A Lump on the Foot

ABSTRACT

Kaposi's sarcoma (KS) is an angioproliferative tumour that requires infection by Human Herpesvirus 8 (HHV-8). It most commonly affects elderly men of Mediterranean/Eastern European backgrounds and HIV-infected patients. KS presents clinically as lesions on the skin, but may also arise in the gastrointestinal tract, lungs, and lymph nodes. There is no definitive cure for KS; therapeutic goals are to decrease the size of the lesions, prevent progression and improve function. Management depends on the type of KS, extent of disease and overall health of the patient. Observation is acceptable if the patient is asymptomatic; HAART is often sufficient to control lesions in HIV-infected patients. Cryotherapy and local excision can be used to treat solitary symptomatic lesions. Radiation therapy can be used for advanced and extended KS and in those patients for whom surgery is contraindicated. Intra-lesional injection of interferon alpha-2a or chemotherapeutic agents like vincristine have been reported to be effective in treating nodular KS lesions, but may be associated with inflammation and discomfort. Systemic chemotherapy such as pegylated liposomal doxorubicin is indicated when KS is widespread or rapidly progressive. The prognosis for KS is generally great with most patients dying from unrelated causes.

KEYWORDS: Kaposi's Sarcoma, HHV-8, HIV/ AIDS

CME Pre-test Quiz

A 78-year-old male presents with a violaceous nodule on the right sole. He has had similar lesions developing on the legs and soles over the past 14 years and they have all been removed with no sequelae. This patient is otherwise healthy and is on no medication. He has been tested for HIV multiple times before because of his current cutaneous finding; the results were all negative.

ABOUT THE AUTHORS

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What is the diagnosis?

Kaposi's sarcoma (KS) is a type of tumour that arises from the infection of human herpesvirus 8 (HHV-8). In most cases, KS lesions are localized and slow-growing. However, it can occasionally grow rapidly and become disseminated and cause significant disability and death.

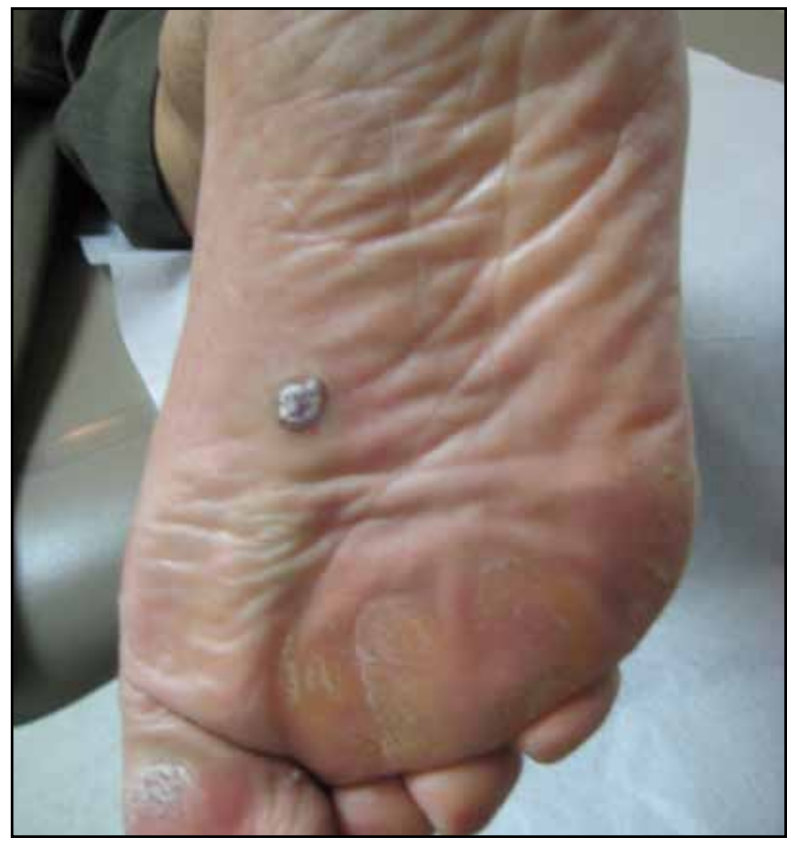
There are four types of KS based on the circumstances in which it develops: classic (CKS), AIDS-related or epidemic (EKS), endemic and iatrogenic:

- CKS is most prevalent among the elderly with Mediterranean/Eastern European backgrounds and 15 times more common among men than women.
- EKS is the most common tumour affecting HIV-infected individuals. EKS is more common among those who contract HIV through homosexual contact compared to other subgroups of people who are infected with HIV[1] and 3 times higher in males compared to females.[2]
- Endemic KS is endemic to Africa, particularly sub-Saharan Africa prior to the HIV epidemic. With the HIV epidemic, the incidence of Endemic KS and EKS in these regions has increased substantially.
- Iatrogenic KS is usually post-organ transplant. The transplanted organ may directly transmit the HHV-8 virus, and chronically immunosuppressed patients are especially susceptible.

In general, the median survival for patients diagnosed with Classic KS is years to decades[3] and given the affected demographic (elderly males), patients are more likely to die from unrelated causes. Historically, EKS had a median survival of weeks to months but the development of anti-retroviral therapies has pushed the 5-year survival to over 80%.[4]

It is believed that the oncogenic HHV-8 virus promotes tumour formation by infecting human endothelial cells and encoding for gene products that affect cell cycle regulation and apoptosis. Other HHV-8 viral gene products stimulate growth factors like VEGF in order to promote angiogenesis and provide blood supply for the tumour. Interestingly, while infection with HHV-8 is required for the development of KS, not everyone

Figure 1: Kaposi's sarcoma



SUMMARY OF KEY POINTS

Kaposi's sarcoma is a common tumour affecting HIV-infected patients. Classic Kaposi's sarcoma most commonly affects elderly men of Mediteranean/ Eastern European background.

Environmental and genetic factors are believed to predispose patients to Kaposi's sarcoma. KS requires the infection of HHV-8. Chronic immune-suppression contributes to KS development.

KS presents with red/purple macules, plaques and nodules on the skin. Lesions may also arise in the oral cavity, gastrointestinal tract and lungs. Lesions affecting lymph nodes cause lymphedema. Consider KS in an HIV-infected patient who presents with erythematous and/or violaceous nodules or plaques.

Management of KS depends on the type of KS, extent and location of lesions and overall health of the individual. Observation is sufficient for asymptomatic patients. For patients with EKS, HAART is recommended and may be the only therapy needed.

Local control of KS lesions can be achieved through cryotherapy, local excision, intra-lesional injection of chemotherapeutic agents or radiation therapy.

Distant spread of KS can be controlled through systemic chemotherapy.

harbouring HHV-8 develops KS suggesting other cofactors mediate an individual's risk of developing KS after HHV-8 infection.[5]

There are many cofactors that increase the risk of an individual developing CKS. Immunosuppression through systemic illness, such as diabetes, or by oral[6] and topical corticosteroid medications[7] increase the risk for developing KS. Certain environmental factors have been associated with an increased risk of developing KS. These include chronic exposure to volcanic[8] and luvisol[9] soils, living in areas with high populations of promoter arthropods[10] and infrequent bathing.[7] A history of asthma or allergies is a risk factor for KS among men but not women.[7] Remarkably, EKS is more common in individuals who have completed college[11] and cigarette smoking actually reduces the risk of developing KS.[6]

Kaposi's sarcoma is characterized by the presence of macules, plaques and nodules on the skin that range from purple to reddish-blue to brown/black in colour. The size of these lesions can also vary from extremely minute to several centimeters in diameter and can remain unchanged for years or grow rapidly in a few weeks and

disseminate. About ten percent of patients develop extracutaneous involvement including gastrointestinal tract, lung and regional nodal involvement. Tumours in the lymph nodes can frequently cause lymphedema in the legs and face. The clinical presentations of the different types of KS do not differ.

THE INITIAL WORK-UP OF A PATIENT WITH KS INVOLVES THOROUGHLY EXAMINING AREAS TYPICALLY AFFECTED BY THE DISEASE INCLUDING THE FACE, ORAL MUCOSA, GENITALIA, AND LOWER EXTREMITIES.

The diagnosis of Kaposi's sarcoma is typically suspected based on characteristics and distribution of the lesions. A definitive diagnosis requires a biopsy to examine the histological features of the lesion and to detect HHV-8 DNA through polymerase chain reaction.

The initial work-up of a patient with KS involves thoroughly examining areas typically affected by the disease including the face, oral mucosa, genitalia and lower extremities. Evaluation for spread to the viscera (ie. lungs, gastrointestinal tract) should be limited to symptomatic patients at which point imaging studies such as endoscopy and chest x-ray may be indicated.

Staging for Kaposi sarcoma is not always necessary. While it is occasionally done for patients with EKS, there is no universally agreed-upon staging system for CKS.

There is currently no definitive "cure" for Kaposi sarcoma due to the absence of therapy capable of eradicating the HHV-8 infection. As such, therapeutic goals of KS management focus on decreasing the size of cutaneous or visceral lesions, preventing disease progression and symptom palliation and improving function. Treatment options depend on the type of KS, the number and location of lesions, as well as the patient's immune function and general health.

In treating KS, if patients are immunocompetent and asymptomatic, observation alone may be sufficient.[12] For patients with EKS, combination anti-retrovirals (HAART) are recommended for all patients and may be the only therapy necessary. Post-organ transplant patients may have the dose of immunosuppressant drugs lowered or type altered.

Surgery for KS includes local excision, curettage and electrodessication. Surgery should be considered when the lesion is solitary, symptomatic (e.g. bleeding or chafing on clothing) or for cosmetic reasons (e.g. visible and unsightly to patient).[13] However, control is local and new lesions may continue develop in others locations. Alternatively, local lesions may be

treated with liquid nitrogen[14] or photodynamic therapy.[15,16]

Unresectable lesions or more advanced disease may necessitate radiotherapy.[13] There is no consensus as to indications for radiation or the best radiation technique. In general, radiation dose depends on the location of the lesion. One of the most commonly used radiation treatment regimes for cutaneous lesions is 30 Gy in 15 daily fractions of 2 Gy.[17] When the lower extremities are affected extensively, treatment involves submerging the affected extremities in water to achieve homogenous radiation.[18] Oral lesions have been successfully treated using a dose of 15 Gy while lesions involving eyelids, conjunctiva, and genitals respond to 20 Gy.[19] Dosimetric issues can arise with numerous solitary lesions in adjacent irradiation fields. Local control and symptom relief is achieved in over 90% of cases, however, therapy is again local, and many patients require additional local or systemic therapy.

Intra-lesional injection of chemotherapeutic agents such as vincristine and bleomycin have been reported to be safe and effective in treating nodular lesions in CKS.[20] Interferon alpha-2a injected intra-lesionally has also been shown to be useful in treating CKS lesions. However, the regime involves 2 to 3 weekly injections for 4 to 6 weeks, which may be impractical for patients with numerous lesions.[21] Additionally, it is associated with inflammatory reaction and pain.[20]

Systemic chemotherapy is indicated when KS is widespread, bulky or rapidly progressive, particularly when it is symptomatic or interferes with function.[13] A number of chemotherapeutic drugs have been used either as initial therapy or after failure of prior treatment, including pegylated liposomal doxorubicin, vinblastine and oral etoposide.[22,23,24] Response rates for each drug ranges from 60 to >90%, and treatments are well tolerated, even in the older population generally affected by CKS. Median response durations range from 4 months to more than 2 years.

CME

Post-test Quiz

Members of the College of Family Physicians of Canada may claim MAINPRO-M2 Credits for this unaccredited educational program.

- *All of the tables and photos are original.*
- *No competing financial interests exist in preparation of this case study.*

References

1. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. Jan 1990;335(8682):123-8.
2. Kaldor JM, Coates M, Vettom L, Taylor R. Epidemiological characteristics of Kaposi's sarcoma prior to the AIDS epidemic. Br J Cancer. Oct 1994;70(4):674-6.
3. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med. April 2000;342:1027-38.
4. Bower M, Dalla Pria A, Coyle C, Andrews E, Tittle V, Dhoot S, Nelson M. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. J Clin Oncol. Feb 2014;32(5):409-14.
5. Vitale F, Briffa DV, Whitby D, Maida I, Grochowska A, Levin A, Romano N, Goedert JJ. Kaposi's sarcoma herpes virus and Kaposi's sarcoma in the elderly populations of 3 Mediterranean islands. Int J Cancer. Feb 2001;91(4)558-91.
6. Anderson LA, Lauria C, Romano N, Brown EE, Whitby D, Graubard BI, Li Y, Messina A, Gafà L, Vitale F, Goedert JJ. Risk factors for classical Kaposi sarcoma in a

population-based case-control study in Sicily. Cancer Epidemiol Biomarkers Prev. Dec 2008;17(12):3435-43.
7. Goedert JJ, Vitale F, Lauria C, Serraino D, Tamburini M, Montella M, Messina A, Brown EE, Rezza G, Gafà L, Romano N. Risk factors for classical Kaposi's sarcoma. J Natl Cancer Inst. Nov 2002;94(22):1712-8.
8. Ziegler JL. Endemic Kaposi's sarcoma in Africa and local volcanic soils. Lancet. Nov 1993;342(8883)1348-51.
9. Pelser C, Dazzi C, Graubard BI, Lauria C, Vitale F, Goedert JJ. Risk of classic Kaposi sarcoma with residential exposure to volcanic and related soils in Sicily. Ann Epidemiol. Aug 2009;19(8):597-601.
10. Ascoli V, Senis G, Zucchetto A, Valerio L, Facchinelli L, Budroni M, Dal Maso L, Coluzzi M. Distribution of "promoter" sandflies associated with incidence of classic Kaposi's sarcoma. Med Vet Entomol. Sept 2009;23(3):217-25.
11. Nawar E, Mbulaiteye SM, Gallant JE, Wohl DA, Ardini M, Hendershot T, Goedert JJ, Rabkin CS. Risk factors for Kaposi's sarcoma among HHV-8 seropositive homosexual men with AIDS. Int J Cancer. Jun 2005;115(2):296-300.
12. Brenner B, Rakowsky E, Katz A, Gutman H, Sulkes A, Schacter J, Fenig E. Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. Int J Oncol. Jun 1999;14(6):1097-102.
13. Zurrida S, Bartoli C, Nolé F, Agresti R, Del Prato I, Colleoni M, Bajetta E. Classic Kaposi's sarcoma: a review of 90 cases. J Dermatol. Sept 1992;19(9):548-52.
14. Webster GF. Local therapy for mucocutaneous Kaposi's sarcoma in patients with acquired immunodeficiency syndrome. Dermatol Surg. Mar 1995;21(3):205-8.
15. Chun YS, Chang SN, Park WH. A case of classical Kaposi's sarcoma of the penis showing a good response to high-energy pulsed carbon dioxide laser therapy. J Dermatol. Apr 1999;26(4):240-3.
16. Marchell N, Alster TS. Successful treatment of cutaneous Kaposi's sarcoma by the 585=nm pulsed dye laser. Dermatol Surg. Oct 1997;23(10)973-5.
17. Hauerstock D, Gerstein W, Vuong T. Results of radiation therapy for treatment of classic Kaposi sarcoma. J Cutan Med Surg. Jan-Feb 2009;13(1)18-21.
18. Weshler Z, Loewinger E, Loewenthal E, Levinson R, Fuks Z. Megavoltage radiotherapy using water bolus in the treatment of Kaposi's sarcoma. Int J Radiat Oncol Biol Phys. Nov 1986;12(11):2029-32.
19. Kirova YM, Belembaogo E, Frikha H, Haddad E, Calitchi E, Levy E, Piedbois P, Le Bourgeois JP. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. Radiother Oncol. Jan 1998;46(1):19-22.
20. Brambilla L, Bellinvia M, Tourlaki A, Scoppio B, Gaiani F, Boneschi V. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. Br J Dermatol. April 2010;162(4):854-9.
21. Trattner A, Reizis Z, David M, Ingber A, Hagler J, Sandbank M. The therapeutic effect of intralesional interferon in classical Kaposi's sarcoma. Br J Dermatol. Nov 1993;129(5):590-3.
22. Di Lorenzo G, Kreuter A, Di Trolio R, Guarini A, Romano C, Montesarchio V, Brockmeyer NH, De Placido S, Bower M, Dezube BJ. Activity and safety of pegylated liposomal doxorubicin as first-line therapy in the treatment of non-visceral classic Kaposi's sarcoma: a multicenter study. J Invest Dermatol. 2008 Jun;128(6):1578-80.
23. Brambilla L, Miedico A, Ferrucci S, Romanelli A, Brambati M, Vinci M, Tedeschi L, Boneschi V. Combination of vinblastine and bleomycin as first line therapy in advanced classic Kaposi's sarcoma. J Eur Acad Dermatol Venereol. 2006 Oct;20(9):1090-4.
24. Tas F, Sen F, Keskin S, Kilic L. Oral etoposide as first-line therapy in the treatment of patients with advanced classic Kaposi's sarcoma (CKS): a single-arm trial (oral etoposide in CKS). J Eur Acad Dermatol Venereol. 2013 Jun;27(6):789-92.