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Review

Epidemiology of Kaposi sarcoma: review and description of the nonepidemic variant

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Abstract

Kaposi sarcoma (KS) is a rare angioproliferative tumor whose etiology is associated with human herpesvirus 8 (HHV 8). KS lesions typically involve the skin or mucosal surfaces and are characterized by purplish, red-blue, or brown-black macules, papules, and nodules which are prone to bleeding and ulceration. Definitive diagnosis requires biopsy revealing characteristic angioproliferative features. There are four widely recognized types of KS, which are histologically indistinguishable but differ in epidemiology and prognosis. These include classic, endemic, iatrogenic, and epidemic. KS has been increasingly recognized in a new subgroup of patients: men who have sex with men (MSM) but who are HIV-seronegative human immuodeficiency virus-seronegative and have no identifiable immunodeficiency. This fifth variant of KS, termed nonepidemic KS, resembles classic KS in presentation and prognosis. In this literature review, we report the characteristics of nonepidemic KS based on all published cases and highlight the need for clinicians to recognize this new clinical variant.

Introduction

Kaposi sarcoma (KS) is a rare borderline angioproliferative tumor that commonly presents with multiple vascular cutaneous and mucosal nodules. Major differences in clinical presentation and in prognosis among those groups have led to the following classifications: classical KS, endemic or African KS, iatrogenic KS, and acquired immune deficiency syndrome (AIDS)-associated or epidemic KS. It is caused by human herpes virus 8 (HHV 8), which is strongly implicated in the pathogenesis of all types of KS.[1] Humans are the natural hosts of HHV 8, and the virus establishes a lifelong latency in CD19 + B-cells.[2] HHV 8 is spread by saliva and sexual contact.[1,3]

Biopsy is required for definitive diagnosis. Characteristic angioproliferative histologic features include spindle-shaped tumor cells, aberrant proliferation of blood vessels with extravasated erythrocytes, and inflammatory infiltrates.[4] KS spindle cells are proliferating HHV 8-infected endothelial cells that have undergone reprogramming and differentiation.[5] Immunohistochemical staining of biopsy specimens confirms diagnosis by detection of HHV 8 latent nuclear antigen within the spindle cells.[4]

Epidemiology

KS was initially described in 1872 as a lower extremity tumor among elderly men by Moritz Kaposi.[6] This variant has been called classic KS. Classic KS is typically seen in older men (64–72 years) of Mediterranean, Eastern European (Ashkenazi) Jewish, and South American origin and has a chronic course.[4,7] It typically presents with cutaneous tumors on the lower extremities; however, it may also involve the gastrointestinal tract and/or lymph nodes.[4] Age is an important risk factor, and classic KS development may be promoted by immunosenescence.[8]

Endemic KS is limited to sub-Saharan Africa and is typically seen in young (25–40 years) black HIV-negative men.[9] Clinical manifestations can be indolent to aggressive and lethal.[10] Its presentation can be locally invasive or aggressive with visceral and/or mucocutaneous involvement.[10] The most aggressive form presents with lymphadenopathy and is associated with African children aged 1–5 years.[10]

Iatrogenic KS is seen in patients with solid-organ transplantations and those treated with immunosuppressive agents.[11] Drugs that are implicated in the development of iatrogenic KS include cyclosporine, azathioprine, corticosteroids, and rituximab.[11,12] These are particularly important in the setting of transplantation, but they are also relevant in the setting of chronic immunosuppression for autoimmune conditions or treatment of HHV 8-infected patients with other malignancies.[11] Solid-organ transplantation increases the risk of KS in the general US population by 500-fold.[13] Lesions are primary limited to

cutaneous involvement and often regress with discontinuation of immunosuppressive therapy if appropriate, or switching to sirolimus.[13] Rare reports of more aggressive outcomes of immunosuppression-related KS have been reported, including gastrointestinal hemorrhage.[14]

The rising incidence of KS among young homosexual men in the United States was a harbinger of the AIDS epidemic.[15] In this aggressive variant, patients present with multifocal skin lesions and frequent visceral involvement.[16] Patients present with systemic symptoms such as fever, weight loss, and diarrhea.[16] It runs a more aggressive course, often requiring highly active antiretroviral therapy and/or systemic chemotherapy.[16]

The seroprevalence of HHV 8 worldwide is estimated to be between 5 and 20%.[17] Africa and the Brazilian Amazon have the highest seroprevalence (>50%), the Mediterranean, Eastern Europe, Caribbean, and the Middle East have intermediate seroprevalence (5–20%), while North America and Asia are geographic areas with low HHV-8 seroprevalence (<5%).[17] The incidence of KS follows a similar pattern – a lower incidence is observed in Asia, North America, and Western Europe, compared to a high incidence in parts of Africa and the Mediterranean region.[18]

Clinical characteristics

The age at presentation varies between the epidemiologic subtypes of KS, with AIDS and transplantation-related KS more commonly affecting younger patients (Table 1).[1] Moreover, in immunocompetent patients, KS usually occurs in the lower extremities and may have a more indolent course.[1] Posttransplantation KS and AIDS-associated KS may be more diffuse in presentation, often involving the face or trunk or lymph nodes, oral mucosa, and visceral organs.[19] Visceral disease sometimes occurs in the absence of skin lesions. Besides lung and gastrointestinal (GI) involvement, KS has been observed in the liver, pancreas, heart, testes, bone marrow, bone, and skeletal muscle.[1] In HIV-infected children, severe KS, often involving lymph nodes, has been described.[20] Similar presentations occasionally occur in adults with HIV or transplant-related immunosuppression.[1]

Nonepidemic KS

Beginning in the late 1980s, KS has been sporadically reported in middle-aged HIV-seronegative MSM who have no evidence of immunodeficiency (Table 2).[21–32] "Nonepidemic" KS, defined as classic KS arising in middle-aged individuals without AIDS, has also been described in patients from Okinawa, Japan, in the early 1990s, but no mention of sexual activity was noted; thus, these cases will not be discussed further.[31] Its clinical presentation resembles classic KS, with cutaneous involvement, which most commonly occur on the lower limbs but also arms, genitals, and trunk. KS in the HIV-negative MSM population runs an indolent course similar to classic KS; it is usually chronic, persisting over many years, and presenting as nodules or plaques on the lower extremities.[21–30] This recently recognized subtype has been termed "nonepidemic KS."[30]

Afrasiabi et al. first described three homosexual male patients who were initially classified as having AIDS when first seen in 1983 and 1984 however were subsequently noted to have a normal CD4 cell count and normal CD4:CD8 ratio. The immunologic parameters in these patients did not change with follow-up, and no disease progression was noted. Testing for antibodies associated with the AIDS virus (HTLV-III/LAV) was negative in all three patients, which led the authors to observe a new variant with "findings…not frequently encountered in other healthy, homosexually active men or in classic Kaposi's sarcoma."[21] In 1986, Marquart et al. described the case of a 44-year-old HIV-seronegative bisexual man who developed a slowly progressing KS nodule on the glans penis.[22] In 1989, Archer et al. described a case of a 49-year-old MSM with cutaneous KS that had been indolent for 10 years and with no evidence of positive seroconversion to HIV.[23] One year later, García-Muret et al reported the case of a 42-year-old white bisexual HIV-seronegative man with disseminated KS of the skin and gastrointestinal tract.[24] The CD4:CD8 ratio was normal, and the KS remained indolent over a 30-month follow-up period.[24] In the same year, KS was reported in six HIV-seronegative MSM by Friedman-Kien et al.[25] The mean age of the group was 45 years (range 32–62).[25] Three of the patients had KS lesions limited to the legs only, and two patients presented with a single KS lesion on the penis.[25] In 2004, Kua et al. reported the case of a 53-year-old homosexual man with KS of the buccal mucosa.[26] The patient was observed over a 6-year period without evidence of HIV, and no other cause of immunodeficiency was identified.[26]

Lanternier et al. published the largest case series of nonepidemic KS to date in 2010.[27] They identified 28 HIV-seronegative MSM patients with histologically proven KS over a 12-year period.[27] The mean age at diagnosis in this cohort was 55 years (range 35–83).[27] Latent immunofluorescence assay for HHV 8 was positive in 88% of patients, indicating previous exposure.[27] Most patients (89%) had at least one lesion located on the lower extremity. Other sites of involvement included the upper limbs, face, trunk, and genitalia.[27] In the same year, Pothoff et al. reported a 53-year-old MSM with KS involving the trunk and left foot.[28] Immunohistological staining for HHV 8 showed strong immunopositivity.[28] HIV testing was negative, and there were no abnormalities in the differential blood and B and T cell subcounts.[28]

In 2014, Rashidgamat et al. published a case series of eight HIV-seronegative MSM patients with Kaposi sarcoma that were seen between 1997 and 2011.[29] Immunohistochemistry for HHV 8 latent nuclear antigen 8 was positive in all cases.[29] The median age of the patients was 53 years (range 37–65).[29] The majority of patients were treated conservatively with surgical excision.[29] Patients were followed for a median of 3.5 years

Table 1 Epidemiology of Kaposi sarcoma

Variant	Risk group	Clinical presentation	Prognosis
Classic	Elderly (60–70s) males of Mediterranean, eastern European, South American descent	Cutaneous, GI involvement, occasional lymph node and other organ involvement	Chronic course
Endemic (African)	Young – middle-aged sub-Saharan African males	Four subtypes: **(1)** benign nodular **(2)** locally aggressive, invading soft tissue and bone **(3)** florid disseminated, with skin and visceral involvement	Variable – indolent to locally invasive to aggressive and fatal (especially the lymphadenopathic variant)
	Children (1–3) – lymphadenopathic variant	**(4)** lymphadenopathic, rapidly disseminating to lymph nodes and visceral organs (29)	
Iatrogenic	Solid-organ transplant recipients Patients on immunosuppresion	Cutaneous, risk of GI hemorrhage	Variable – indolent to aggressive; resolves with cessation of immunotherapy
Epidemic (HIV-associated)	HIV positive	Multifocal cutaneous lesions, mucosal, visceral	Variable – chronic to rapidly progressive, requiring highly active antiretroviral therapy and/or chemotherapy
Nonepidemic	Middle-aged (40–50s), MSM	Cutaneous, with rare mucocutaneous involvement	Indolent

GI, gastrointestinal; HIV, human immunodeficiency virus; MSM, men who have sex with men.

Table 2 Reports of nonepidemic Kaposi sarcoma in the literature

Authors (year)	Number of patients, age(s), location of KS
Marquart et al. (1986)	*N* = 1, 44, penis
Garcia-Muret et al. (1990)	*N* = 1, 42, disseminated: cutaneous and GI tract
Friedman-Kien et al. (1990)	*N* = 6, 32–62 (mean age 45), lower extremity and penis
Kua et al. (2004)	*N* = 1, 52, buccal mucosa
Lanternier et al. (2008)	*N* = 28, 35–83 (mean age 55), face, trunk, upper extremity, genitalia, lower extremity, genitalia
Potthoff et al. (2010)	*N* = 1, 53, trunk, lower extremity
Rashidgamat et al. (2014)	*N* = 8, 36–65 (mean age 53), upper extremity, lower extremity, penis
Hinojosa et al. (2017)	*N* = 1, 55, face, lower extremity

(range 0.2–15 years); all patients were alive at that point.[29] The latest case of KS in an HIV-negative MSM was published in 2017.[30] In this report, a 55-year-old homosexual male presented with KS involving the temple and the lower extremity.[30] Immunohistochemistry for HHV 8 was positive.[30] He was treated conservatively with imiquimod and tretinoin creams with good response and continues to have an indolent course without evidence of HIV.[30]

Association with HHV 8

Most published cases of nonepidemic KS are associated with HHV 8 infection.[21–32] While HHV 8 seroprevalence is <5% in the general US population, it is markedly elevated in MSM, with estimates ranging from 25 to 60% among HIV-infected and 20–30% of HIV-uninfected MSM.[32] Risk factors for HHV 8 include age, increasing years of sexual activity with men, increased number of sexual partners, history of sexually transmitted diseases, and having a partner with KS.[32] HHV 8 infection in HIV-uninfected MSM in other countries also appears common.[33] Behavioral risk factors for HHV 8 transmission are incompletely understood and appear to vary in endemic and nonendemic regions.[33] For MSM in the United States, a sexual route of acquisition is likely to be particularly important, with seropositivity associated with a history of sexually transmitted diseases (STDs) and a higher number of sex partners.[33] In addition, saliva exchange during sexual activities appears to be the major source of transmission among MSM.[34–37] Thus, the increased risk of nonepidemic KS may be secondary to the increased prevalence of HHV 8 within this population, although further work is needed to elucidate this theory.

Conclusion

Kaposi sarcoma is a rare angioproliferative tumor associated with HHV 8. Four clinical variants of KS are widely recognized: classic, endemic, iatrogenic, and HIV-associated. KS in HIV-negative middle-aged MSM has only been reported sporadically, and most cases are associated with HHV 8. It has been termed "nonepidemic KS." Nonepidemic KS clinically resembles classic KS but occurs at a younger age, is limited to the skin, and is associated with a good prognosis. It is important for clinicians to recognize that KS may present in middle-aged MSM

who have no evidence of HIV or other immunodeficiency. Further studies are required to further analyze the association of HHV 8 in this population.

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