Kaposi sarcoma (KS) is a low-grade vascular tumor associated with Kaposi sarcoma herpes virus (KSHV) infection. The tumor is caused by an excessive proliferation of spindle cells, thought to be of endothelial cell origin, Human herpes virus 8 (HHV-8) DNA has been identified in more than 90 percent of all types of KS lesions, suggesting a causative role. Kaposi sarcoma lesions present predominantly at mucocutaneous sites, but may involve all organs and anatomic locations. Four main types are described in the literature: classic, epidemic (AIDS-related), endemic, and immunosuppression-associated or transplant associated. Classic KS typically occurs in elderly men between 50-70 years old of Mediterranean or Eastern European origin, and rarely in men of Asian descent. It consists of violaceous macules and papules with subsequent development of plaques and red-purple nodules. This type is rarely aggressive and is limited to the skin, lacking visceral involvement. Epidemic or AIDS-related KS occurs in patients with advanced HIV infection and is by far the most common and most aggressive presentation of KS today. The immunocompromised individual has been described in transplant patients and others receiving immunosuppressive therapy.

Described below are two cases of patients who presented with a form of KS that does not fit into any of the previously described epidemiological categories.

CLINICAL HISTORY
Case 1. A 79-year-old African-American male with history of prostate cancer presented for further evaluation of previously diagnosed KS on his left big toe (Nov. 2013). He complained of “soreness” of both of his feet and noted that the problem began while he was exposed to missiles during active duty. The patient denied any history of HIV and an HIV test performed six months earlier was negative. He identified as heterosexual, and sexual history is unknown. Physical examination at the time was remarkable for bilateral, 2+ pitting edema over the dorsal surfaces of both feet, with multiple, various-sized, erythematous macules and violaceous to hyperpigmented patches, mostly over the malleoli and dorsal feet. There were no other similar lesions noted elsewhere on the body. A follow-up visit months later showed...
multiple variably sized hyperpigmented to violaceous macules, patches, and papules on dorsal feet, ankles, and malleoli bilaterally. Throughout the patient’s care, histopathologic examination of several biopsy samples from lesions on his left big toe and right medial plantar foot demonstrated a proliferation of spindle cells with thin, slit-like vascular spaces, mild erythrocyte extravasation, with HHV-8, CD31 and CD34 positivity on immunostaining, supporting a KS diagnosis.

During the course of one year, the patient was treated with imiquimod 5% cream, crotetherapy with liquid nitrogen, and topical hydrocortisone cream without resolution. He was referred to oncology due to his systemic symptoms of swelling and tenderness, but was hesitant to begin systemic chemotherapy due to side effects.

His condition ultimately improved with the application of alitretinoin gel after a trial period of 14 weeks, and eventually reached the point of complete resolution three years after his initial presentation.

**Case 2.** A 47-year-old, obese, African-American male with a history of genital herpes presented to the dermatology clinic for evaluation of painful lesions on his feet that affected his ambulation. He reported that the lesions had been there for about 10 months, first starting on the left foot, then also developing on the right as well. He self-identified as bisexual and reported unprotected sex with male and female partners. He first thought that the lesions were warts and tried treating them with over-the-counter therapies without success. He was evaluated subsequently by a podiatrist who also treated them as warts and excised several from the left foot. He denied any history of HIV or any other systemic symptoms such as fever, chills, or weight loss. HIV antibody and RPR/VDRL were both negative at that time, and CBC and BMP were unremarkable. Two shave biopsies were obtained from lesions on the left first toe and right second toe, and both specimens revealed atypical spindle cell proliferations with hypercellularity, nuclear atypia, and erythrocyte extravasation. The tumors were positive for CD34, CD31, vimentin, and HHV8, and were negative for desmin and S100. These findings were consistent with a KS diagnosis. Following failed treatment attempts with crotetherapy and the application of topical alitretinoin 0.1% gel twice daily for several weeks, the patient’s residual lesions were excised by plastic surgery without recurrence and to the patient’s satisfaction.

**DISCUSSION**

As discussed above, KS is typically categorized into one of four subtypes: classic, AIDS-related, transplant-associated, and endemic. Our patients do not fall into any of these categories.

In general, KS arises less commonly in patients who are HIV-negative. Even less commonly, cases may not fit into any of the previously described epidemiological categories. These cases of KS are thereby uncategorizable by the current classification system. However, several similarly uncategorized cases are described in the literature. After a careful review for such documented cases, many of these uncategorizable cases may fall into categories of their own.

Notably, within the uncategorizable cases of KS reported in the literature, there exists a pattern of men who have sex with men having KS involvement of their lower limbs. A case series of eight men who have sex with men between the years of 1997 and 2011 with KS that did not fit into any of the previously described categories was published in the British Journal of Dermatology in 2014. The mean age of these patients was 53 years old (range 37-65), and 88 percent of them were not African American. Half of these patients had KS confined to their lower limbs. This particular publication noted that epidemiological studies have shown that approximately one-quarter of HIV-seronegative MSM have serological evidence of KSHV infection. Risk factors for KSHV infection in HIV-seronegative MSM include the number of years of sexual activity with men, older age, a higher number of partners, a history of sexually transmitted diseases, and having a sexual partner with KS. KS in the HIV-negative MSM population is usually chronic, persists over many years, and presents as nodules or plaques on the lower extremities. This correlates with our patient in Case 2, who did endorse having sex with men, placing him within this newly emerging subtype of KS. Although the patient in Case 1 identified as heterosexual, there was no further information documented regarding his sexual practices throughout his life. The above evidence may suggest that this knowledge could have played a role in subcategorizing his KS with the above cases, or deeming his case truly unique in the literature. This pattern of cases of KS appearing in the lower limbs of immunocompetent MSM could be due to a variety of factors to be explored in future studies.

One of these factors could be spread of the HHV-8 virus during sexual contact. It is well documented that HHV-8 can be spread via exchange of saliva and through sexual contact via shedding in genital secretions. Furthermore, HHV-8 virus is frequently detected in immunocompetent MSM, even if these patients are asymptomatic. A question arises as to what extent the sexual history of these individuals contributed to the eventual development of KS, and whether or not transient fluctuations in their immunities contribute to the pathogenesis of KS.
How Effective is Telemedicine-based Dermatology? New Study Seeks to Find Out

Science 37, a company that facilitates virtual clinical trials, and the Keck School of Medicine of the University of Southern California (USC) are partnering to support the execution of a $3.4 million dollar study funded by the National Institutes of Health (NIH). It will be the largest telemedicine-based dermatology study ever funded by the organization and will explore whether telemedicine can deliver care that is equivalent to being seen in-person for patients with eczema.

“Our experts are committed to exploring innovative ways to provide advanced care for our patients,” says David Peng, MD, MPH, chair and professor of clinical dermatology at the Keck School. “This includes examining how technology-enabled healthcare delivery can be used to allow patients to more easily access the care they need.”

The study, led by April Armstrong, MD, MPH, associate dean of clinical research and professor of dermatology at the Keck School, and supported by the NIH grant, will evaluate telemedicine as a method of care for more than 300 patients with atopic dermatitis. Poor health outcomes for many patients with eczema or other chronic skin conditions have been blamed on lack of regular access to dermatologists. Dr. Armstrong and her research team will determine whether telemedicine can improve access, reduce disease severity, improve quality of life, and save healthcare costs.

“A research partnership with the Keck School of Medicine of USC underscores the bright future ahead for telemedicine, virtual studies, and patient-centered research,” says Jonathan Cotlier, MD, chief medical officer at Science 37. “The road to improved health outcomes begins with delivering care at the patient’s convenience whenever possible, and we’re excited to embark on research with USC that could transform the patient experience for those with eczema.”

Researchers will use NORA® from Science 37, the industry’s first and only comprehensive tool to fully operationalize a virtual study, to communicate with patients during the study. Patients will also submit ePROs (electronic patient-reported outcomes) through NORA. The platform is purpose-built to support the unique workflows, processes, and systems of virtual studies and adheres to the highest industry quality and regulatory standards. It digitally centralizes data collection and is integrated into a sponsor’s system to ensure the automated exchange of reliable and high-quality data available in near-real-time.

in these cases. One could infer from the existing data that HHV-8 infection is a sexually transmitted precursor to KS in the MSM population, regardless of their immunocompetence.

Our patients present interesting cases because although they have features of several of the subtypes of KS, they defy standard classification into one of the four accepted subtypes. While the lesions appeared in a very common site of disease, our patients’ epidemiological characteristics are unique. Additionally, the importance of a comprehensive sexual history cannot be understated when KS is in the differential diagnosis, and may also play an important role in the categorization of KS in the future.

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Sources