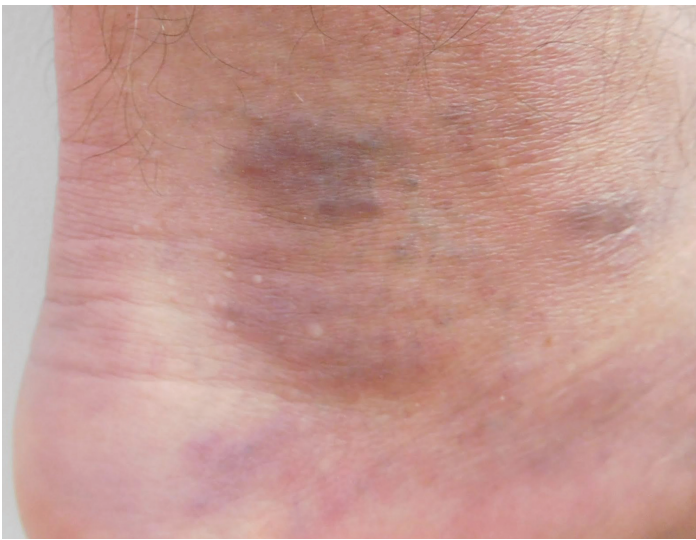


Figure 4. Kaposi sarcoma in an HIV-infected 52-year-old man. There has been neither progression of cutaneous KS nor development of systemic involvement during a 3 year period during which the patient has been monitored on HAART. On the left medial malleolus and lower shin, there are multiple, grouped, violaceous papules and plaques of varying size and shape (Top). On close examination, multiple violaceous to faintly erythematous grouped papules coalescing into plaques are noted on the left medial malleolus (Bottom).

latency-associated nuclear antigen (LANA) (**Figures 1, 2 and 3**). The clinical presentation and pathology findings established a diagnosis of patch stage Kaposi sarcoma.

He was referred to an oncologist for evaluation. A comprehensive workup was performed including a chest roentgenogram, stool immunochemical test for occult blood, esophagogastroduodenoscopy, and colonoscopy. All of these studies were negative for visceral involvement of his sarcoma.

Since his KS cutaneous involvement was limited without any evidence of systemic disease and because his HIV status (CD4 count and viral load) was well controlled, the patient was continued on his HAART regimen without any KS-directed antineoplastic treatment. He subsequently experienced complete resolution of pain and pruritus. In addition, there has been no progression of KS skin lesions (**Figure 4**) or onset of systemic involvement for three years.

Patient 2

A 34-year-old man, diagnosed with HIV-AIDS in 2008, presented to the hospital for lower extremity cellulitis. His HIV was poorly controlled with the most recent CD4 count of 22 and a viral load of 150,715.

Physical examination revealed edema and tenderness of the left lower extremity. There was a fluctuant area measuring approximately two to three centimeters in diameter on the left medial foot. In addition, both legs were indurated and hyperpigmented. A one centimeter nodule with a peripheral collarette of scale was noted on his left lower leg.

Histopathologic examination of the shave biopsy of the left lower leg lesion revealed large nodules of vascular tumor cells filling the dermis with extravasation of erythrocytes interspersed throughout (**Figure 5A, B**). Immunohistochemical studies demonstrated expression by the tumor cells of CD34 and HHV-8. Interpretation of the clinical presentation and pathology findings established a diagnosis of nodular stage Kaposi sarcoma.

Computerized tomography of his chest, abdomen, and pelvis revealed bilateral axillary and inguinal lymphadenopathy. There was no evidence of solid organ involvement by the sarcoma. He had developed resistance to prior therapies and was restarted on HAART therapy (etravirine 200 mg BID, dolutegravir 50 mg BID, darunavir 600 mg BID, and ritonavir 100 mg BID).

Follow up evaluation after 3 months revealed improvement of HIV control with a CD4 count of 173 and the viral load decreased to 46. There had been some regression of his KS lesions following the improvement of his immune status (**Figure 6A, B**). However, owing to the persistent, extensive

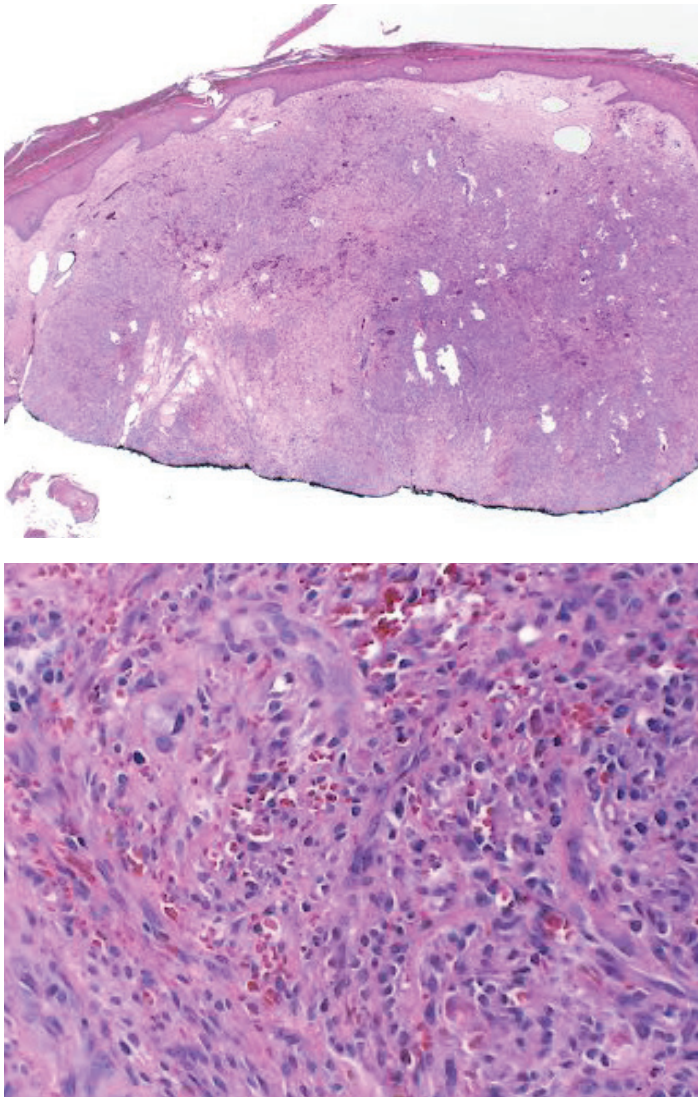


Figure 5. Distal (A) and closer (B) views of Kaposi sarcoma. There are large nodules of vascular tumor cells that fill the dermis. Intravascular and extravasated erythrocytes are present. H&E; Top, 2x; Bottom, 20x.

cutaneous involvement of his sarcoma with inguinal lymphadenopathy, the patient opted to move forward with chemotherapy to manage his KS.

Case Discussion

Kaposi sarcoma is a neoplasm caused by an oncogenic virus whose pathogenesis hinges on immune dysfunction [2, 3, 9]. Immune suppression puts patients at an increased risk for developing certain cutaneous malignancies and cancers of infectious etiology—such as KS—are of particular concern in this population [11-13]. Indeed, the incidence of KS is increased in both solid organ transplant patients receiving immunosuppressive therapy and HIV infected patients with low CD4 counts and high viral loads [4, 9, 11, 13, 14].

The incidence of KS in post-transplant patients compared to the general population is 400-500 times greater [1, 5, 9]. Certain drugs have been associated with iatrogenic KS such as anti-tumor necrosis factor (TNF) drugs, azathioprine, corticosteroids, cyclosporine, and rituximab. However, there is no clear relationship between either the dose or the duration of treatment and development of neoplastic disease [4]. There is no uniform consensus on treatment of KS in post-transplantation patients. However, the mainstay of therapy is immune reconstitution by immunosuppressant-associated medication de-escalation, which leads to remission in most patients [1, 3-5, 15].

KS is classified as an AIDS defining condition by the Centers for Disease Control and Prevention, and the risk of developing KS in patients infected with HIV is over 2,000 times that of the general population [8, 12-14, 16, 17]. A similar trend that shows an increased incidence of KS associated with immunodeficiency and subsequent resolution of malignancy with immune constitution is evident in HIV infected patients. Indeed, since the introduction of HAART, the incidence of KS in this population of patients has fallen dramatically [2,4,5,8,16-20].

The prognosis of KS in both transplant recipients and HIV-infected patients predominantly depends on the extent of disease and rate of tumor growth at the time of diagnosis [1, 2]. Patients with KS lesions limited to the skin have more favorable outcomes in comparison to the high mortality rate observed in patients with visceral involvement [1]. There is no universally accepted protocol for KS management. The first step is diagnosis. Following a complete physical examination, biopsy of suspected lesions for routine hematoxylin and eosin staining should be performed. In addition, immunohistochemical staining for KS markers such as CD31, CD34, and LANA, and polymerase chain reaction studies for HHV-8 DNA can be done [1, 5, 6, 9, 18].

Next, disease staging should be defined by conducting a comprehensive work up. This, in part, should be based on symptoms. It may include bronchoscopy, colonoscopy, esophagogastroduodenoscopy, and thoraco-abdominopelvic computerized tomography [1, 5, 9, 18].



Figure 6. HIV-associated Kaposi sarcoma in a 34-year-old man presenting as woody induration with thickening and hyperpigmentation of the skin of the left lower leg. A solitary, shiny, dome-shaped papule with peripheral collarette of hyperkeratosis can be seen on the medial lower shin (Top). A hyperpigmented plaque with overlying hyperkeratosis and central, punched out, circular erosion can be seen on the left mediolateral foot. Hyperpigmented, poorly defined macules and indurated papules extend onto the central plantar surface (Bottom).

Treatment options for KS in transplant recipients and HIV-infected patients range from clinical observation with efforts to improve immune status, to chemotherapy, radiation, and surgical excision [1]. If the tumor is determined to be limited to the skin, several investigators suggest that the mainstay of therapy should be immune reconstitution [2, 3, 9]. Similar to transplant patients who experience KS improvement following immunosuppressive de-escalation, HAART alone may result in disease stabilization or remission in HIV-infected patients with

slowly progressive cutaneous KS [2-5, 9, 15, 18, 20]. HAART with concomitant systemic chemotherapy should be reserved for patients with rapidly progressive, extensive disease, visceral involvement, or lack of improvement with HAART alone [2, 18].

We present two patients with HIV-associated, cutaneous-limited KS for whom immune reconstitution with careful clinical observation was appropriate initial management. The first patient experienced improvement of symptoms with no change in lesion appearance or distribution for three years while on HAART. He continues to be monitored closely through regular follow up. The second patient also had improvement of symptoms and some of his lesions; however, he was subsequently deemed a chemotherapy candidate owing to his more extensive initial disease and sluggish response to immune reconstitution. Both of these patients highlight the importance of individualized management of HIV-associated KS. Our findings suggest that an initial comprehensive evaluation, driven by symptomology, should be performed in HIV-positive patients with limited cutaneous KS. For these HIV-infected individuals with KS localized only to their skin, a reasonable treatment strategy may be immune reconstitution with HAART and periodic follow up examination to confirm the continued absence of systemic disease.

Conclusion

Kaposi sarcoma is a virus-associated malignancy that develops in the setting of immune dysfunction. Similar to transplant recipients who experience KS improvement following immunosuppressive therapy de-escalation, HAART improves immune function in HIV patients and can halt KS progression. We present one patient who experienced disease stabilization on HAART alone and one patient requiring HAART and chemotherapy owing to lack of adequate response to HAART alone. Therefore, after the diagnosis of KS is confirmed by biopsy and neoplastic disease staging (through endoscopy and CT scans) has been performed to exclude systemic disease, HAART-mediated immune reconstitution with careful clinical follow up is an appropriate initial management approach to limited cutaneous HIV-associated KS. Antineoplastic therapy should be instituted in patients with more extensive disease or

lack of response to HAART alone.

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