CHAPTER **37**

UNSUSPECTED CLASSIC KAPOSI SARCOMA LESION WITH A PYOGENIC GRANULOMATOUS-LIKE PRESENTATION IN A NON-HUMAN IMMUNODEFICIENCY VIRUS-INFECTED, IMMUNOCOMPETENT PATIENT: Case Report and Literature Review

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INTRODUCTION

Kaposi Sarcoma (KS) was first described by the Hungarian pathologist, Mortiz Kaposi in 1872 (1). It is a monoclonal, neoplastic, low-grade tumor with angioproliferative characteristics (2-5). Although still an enigma to many, there has been much advancement since its discovery in 1872, where in Kaposi's original interpretation of the disease, it was described as "incurable and deadly" and gave the prognosis of one that "leads to death …within a short period of two to three years"(1). Fortunately, with advancement of today's medicine, there is better hope and better survival than the presumed years as predicted by Kaposi. KS has become almost commonplace among the human immunodeficiency virus (HIV)-positive and the AIDS population as one of the more familiar cutaneous neoplasms. However, KS has four well-defined clinical presentations that have been categorized: chronic or classic, lymphangiopathic or endemic (African), transplant-associated or iatrogenic, and AIDS-associated or epidemic KS (2,3,6).

Although there are a few case reports regarding the different types of rare, atypical presentations such as lymphangioma-like KS sarcoma as described by Garcia et al (7) and classic KS with a sarcoid-like granuloma presentation as described by Kandemir et al (8), there have only been a few accounts of pyogenic granulomatous-like KS in the English literature as described by Cabibi et al (9). The lesions mentioned appear on the hand, and another which reported 1 of 6 patients had such a lesion located at the left second toe as described by Urquhart et al (10). There are few reports of classic KS in the distal toes masked as pyogenic granulomas, as well as a few accounts of KS-like pyogenic granulomas that have been recognized.

CASE REPORT

A 78-year-old Ukrainian man presented to the senior author's practice with a small pruritic plaque-like lesion located on the medial distal phalanx of the right second toe (Figure 1). He was unaware of the duration of this lesion but to his knowledge, there were no other similar lesions elsewhere on his body. The past medical history was remarkable for coronary artery disease, hyperlipidemia, benign vertigo, and depression. He had denied recent history of weight loss, anorexia, recurrent fever, fatigue, night sweats, or dietary and activity changes. The patient had never received any blood transfusions or had any memorable recent history of sick contacts, viral syndromes, or travel outside of the US. There was no significant family history for malignancy or blood dyscrasias. The patient is a non-smoker, nondrinker, and denies any history of drug abuse.

Pertinent laboratory tests showed a white blood count 6.8, hemoglobin 13.8, MCV 91.4, and platelet 265. Serum chemistries were within normal limits and on physical

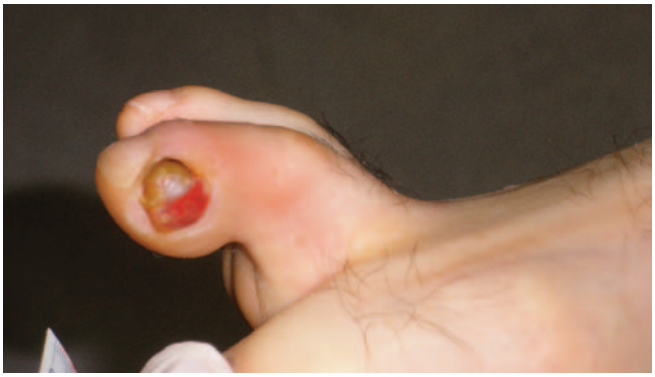

Figure 1.

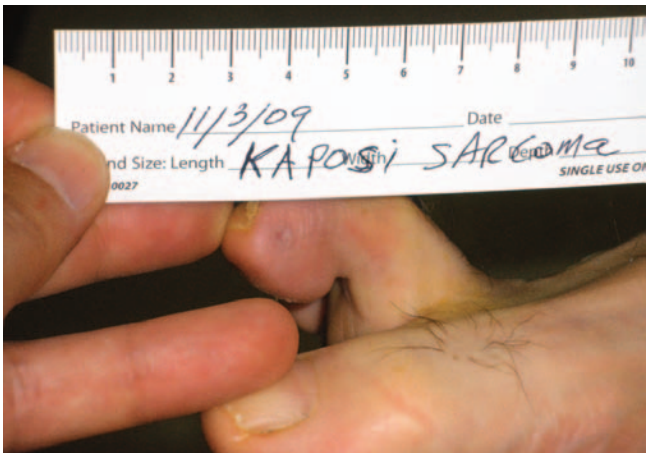

Figure 2.

examination, all systems were normal with no loss to musculoskeletal or neurological systems and no organomegaly or adenopathies. On physical examination, the patient's only complaint was the pruritic nature of the lesion and was otherwise asymptomatic. The lesion was more accurately described as tan-red, moderately firm and crusted, measuring approximately 1.0 cm x 0.8 cm x 0.5 cm situated on the medial aspect of the distal phalanx of the right second toe. The provisional diagnosis was a pyogenic granuloma due to its bright red, granular, vascular presentation. An excisional biopsy was performed under local anesthesia and the specimen was sent for pathological examination (Figure 2).

The surgical pathology report indicated the specimen to be highly suggestive of KS or hemangioendothelioma with the higher index of suspicion for KS due to the presence of atypical dermal vascular proliferation with spindle cells. The histological examination and staining performed with the use of immunoperoxidase for KI-67, which is a nuclear antigen detected in proliferating cells, showed a proliferative positive low index of 8%. KI-67 of 8% was deemed to be a typical finding for KS. Four other stains were examined: CD34, Factor VIII, Vimentin, HHV-8. All 4 stains were 3+ positive, which confirmed the diagnosis for KS, especially with the presence of HHV-8 latent antigen.

The patient completed a seroprevalent antibody test for HHV-8 (herpesvirus-8 IgG, IFA HHV-8). The reference range is <1:20 = normal or no antibodies detected, ≥1:20 = positive for antibodies detected. The patient's result was a 1:80 ratio, which confirmed the presence of antibodies to HHV-8. Note, HHV-8 or KS herpes virus (KSHV) IgG antibodies are found in more than 80% of KS patients, and approximately 30% of HI-positive individuals do not have KS, but less than 5% of healthy blood donors. The patient's HIV screen was negative.

Following the diagnosis of KS, patient was quickly referred to a hematology/oncology group. They decided that because of the patient's overall healthy physical examination and normal serological workup, a conservative approach with close observation was warranted. Immunodeficiency states were screened and the patient tested negative for HIV and hepatitis. At the one-year follow up, a repeat magnetic resonance image of the right lower extremity showed no evidence of residual or recurrent sarcoma and presently, patient is deemed to have a good prognosis with a low risk of recurrence. Future plans are to continue close monitoring.

DISCUSSION AND LITERATURE REVIEW

KS is a multifocal, low grade, vascular proliferative neoplasm with extensive contributions to its vitality from a host of disrupted immunological mechanisms (3,5). It is most commonly a tumor of malignant concern in the HIV-positive or AIDS patient population so it is unexpected when a solitary lesion demonstrates histological positivity for KS. Some of the most common characteristics of KS include spindle cells that share features with endothelial and smooth muscle cells, extravasated erythroctyes, and proliferative vascular channelization. There are four types of KS: 1) chronic or classic, which is found primarily in older men of Eastern European or Mediterranean descent. The presentation is typically a red or purplish skin plaque or nodule located on the distal lower extremities. Manifestation will usually occur in altered immune states without HIV association. 2) Lymphangiopathic or endemic (African) KS is found in young Bantu children and is described as extremely aggressive where skin lesions are not frequent. 3) Transplant-associated or iatrogenic KS appears months to years following long-term immunosuppressive therapy. The neoplasms present as multifocal skin lesions and are widely metastatic. 4) AIDS-associated (epidemic) KS is present in approximately one-quarter of AIDS patients. These lesions have no site of predilection and early wide dissemination of the disease. It is also clinically different from classic KS in that tumors are more aggressive and widespread affecting multiple organ systems including but not excluding skin, mucous membranes, gastrointestinal tract, lymph nodes, and lungs (3, 11).

We will discuss classic KS in this review and focus specifically on the rare instance of a classic KS with a pyogenic-granuloma-like appearance. In classic KS, skin lesions occur particularly in the lower legs and feet. The lesions can range in appearance from purplish, bluish-red, to dark brown/black and present as macules, plaques, or nodules. Nodular lesions have been shown to ulcerate and bleed. The size of the lesion also vary from very small to

several centimeters in diameter and can remain unchanged for months to years or change rapidly from weeks to months. There are cavernous and lymphangioma-like presentations, which are common for CKS, especially with an accompanying lymphedema of the lower extremity (2,7,12). Although rare in this form of KS, it has been reported to affect the mucous membranes of the mouth, gastrointestinal tract, and regional lymph nodes; gastrointestional tract involvement, however, has been usually asymptomatic with rare cases of bleeding, diarrhea, enteropathy, and perforation (11). Compared to its counterparts, CKS is considered to be a chronic, idly stable disease that has little influence on the recipient's survival. That, however, does not exclude the few cases of acute onset followed by rapid progression or even sudden rapid progression after a long, indolent course (13,14). In our patient's case, the complete excisional biopsy is considered the standard protocol for a definitive diagnosis with histological evaluation for presence of HHV-8 latent antigen and microscopic presence of spindle cells (15). Radiographic evaluation in asymptomatic patients is deemed unnecessary due to the disease's indolent nature, and screening for distant organ involvement is also not recommended due to the low frequency of metastases. For our patient, we recommend a colonoscopy to rule out any gastrointestinal involvement since gastrointestinal presence is usually asymptomatic.

The American Joint Committee on Cancer (AJCC) TNM staging system for soft tissue sarcomas specifically excludes KS. Therefore, there is no defined staging criteria based on disease distribution and clinical progression. One group of investigators, however, proposed the following staging criteria based on a study of 300 CKS patients (16): Stage I: maculonodular (lower extremity confined macules and nodules); Stage II: infiltrative (plaques with some nodular involvement primarily located in the lower extremities); Stage III: florid (multiple angiomatous plaques and nodules dispersed throughout the lower extremities often found to be ulcerated); and Stage IV: disseminated (same as Stage III but extending beyond the lower extremities). Stage III and IV patients had a more rapid, progressive disease with higher incidence of gstrointestinal tract and visceral involvement, local complications, and functional impairment.

Fortunately, our patient fell within the realm of Stage I and we were in agreement with the oncologist that a conservative approach with close monitoring was the appropriate measure taken in this case due to the indolent course of this disease.

HISTOLOGY

There are 3 distinctive stages in the evolution of a KS lesion: patch, plaque, and nodular stage. The early phase presents as a macular lesion with a nondistinct proliferation of thin-walled, angulated vessels with scarce inflammatory infiltrate of plasma cells, lyphmocytes, and hemosiderin deposits found throughout the dermis. As the lesion advances to the next stage, the vascular component becomes more abundant with areas showing an arrangement of short fascicls of angiomatoid vascular spaces filled with red blood cells surrounded by spindle cells. This represents the plaque stage, which extends into the reticular and subcuticular dermis. In the nodular stage, a more extensive arrangement of uniform spindle cells in sheets increases the solidity of the tumor and intra- or extracellular eosinophilic hyaline globules can be located that are approximately 0.5-10 micrograms in diameter. The differential diagnosis for KS includes inflammatory dermatosis, bacillary angiomatotosis, angiodermatitis, pseudo-Kaposi's, pyogenic granuloma, bullous KS, and arterio-venous malformations. Although bacillary angiotomatosis and pyogenic granuloma can clinically mimic KS, the distinction can be easily determined histologically (3-5,7-10,12,17,18).

Two studies discuss the histological distinction of pyogenic granulomatous-like KS: Cabibi et al and Urquhart et al (9,10). As stated earlier, the clinical picture of KS has been mistaken for pyogenic granuloma, however, recently there have been a few cases where a lesion contained features of both pyogenic granuloma and KS. This brings the possibility that prior studies may not have differentiated between KS-like pyogenic granuloma and pyogenic-like KS 33-35. In Cabibi et al, a lesion had the characteristics of both pyogenic granuloma and KS and initially the lesion was thought to be a KS-like pyogenic granuloma (KS-l PG) since all PGs were considered benign. It has since been established that it is a true KS due to the presence of human herpes virus-8 DNA and the clinical course of the lesion. The lesion in Cabibi's study was on the hand; however in a different study, Urquhart et al found the same in 6 cases with one case having a lesion on the second left toe. Both studies discussed the histological significance of using immunohistochemical procedures to determine how both PG and KS characteristics were used identify this lesion to be a PG-like KS. Cabibi reported that microscopically, the lesions found in the hand resembled PG rather than KS in the fact that at high magnification, there was a lack of a true sarcomatous appearance with mild cell atypia and little to no mitosis which deemed the lesions more benign in nature, however, solid areas of spindle cells, typical of KS, were present.

In immunohistochemical terms, PG presents with a dual cell population with SMA highlighting the profuse presence of pericytes and Factor VIII with expression of Cd34 and Cd31 on the mature endothelial cells forming vessels. In contrast, KS has solid spindle cells, which have a single cell population that express Cd31 and Cd34, but lack Factor VIII and SMA due to the lack of pericytes and mature endothelial cells. In both reports discussing PG-l KS, immuohistochemistry demonstrated few spindle cell areas expressing both SMA and FVIII, like PG, and CD31 and CD34, like KS. Further maintaining the lesion to be KS in nature is the immunostaining with LNA-1 for HHV-8, which is the anti-latent nuclear antigen 1 that has intranuclear labeling specifically for the spindle cells. Positive expression of LNA-1 for HHV-8 confirmed the diagnosis for KS and because dual characterization was present in such lesions, the diagnosis of PG-like KS was made. Urquhart et al reported that immunoperoxidase staining of HHV-8 LNA-1 is a useful tool for making the diagnosis of PG-like KS. As stated in their study, "HHV-8 does not seem to be present in vascular neoplasms other than KS," which proves that it is a true KS and not PG (4,9,10).

THERAPY

The literature pertaining to KS does not focus on the goal of eliminating the disease but rather on in achieving the therapeutic goal of symptom palliation, functional improvement, delaying and preventing disease progression and/ or decreasing the size of the lesions. There is no apparent "best approach." Standard empirical therapies include observation without specific treatment in asymptomatic presentations, surgical excision for solitary lesions (15), radiation therapy (RT) doses (19-22), cryotherapy or laser therapy (good for local control), and intralesional injection of chemotherapy such as vinblastine or bleomycin, which has shown local regression of cutaneous-type lesions (23,24). Topical therapies have been used such as Alitretinoin (9-cis-retinoic acid) gel, which is the Food and Drug Association-approved for cutaneous AIDS-associated KS. It has limited efficacy (25). Another topical medication, Imiquimod, is the subject of an ongoing prospective trial and has showed an objective response (26). In the exceptional cases of classic KS, which have systemically advanced and resulted in multifocal spread, chemotherapy has been effective in treating widespread, rapidly progressive, and bulky CKS where functionality is impaired and lymphedema or visceral organ involvement plays a comorbid role (27). Although there is no one cytotoxic agent approved to target CKS specifically, a number of drugs have been approved and used for treatment of AIDS-associated KS or other sarcomatous neoplastic diseases. These include: liposomal doxorubicin, vinblastine, bleomycin, paclitaxel, oral etoposide, oral thalidomide and gemcitabine; however some studies claim ineffectiveness in localized CKS therapy (24,27-30,31-37). Immuno-modulators such as recombinant interferon alpha (IFNa) and IgG treatments have been shown to provide disease regression (33,38).

There are a few interesting case report studies that mention effective treatments for CKS. In one study, the use of gemcitabine at a fixed infusion rate of 10mg/ m-squared/minute on 3 separate occasions over 28 days showed dramatic improvement for a total of 6 courses in a patient where pretreatment of local radiotherapy, IFNa, and multiple lines of chemotherapy had failed (37). In another study, thalidomide taken at a dosage of 100mg/day for 12 months was used on 3 patients with non-AIDS related KS. They showed partial remission after 4 months of therapy and complete remission at the 12 month (34,35). A study of 151 patients that tested the safety and efficacy of intralesional vincristine therapy for CKS, proved the therapy to be well tolerated and effective in nodular lesions as a first-line therapy in initial stages and support therapy for advanced stages of Classic KS (23). Also mentioned is the use of intralesional 5-aminolevulinic acid injection photodynamic therapy (PDT) for the treatment in CKS. In this study, PDT demonstrated effective basic antitumor activity with injury to vasculature of the tumor that resulted in the disappearance of HHV-8 in the PDT-treated lesion; however, the authors denote that for PDT to work, the photosensitizer must sufficiently penetrate the whole lesion, which indicates that PDT may not work in thicker lesions (39).

We found this case to be unique in that, CKS, is less common than its counterparts and, second, CKS has the ability to disguise itself as a solitary benign cutaneous lesion that can be found in unexpected locations. We hope to raise awareness and to suggest all practices of clinical podiatric medicine to include CKS as a differential diagnosis when one comes across a solitary lesion that is seemingly commonplace in any aspect of the foot.

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