Lymphadenopathic Form of Endemic Kaposi Sarcoma in an HIV-negative Gambian Male

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Abstract
Kaposi sarcoma (KS) is a multicentric neoplasm of vascular and lymphatic endothelial origin that can involve the skin, lymph nodes, and visceral organs. Human herpesvirus 8 has been implicated in the etiology of this disorder. Commonly seen in association with AIDS and an immunocompromised state, KS also occurs in HIV-seronegative, immunocompetent populations in parts of Africa. We report the case of a 21-year-old male from Gambia, West Africa, who presented with multiple painful nodules on the hands and feet. Histopathology confirmed a diagnosis of Kaposi sarcoma, whereas serology for HIV was negative. Positron emission tomography revealed higher-stage disease with uptake in retroperitoneal lymph nodes, also subsequently biopsy-confirmed. The patient received radiation therapy but continues to have a progressive disease course with development of new cutaneous lesions. Herein we provide a review of contemporary knowledge on the clinical features and management of this aggressive endemic subtype of Kaposi sarcoma.

Introduction
Kaposi sarcoma (KS) is a mesenchymal, angioproliferative, low-grade malignancy. Although multi-focal, KS does not become metastatic. KS is etiologically related to infection by human herpesvirus 8 (HHV-8). HHV-8 has been found in tissue biopsies of all stages and epidemiological forms of KS. Aside from causing KS, this oncogenic virus also gives rise to two other malignancies: a rare form of B-cell lymphoma called primary effusion lymphoma and a plasmablastic form of multicentric Castleman disease. HHV-8, however, is not involved in epithelial tumors. Viral infection is necessary for the occurrence of KS but not always sufficient. HHV-8 seropositivity throughout the world has been found to be greater than the prevalence of KS, with up to 80% seropositivity in some parts of sub-Saharan and equatorial Africa. Consequently, it has been speculated that there are also ethnic and genetic cofactors involved in the development of KS.

KS classically presents with the cutaneous manifestations of discrete violaceous patches, plaques, or nodules, most commonly on the lower extremities. The four most common clinical variants of the disease are classic KS, African (endemic) KS, iatrogenic/transplant-associated KS, and AIDS-associated (epidemic) KS. In 1982, Kaposi was the first to describe the disease, which he called "sarcoma idiomathicum multiple hemorrhagicum." In 1912, Sternberg labeled this condition "Kaposi sarcoma." Two years later, in 1914, the first case of African or endemic KS was described to be a more aggressive form with a higher rate of extracutaneous manifestations.

KS classically progresses through three stages representative of its morphological features: the patch, plaque, and nodular stages. These stages are common in all four of the clinical variants mentioned and correspond to certain histological features. The earliest phase of KS, the patch stage, is the most difficult to diagnostically identify, manifesting as something more akin to a mild inflammatory dermatosis. However, on histology, there may be subtle indications of newly formed ectatic, vascular spaces with protrusion of native vascular structures into these channels creating the characteristic promontory sign. The plaque-stage lesions of KS are characterized by a more diffuse dermal vascular infiltrate and greater cellularity. Commonly, a phenomenon known as autolymphoidosis is seen, where an erythrocyte is contained in a paranuclear vacuole in a spindled endothelial cell. Nodular-stage KS is more apparent in diagnosis, characterized by dermal expansion by variable cellular proliferation of neoplastic spindled cells. The viral load in lesions correlates with the clinical progression through the patch, plaque, and nodular stages. Staining with antibodies to HHV-8 LNA-1 and lymphatic endothelial cell marker D2-40 has proven useful in the identification of early KS development.

There are myriad other histological KS variants, including those described in older literature, such as anaplastic, lymphohematomatous, lymphangiomatous, lymphangiectatic, bullous, and telangiectatic KS. Anaplastic KS is rare and poorly documented. Telangiectatic KS is identified in a single case report. More contemporary variants include hyperkeratotic ( verrucous), keloidal, micronodular, pyogenic granuloma-like, eczematous, intravascular, glomeruloid, pigmented, regressing KS (AIDS-treatment related), and KS with myoid nodules.

Case Report
A 21-year-old African male presented to our dermatology clinic with complaints of multiple painful lesions on the hands and feet. The lesions had appeared about two years earlier. Before the lesions appeared, he noticed swelling and pain in his right foot, which started seven years prior. The pain was worst upon waking in the morning and when weight bearing. Six weeks before presentation, the patient had emigrated from Gambia, West Africa. His lesions had been evaluated by physicians in Africa, and, according to the patient, they were unable to identify a diagnosis. One of the treatments tried was 100% tea tree oil, which had little effect on the lesions or his symptoms. Associated symptoms included constant sweating in the feet and ankles and knee arthralgia bilaterally. Ibuprofen did not alleviate his joint pain. The patient’s past medical history was unremarkable, and his immunizations were up to date, per the patient. At the time of initial presentation, he was not on any medications. The patient denied any recent fever, chills, nausea, or vomiting. He had not had any excessive fatigue or weight loss. He denied noting any palpable or tender lymph nodes. He had not appreciated any gastrointestinal symptoms, including abdominal tenderness, distention, or generalized discomfort. He denied any constipation, diarrhea, or blood in the stool.

Skin examination revealed multiple hyperpigmented, firm and hyperkeratotic papules, nodules, and small tumors on the dorsal and plantar surfaces of the feet and ankles (Figure 1). On the plantar surface of the right foot, there were multiple well-circumscribed, exophytic, hyperkeratotic plaques in a cluster near the ball of the foot (Figure 2). Smaller nodules were present on the hands and fingers (Figure 3). There was mild nonpitting edema up to the mid-calf. No other cutaneous lesions were noted elsewhere.

On general physical exam, the patient was fully alert and oriented, and in good spirits. No lymphadenopathy was noted in the neck,
A complete blood count showed a white blood cell count of 6,500 per microliter, containing an elevated portion of lymphocytes (46.2%). The remainder of the values were within the normal range for hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hematocrit concentration, and platelet count. The complete metabolic panel was unremarkable other than a slightly elevated glucose level of 106 mg/dL. The patient underwent HIV testing, was found to be seronegative, and was referred to oncology.

Despite several rounds of radiation therapy, oncology noted new lesions developing on the right side of his neck and on the right hand. A PET/CT scan was performed, which showed lymphadenopathy in the retroperitoneum. The largest lymph node measured 2.7 cm in diameter. Biopsy of the lymph nodes confirmed the presence of Kaposi sarcoma there as well.

**Discussion**

Endemic KS is found most commonly in Uganda, the Congo, the Congo Republic, Burundi, and Zambia.9,10 It comprises up to 10% of malignancies in central Africa and has a male-to-female ratio of nearly 15:1 in adults. Interestingly, the ratio of KS in children is nearly 1:1 male to female. The incidence of KS varies widely with the geographic variations of the HIV/AIDS epidemic, as approximately 80% of those presenting with KS are HIV positive.12,15-18 Consequently, the highest incidence rates of KS are seen in central and eastern Africa, where HIV infection rates are high. Across the entire continent, KS is the third most common cancer behind liver and prostate and is one of the leading causes of cancer death.11-13 In endemic areas like Uganda, for example, where the prevalence of HIV has reached up to 10%, the incidence of KS has increased tenfold compared with the pre-HIV/AIDS era.2,10,14 When regarding hospitals in and around Kenya, KS comprises 25% of all cutaneous malignancies, second only to squamous cell carcinoma (44%). Similar rates have been observed in studies in Nigeria.15,19,20

HHV-8, a virus that can be spread via saliva and semen, is the underlying culprit to all KS. However, as mentioned earlier, HHV-8 seropositivity does not perfectly correlate with the appearance of KS. In fact, there are countries where HHV-8 seropositivity rates are high and KS is rarely reported. This includes Brazil, Thailand, Gambia, and the Ivory Coast.21 Investigators have struggled to identify additional factors that may play a role in the manifestation of KS. There are eight distinct subtypes distributed over certain geographical regions: namely A/C, J, K/M, D/E, B, Q, R, and N groups. Subtypes B, N, Q, and R are found almost exclusively among the Sub-Saharan African cases, with subtype B predominating. It is not certain whether the subtypes have different pathogenic properties.4,22

A multitude of co-factors have been proposed in the pathogenesis of endemic KS. One of the risk factors identified for endemic KS is barefoot exposure to wet soil. The proposed mechanisms are various and include the role of high iron levels and quartzite content in African soils. In a clay emulsion, quartz particles of less than 2 um can readily enter sweat glands of the feet. Quartz can cause micro-abrasions when exposed to the skin of the feet. These quartz particles may induce lymphatic damage and fibrosis, resulting in an inflammatory response and local immune system impairment.2 This lymphedematous region is predisposed for malignancy, especially vascular tumors.21 After aluminum, iron is the most abundant mineral in African clay soils. Multiple pathways have been suggested for the role of iron. Iron may lead to immune impairment via inhibition of CD4 lymphocytes and suppression of macrophages. It can also induce production of reactive oxygen species and even directly promote
growth of spindle cells. Iron has also been found to induce anti-apoptotic signals in endothelial cells that are potential progenitors for KS cells. Lastly, iron may be conducive to KS development via increased host-cell production of viral nucleic acids.24-26 This theory is supported in part by the observation that endemic KS in Africa seems to be in proximity to volcanoes.29 Similarly, higher rates of KS have been seen in populations of southern Italy near Mount Vesuvius. However, further studies are warranted.30,31

Another potential co-factor is quinine and other drugs used for malaria treatment. KS and malaria show similar distribution patterns throughout sub-Saharan Africa, Italy, Greece, and Asia. In addition, quinine, chloroquine, and hydroxychloroquine may decrease immune response toward viruses. Chloroquine has been found to reduce the antibody response when given concomitantly with the rabies vaccine. These medications have been used for their immunosuppressive properties in the treatment of lupus erythematosus and rheumatoid arthritis. Quinine may act as an activating agent, converting latent HHV-8 to its lytic form.32,33

Table 1: Classification system for Kaposi sarcoma

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<th>Stage</th>
<th>Description</th>
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<tr>
<td>Stage I</td>
<td>Localized nodular KS, with ≤ 15 cutaneous lesions or involvement restricted to one bilateral anatomic site, and few, if any, gut nodules</td>
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<tr>
<td>Stage II</td>
<td>Includes both exophytic destructive KS and locally infiltrative cutaneous lesions and locally aggressive KS or nodular KS, or &gt; 15 cutaneous lesions or involvement of more than one bilateral anatomic site, and few or many gut nodules</td>
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<tr>
<td>Stage III</td>
<td>(Generalized lymphadenopathic KS) Widespread lymph node involvement, with or without cutaneous KS, but with limited, if any, visceral involvement</td>
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<tr>
<td>Stage IV</td>
<td>(Disseminated visceral KS) Widespread KS, usually progressing from stages II or III, with involvement of multiple visceral organs with or without cutaneous KS</td>
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In HIV-infected patients, highly active antiretroviral therapy (HAART) plays an indispensable first-line role in management, alone and in combination with other treatments. HAART exerts its therapeutic effects by inhibiting HIV replication and augmenting the immune response against HHV-8. Protease inhibitors have also been shown to have direct antiangiogenic effects. However, the KS may initially flare in patients with very low CD4+ T-cell counts, as a result of immune reconstitution inflammatory syndrome.

Systemic chemotherapy is reserved for cases of disseminated, rapidly progressive, or life-threatening disease with visceral involvement. Intravascular vinblastine in combination with bleomycin is first-line therapy for advanced classic KS.40 Other chemotherapy agents include liposomal anthracyclines, paclitaxel, oral etoposide, and single-agent and combinations of doxorubicin, bleomycin, and vincristine. The response rates for combination agents range widely, from 25% to 88%, in treatment for AIDS-KS. Liposomal anthracyclines are considered first-line treatment for advanced AIDS-KS. The use of doxorubicin is supported by the fact that preclinical data shows PEPlated liposomes preferentially accumulate in KS lesions.37 Paclitaxel has shown a response rate of 59%.4

Immunological agents such as interferon-alpha and sirolimus have also been tried. In one study, sirolimus demonstrated complete regression of iatrogenic KS in 15 patients.38 Newer therapeutic approaches include anti-angiogenic agents, VEGF inhibitors, tyrosine kinase inhibitors, and matrix metalloproteinases. Irinotecan, an anticancer drug that targets DNA topoisomerase I, has been used in advanced AIDS-KS.39 Antiviral therapy with cidofovir, foscarnet, or ganciclovir has demonstrated a suppression of HHV-8 replication.40 Even oral shark cartilage has been used as a treatment option.41

Conclusion

Kaposi sarcoma is an HHV-8 associated neoplasm originating from vascular and lymphatic endothelium. Endemic KS is a more aggressive form found most commonly in HIV-seronegative Africans. The etiology of disease is multi-faceted, given that HHV-8 seropositivity does not confer the disease state. There are multiple proposed factors that potentially play a role in the development of endemic KS, including HHV-8 subtypes, soil conditions, and drug interactions, to name a few. The broad range of disease manifestations lends to the wide spectrum of treatment options, and there is currently no standard of care.

References


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