Kaposi Sarcoma

Oana Radu, MD; Liron Pantanowitz, MD

Kaposi sarcoma (KS) was first described by the Viennese dermatologist Moritz Kaposi1 (1837–1902) more than a century ago. This enigmatic vascular neoplasm has since received much attention in the literature, especially after recognition of its association with the acquired immune deficiency syndrome (AIDS) in the early 1980s. The etiologic agent Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) was identified in KS lesions by Chang et al2 in 1994. This triggered the accrual of much more information about KS, particularly as KS is used as a model to study various aspects of carcinogenesis, including viral oncogenesis, angiogenesis, and cancer immunology. Worldwide HHV8 seropositivity exceeds the incidence of KS, suggesting that other cofactors (eg, blood-sucking arthropods and iron) may be implicated in KS development.

Kaposi sarcoma is a low-grade vascular tumor that may involve the skin, mucosa, and viscera, developing in 1 of 4 epidemiologic-clinical forms of KS include classic, African (endemic), AIDS-associated (epidemic), and iatrogenic KS. New clinical manifestations have been described, such as antiretroviral therapy–related KS regression or flares. Kaposi sarcoma lesions evolve from early (patch stage) macules into plaques (plaque stage) that grow into larger nodules (tumor stage). Newer histologic variants include anaplastic, hyperkeratotic, lymphangioma-like, bullous, telangiectatic, ecchymotic, keloidal, pyogenic granuloma–like, micronodular, intravascular, glomeruloid and pigmented KS, as well as KS with sarcoidalike granulomas and KS with myoid nodules. Latency-associated nuclear antigen (HHV8) is the most specific immunohistochemical marker available to help distinguish KS from its mimics. Since KS remains one of the most common AIDS-defining malignancies, it is important that pathologists be able to recognize KS and its contemporary manifestations.

PATHOGENESIS

With the advent of genomic technologies, we now know that proliferating KS spindle tumor cells are of endothelial origin, confirming former studies that used histochemistry and ultrastructural findings. Circulating blood mononuclear and endothelial “progenitor cells” are believed to be the source of early KS lesions. Infection with HHV8 reprograms the host’s blood endothelial cells so that they resemble lymphatic endothelium, upregulating several lymphatic-associated genes such as lymphatic vessel endothelial receptor 1 (LYVE1), podoplanin, and vascular endothelial growth factor receptor 3 (VEGFR3).6 However, HHV8 infection alone appears to be insufficient for the development of KS. Kaposi sarcoma progression relies also on some degree of host immune dysfunction and the local inflammatory milieu.7,8 Kaposi sarcoma growth involves the upregulation of many key HHV8 gene products, such as the latency-associated nuclear antigen (LANA-1 or LNA-1). Like other herpesviruses, HHV8 remains latent within cells and has developed a variety of mechanisms to evade the host immune system. The growing understanding of these and other molecular events involved in KS development has fueled a number of clinical trials using novel therapeutic agents.9

CLINICAL FEATURES

The 4 recognized epidemiologic-clinical forms include classic, African (endemic), AIDS-associated (epidemic), and iatrogenic (or transplant-associated) KS (Table). Patients of any age may develop KS, even newborns. In general, there is a male predilection. The lack of sex hormone receptors on KS tumor cells argues against a direct effect of sex hormones and suggests that other unknown factors may be involved in this sex bias. Human immunodeficiency virus (HIV)–related KS in

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Different Epidemiologic-Clinical Forms of Kaposi Sarcoma (KS)

<table>
<thead>
<tr>
<th>KS Type</th>
<th>Epidemiology</th>
<th>Clinical Distribution</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Mainly males aged 40–70 years, of Mediterranean or Jewish Ashkenazi origin</td>
<td>Skin of the lower extremities, but mucosal and visceral lesions may develop</td>
<td>Indolent</td>
</tr>
<tr>
<td>African</td>
<td>Middle-aged black adults and children from equatorial Africa</td>
<td>Multiple localized skin tumors, involving lower extremities and lymph nodes</td>
<td>Progressive: lymphadenopathic form is aggressive</td>
</tr>
<tr>
<td>AIDS-associated</td>
<td>Mainly homosexual males and intravenous drug users aged 20–50 years; now equally affects women and children in Africa</td>
<td>Disseminated mucocutaneous and visceral involvement</td>
<td>Aggressive; lesions may regress or flare with initiation of antiretroviral therapy</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Immunosuppressed persons of any age from autoimmune disease, drugs, or transplantation</td>
<td>Localized mucocutaneous or disseminated KS, with possible visceral lesions</td>
<td>Variable; may regress after immunosuppression is discontinued</td>
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Africa, however, has begun to show an equal incidence of KS in men and women. A second non-KS hematologic malignancy is often present in patients with classic KS. African KS follows a more aggressive course than classic KS, especially the lymphadenopathic form that affects young individuals. In HIV-infected persons, KS is an AIDS-defining illness. AIDS-associated KS (AIDS-KS) usually, but not exclusively, arises in HIV-positive patients with low CD4 T-cell counts. AIDS-KS is a much more aggressive disease that typically manifests with disseminated lesions (Figure 1) and visceral involvement. This may be attributed to the fact that HIV infection augments HHV8 replication. Kaposi sarcoma exhibits a less aggressive presentation in patients already receiving highly active antiretroviral therapy (HAART). Exacerbation (also called KS flare) can occur after therapy (e.g., corticosteroids, rituximab) or subsequent to the immune reconstitution inflammatory syndrome that may occur when initiating HAART in HIV-infected persons. Iatrogenic KS is associated with immunosuppression due to drugs or after transplantation. Kaposi sarcoma occurs mainly in renal transplant recipients, and infrequently after other solid organ or bone marrow transplants. Posttransplant KS may result from reactivation of latent HHV8 infection in recipients or from tumor cells contributed from organ donors. Transplant-associated KS has a protracted, but aggressive course. Fortunately, in transplant recipients, KS lesions may regress after discontinuation of immunosuppressive therapy.

In all of the aforementioned clinical settings, KS lesions evolve from early (patch stage) macules into plaques (plaque stage) that may subsequently develop into larger nodules (tumor stage). These tumors may ulcerate, cause marked lymphedema, present as exophytic growths, cutaneous horns, or invade subjacent tissues (e.g., underlying bone). Different stages can coexist in the same individual at the same time. Similar stages of KS growth apply to both cutaneous and mucosal lesions. While KS commonly presents at mucocutaneous sites, tumors may involve lymph nodes as well as visceral organs, most notably the respiratory and gastrointestinal tracts. Extracutaneous KS has also been described in unusual anatomic locations including the musculoskeletal system, nervous system, heart, wounds, within pneumocystis lesions, and in blood clots. A 2-tiered staging system exists for AIDS-related KS, according to the AIDS Clinical Trials Group (ACTG): T0 is used for KS confined to the skin and lymph nodes with minimal oral involvement, and T1 refers to KS with ulceration or associated edema, nodular oral KS, or KS involvement of any other visceral organ. A different staging system is available for classic KS to facilitate therapeutic decision making.

HISTOPATHOLOGY

The histopathology of KS is essentially identical in the different epidemiologic KS types. Nevertheless, some studies have documented minor histopathologic differences between AIDS-KS and non-HIV–associated KS cases, namely, that mitoses and cellular anaplasia are more common in HIV-negative patients, whereas AIDS-KS lesions tend to display more extensive dissecting vessels. Early patch-stage KS is characterized by abnormal vessels lined by thin endothelial cells dissecting the dermis. Ramifying proliferating vessels often surround larger ectatic vessels and skin adnexa, producing the so-called promontory sign. This sign is not pathognomonic for KS, as it has also been described in other vascular lesions including benign vascular tumors and angiosarcoma. Sparse chronic inflammatory cells, extravasated red blood cells, and hemosiderin-laden macrophages are frequently present in patch KS lesions. These early histologic changes may be inconspicuous, and for that reason can be easily missed on biopsy.

Plaque-stage KS lesions are characterized by a proliferation of both spindle cells and vessels, which in the skin involve most of the dermis, and sometimes even the subcutis. Well-developed KS tumors consist of several fascicles of these spindle-shaped tumor cells (Figure 2), often admixed with a variable chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and dendritic cells. Kaposi sarcoma lesions also contain several hemosiderin-laden macrophages. This is not surprising as iron appears to be important in the pathogenesis of KS. Iron staining may help distinguish KS from similar-appearing interstitial granuloma annulare lesions that lack iron. In cross section, KS nodules display a sievelike appearance caused by the transection of spindle cells with intervening slitlike spaces. Fine-needle aspiration specimens show cohesive clusters of these spindle cells, typically present in a bloody background (Figure 3). Eosinophilic and periodic acid-Schiff (PAS)–positive hyaline globules are a common finding in advanced KS lesions. These globules may be located within lesional cells or extracellularly. Electron microscopy may show occasional Weibel-Palade bodies within lesional cells, as well as intracellular fragmented erythrocytes that are believed to correspond to the hyaline globules seen by light microscopy. Typical KS lesions are devoid of marked cellular pleomorphism, necrosis, or a significant number of mitotic figures. In rare instances, AIDS-KS lesions may harbor concomitant pathologic findings, usually an opportunistic...
pathogen (eg, cryptococcosis, mycobacterial granulomas, or molluscum contagiosum).16

In patients with HIV infection, HAART may lead to partial or complete regression (reduced size, flattening, and color change from violaceous to brown) of KS lesions. Partially regressed lesions have some residual spindled cells. However, with complete regression, spindle cells are absent. Completely regressed lesions have an increase in dermal capillary density around native dermal vessels and appendages, an increased perivascular infiltrate containing many plasma cells, and numerous hemosiderin-laden dermal macrophages.17 Regressed lesions may also become sclerotic, especially those that are subjected to intralesional chemotherapy injection.

HISTOLOGIC VARIANTS

Several histologic variants of KS have been described (Figure 4, A through D).18,19 Their clinical significance remains largely unknown. The spectrum of KS has been expanded to include pre-KS lesions, also referred to as an “in situ” form of KS.20 These pre-KS lesions are characterized by groups of abnormal capillary-like vessels admixed with an inflammatory infiltrate, similar to patch-stage KS lesions. They are associated with lymphangiogenesis arising in the setting of chronic lymphedema. On the other end of the spectrum is anaplastic KS, sometimes referred to as pleomorphic KS. Anaplastic KS is an infiltrative, solid proliferation of spindle cells without vascular spaces, seen mainly in AIDS involving acral sites.21 This aggressive variant displays a greater degree of cellular and nuclear atypia, high mitotic index (eg, 5 to 20 mitoses per 10 high-power fields), and occasional necrosis. There are also several lymphematosous variants, best classified according to their association with ectatic lymphatics (lymphangioma-like KS and lymphangiectatic KS) or due to the accumulation of dermal and/or intradermal edema (bullous KS).22 Lymphangioma-like KS (or lymphangiomatous) KS is characterized by many ectatic, interanastomosing vascular channels usually devoid of erythrocytes. Some of these channels may closely abut the overlying epidermis, analogous to lymphangioma circumscriptum. This differs from the telangiectatic variant of KS in which KS lesions contain large, very congested, ectatic vascular spaces. With ecchymotic KS, on the other hand, the intradermal KS proliferation is accompanied by extensive red blood cell extravasation (purpura effect), often so marked that it almost obscures the underlying histologic features of KS. Glomeruloid KS is used to describe KS lesions, or areas within KS lesions, that contain relatively circumscribed, congested glomeruloid vascular structures. Intravascular KS is reserved for those rare cases that have an exclusively intravascular solid spindle cell proliferation.23

Hyperkeratotic (verrucous) KS is related to severe KS-associated lymphedema that causes verrucous epidermal acanthosis, hyperkeratosis, and fibrosis overlying a deep KS lesion. Lymphematosous AIDS-KS may also be associated with exophytic dermal fibroma-like nodules. In keloidal KS, there is marked expansion of the dermis by dense, hyalinized collagen that resembles a keloid.24 Because the abundant collagen obscures the KS spindled cells, this variant may be mistaken for scar tissue. Micronodular KS refers to nodular KS lesions characterized histologically by a small, unencapsulated, circumscribed spindle cell proliferation in the reticular dermis. These small KS tumors may sometimes be entirely removed in a skin punch biopsy. Superficially located KS lesions that protrude from the skin and elicit a peripheral epidermal collarette may resemble a pyogenic granuloma (PG); such lesions have accordingly

Figure 1. Human immunodeficiency virus–positive patient showing disseminated AIDS-associated cutaneous Kaposi sarcoma plaques on his body (image courtesy of Bruce J. Dezube, MD).

Figure 2. Kaposi sarcoma tumor showing fascicles of spindled cells with extravasated red blood cells and scattered chronic inflammatory cells (hematoxylin-eosin, original magnification X200).
been referred to as pyogenic granuloma–like KS. In KS with myoid nodules, nodular KS is associated with intratumoral myoid nodules, similar to those that may be seen in some dermatofibrosarcoma protuberans lesions. Pigmented KS is another rare variant attributed to the presence of increased numbers of melanin-laden dendritic cells intimately admixed with KS spindle tumor cells, often seen in paucivascular anaplastic KS.25 Kaposi sarcoma with sarcoidlike

Figure 3. Cytology specimen of a Kaposi sarcoma lesion showing a cohesive group of spindled tumor cells present in a bloody background (hematoxylin-eosin, original magnification ×200).

Figure 4. Different Kaposi sarcoma (KS) variants. A, Anaplastic KS. B, Telangiectatic KS. C, Glomeruloid KS. D, Keloidal KS. Images courtesy of Wayne Grayson, MBCh, PhD, FCPath (hematoxylin-eosin, original magnifications ×400 [A and C] and ×200 [B]; Masson trichrome, original magnification ×200 [D]).

Figure 5. Kaposi sarcoma spindle tumor cells showing nuclear LNA-1 (latency-associated nuclear antigen) staining (original magnification ×600).
granulomas has also been observed, which appears to be related to mycobacterial infection in AIDS-KS lesions.26

IMMUNOHISTOCHEMISTRY

More than 100 different primary antibodies have been evaluated in KS with immunohistochemistry.27 Kaposi sarcoma lesional cells stain positively with the endothelial markers factor VIII–related antigen, CD31 (PECAM-1), and CD34. CD34 tends to show stronger expression than CD31 in advanced-stage lesions of KS. Kaposi sarcoma spindle cells also express several lymphatic specific markers such as D2-40 (which binds to the podoplanin antigen), LYVE-1 (a homologue of the CD44 glycoprotein receptor for hyaluronan), VEGFR-3 (the receptor for vascular endothelial growth factor C), and Prox-1. Bcl-2 also shows positivity in KS, related to the tumor’s mechanisms of resisting apoptosis. The identification and localization of HHV8 within KS lesional cells by using LNA-1 is the most diagnostically helpful immunostaining technique available to differentiate KS from its mimics. LNA-1 immunoreactivity in KS cells appears as stippled nuclear staining (Figure 5). However, HHV8 is not entirely limited to KS and has been detected in some angiosarcomas, hemangiomatas, and dermatofibromas.28 LNA-1 immunohistochemistry is favored over polymerase chain reaction detection of HHV8 in the evaluation of problematic vascular proliferations because contaminating mononuclear inflammatory cells may also harbor this herpesvirus, especially in HIV–positive patients.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of KS and its variants is broad. Clinical history, such as HIV infection or status post transplant, may strongly support the diagnosis of KS. Even in these clinical settings, patch-stage cutaneous KS lesions may need to be differentiated from targetoid hemosiderotic hemangiomata, fibrous histiocytoma, and interstitial granuloma annulare. The histologic differential diagnosis of plaque-stage KS includes tufted angioma, targetoid hemo- siderotic hemangiomata, microvenular hemangiomata, and acroangiodematitis (“pseudo–Kaposi sarcoma”). Lesions that may potentially be confused with nodular KS include bacillary angiomatosis, other vascular tumors (eg, spindle cell hemangiomata and Kaposiform hemangioendothelioma), fibrohistiocytic tumors (eg, cellular, angiomatoid, and atypical variants of fibrous histiocytoma, and dermatofibrosarcoma protuberans), resolving dermal fasciitis, spindle cell melanoma, and several other spindle cell mesenchymal neoplasms (eg, cutaneous leiomysarcoma). Advanced and more aggressive forms of KS need to be differentiated from angiosarcoma.

Paucivascular anaplastic KS needs to be distinguished from other high-grade sarcomas (eg, leiomysarcoma, spindle cell rhabdomyosarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma), amelanotic spindle cell mel- anoma, and spindle cell carcinoma. Pigmented anaplastic KS may mimick melanoma, especially when present on acral sites. Lymphangioma-like KS may resemble other benign lymphatic tumors such as lymphangioma circumscriptum or a lymphangioendothelioma/acquired progressive lymphangioma. The architectural arrangement of telangiectatic KS may mimick a sinusoidal hemangiomata, an uncommon acquired variant of cavernous hemangiomata. Keloidal KS may be mistaken for a true keloid scar, especially if there has been a previous nearby biopsy. Pyogenic granuloma–like KS may be misdiagnosed as a true PG (lobular capillary hemangiomata), especially if the surface is traumatized and ulcerated. The differential diagnosis of intravascular KS includes intravascular papillary endothelial hyperplasia, intravenous PG, intravascular fasciitis, papillary intralym- phatic angioendothelioma (Dabska tumor), and intravascu- lar myopericytoma. Finally, without any prior clinical knowledge that KS lesions have responded to therapy, regressed KS lesions may be misdiagnosed clinically and histologically as pigmented purpuric dermatitis. For most of the aforementioned vascular entities, immunohistochemis- try using vascular markers (CD31 or CD34) and/or lymphatic markers (D2-40) is not as specific as LNA-1 in diagnosing KS.

THERAPY AND PROGNOSIS

Treatment goals of KS include symptom palliation, prevention of KS progression, improvement of cosmesis, and abatement of associated edema, organ compromise, and psychologic stress.29 At present there is no cure for KS. Surgical excision is restricted for cosmetically disturbing KS lesions, to alleviate discomfort, or to control local tumor growth. Other local therapies used to manage bulky lesions or for cosmesis include external beam radiation, laser therapy, cryotherapy, photodynamic therapy, topical altretinoxin gel, and intraleseal vinblastine. Indications for systemic chemotherapy include widespread skin involvement (>25 lesions), extensive oral KS, marked symptomatic edema, rapidly progressive disease, symptomatic visceral KS, and KS flare. Currently, liposomal anthracyclines and taxanes are the backbone of systemic cytotoxic therapy against KS. Several novel therapies have been tried with some success including interferon α, thalidomide, antipheres therapy, imatinib and matrix metalloproteinase inhibitors (eg, COL-3). While HHV8 is susceptible to antiviral medications (eg, ganciclovir) in the lytic phase, unfortunately most cells in KS lesions harbor HHV8 in its latent phase.

Apart from HAART, treatment options are similar for the different epidemiologic forms of KS. Optimal control of HIV infection, using antiretroviral therapy, is a key component in the treatment of AIDS-KS. HAART has greatly decreased the incidence of AIDS-KS. Before the advent of HAART, the ACTG staging system for AIDS-KS correlated well with survival. Since the introduction of HAART, factors suggestive of an unfavorable prognosis include age 50 years or older, positive HHV8 DNA finding in plasma at the time of diagnosis, advanced KS with systemic disease (especially pulmonary lesions), and a concomitant AIDS-associated illness. For iatrogenic KS, adjustment of immunosuppres- sive therapy may be necessary, as well as the introduction of sirolimus (rapamycin) for patients with posttransplant KS. The discovery of HHV8 and related data about the pathogenesis of KS have resulted in the identification of multiple novel therapeutic targets (eg, bevacizumab targeting possible inhibition of vascular endothelial growth factor), many of which are being investigated in ongoing clinical trials.30

CONCLUSIONS

Kaposi sarcoma is a low-grade vascular tumor of endo- thelial origin that is associated with HHV8 infection. The extent and aggressiveness of KS tumors depends on the epidemiology (classic, African, AIDS-associated, and iatro-
genic KS) and host immunity. The histopathology in these different KS forms is essentially identical. Pathologists need to be aware that there are several newer histologic variants and clinical manifestations, including KS regression and exacerbation. LNA-1 (HHV8) is the most specific immunohistochemical marker available to help confirm the diagnosis and distinguish KS from its mimics. In some regions of the world, particularly sub-Saharan Africa, AIDS–KS remains the most common HIV-associated malignancy encountered and is therefore the leading cancer diagnosed. Fortunately, the expanding knowledge of KS biology is providing increasing opportunities for rational targeted therapies.

**References**