# Lymphangioma-like Kaposi sarcoma of the oral mucosa

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With the epidemic of acquired immunodeficiency syndrome, the clinical and histopathological features of Kaposi sarcoma (KS) became routine for most practicing surgical pathologists. The histological spectrum of KS broadened significantly over time and today a wide variety of rare histological variants are reported, but not widely recognized. Lymphangioma-like KS (LLKS) is a rare histological variant of KS occurring in skin, with banal histological features that can lead to misdiagnosis and inappropriate therapy. We report a series of intra-oral cases of LLKS and review the literature regarding this lesion. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:84-90)

As reported by Weiss et al., Kaposi sarcoma (KS) was originally described as 'idiopathic multiple pigmented sarcoma of the skin' by Moritz Kaposi in 1870.[1] The initial cases described that it affected the skin of the lower extremities in an older male population. This form of KS is now recognized as the classic form of KS. Four different clinical forms of KS have been described, which are characterized by the distinct patient population affected. The classic form occurs more commonly in Poland, Russia, and Italy in elderly males. An endemic African form of KS affects children and young adult males in Africa. Another form of KS occurs in renal transplant patients, known as iatrogenic (or transplant-associated) KS. An acquired immunodeficiency syndrome (AIDS)-associated form of KS has also been described, most commonly affecting human immunodeficiency virus (HIV)-infected individuals.[1]

In all 4 clinical forms of KS, the lesions go through similar histological evolvement. The lesion progressively evolves from patch to plaque to nodular stages.[2] The patch stage, normally seen in early developing KS, presents with flat macules. At this stage, the lesion histologically shows proliferation of new small blood vessels around larger dilated vascular spaces. In more established plaque lesions, the vascular proliferation involves the dermis almost completely with a bland spindle cell proliferation limited to areas around proliferating vessels, resulting in a slightly elevated skin lesion. The nodular stage presents as a spindle cell lesion with slit-like vascular spaces.[1] The causative organism of KS is human herpesvirus 8 (HHV8), which was originally described by Chang et al. in 1994.[3]

In 1957, Ronchese and Kern described patients previously diagnosed with classic KS, who later developed fluid-containing bullae on their lower extremities.[4] Application of pressure with a finger created a marked depression in these bullae, though the depression disappeared slowly after the pressure was removed. Aspiration of these bullae produced a clear fluid. This presentation was later described as "bullous lesions" and was believed to be characteristic of lymphangioma-like KS (LLKS). The term 'LLKS' first appeared in the literature to describe a subtype of KS with histological features resembling lymphangioma, and it often presented as multiple bullae-like lesions on the skin.[5]

Although most reported cases of LLKS had a slowly progressive course, a case described by Leibowitz et al. was different in that the disease was rapidly fatal. In this instance, the lymphangioma-like pattern also confounded the diagnosis, such that the diagnosis of KS was only made postmortem.[6,7] The aggressive behavior of KS in this instance led to debate about the possibility

## Statement of Clinical Relevance

Awareness of intra-oral lymphangioma-like Kaposi sarcoma (KS), a rare histological variant of KS, is important for oral pathologists, especially when the patient's human immunodeficiency virus (HIV) status is not known. In 3 of our cases, this resulted in the diagnosis of unsuspected HIV infection.

The authors disclose that one of the cases reported in the article was previously presented in an abstract in the oral essay session at the American Academy of Oral and Maxillofacial Pathology conference held in May 2011.

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of this variant being subcategorized as a unique clinicopathologic entity. However, later studies demonstrated that LLKS is better classified as a histological variant of KS than as a clinicopathologic entity.[8]

A retrospective study of 7 cases reported by Cossu et al. in 1997 showed that the natural history for LLKS is slowly progressive and there is no prognostic difference associated with this variant. The study also described LLKS clinically occurring as patches, plaques, and nodules on the skin.[8] Also, a recent series of 4 cases reported by Ramirez et al. and a review by Davis and Scott report similar findings.[9,10] Thus, with the absence of a unique clinical presentation and a prognostic difference, LLKS is better described as a histological variant, rather than a clinicopathologic entity.

Fifty-three cases of LLKS have been reported in the English language literature and of these cases 30 were confined to the skin, while 23 were reported in the oral cavity.[11-14] This variant accounts for less than 5% of KS cases in 1 reported series.[15] LLKS histological pattern has also been reported in 3 of the clinical subtypes of KS (classic KS, endemic KS, and AIDS-associated KS), but as yet has not been seen in transplant-associated KS. LLKS in the skin has been reported most frequently in older men between 59 and 80 years of age and most often in the skin of the lower extremity.[8,10,14] However, in their article studying microscopic patterns of intra-oral LLKS, Bunn et al. report LLKS occurring more frequently in females.[11]

The histological features of LLKS vary considerably from the traditional KS, in that they consist predominantly of dilated vascular spaces, dissecting the dermal fibrous connective tissue stroma with a delicate strand-like papillary architecture. The endothelial cells lining the vascular spaces are bland, imparting a lymphangioma-like appearance. At times, typical areas of KS are not present in LLKS and LLKS may share histological features with other vascular tumors including lymphangioendothelioma, hemangioendothelioma, and low-grade angiosarcoma.[9] Similar to conventional KS, the identification of HHV8 in lesional tissue is diagnostic for the LLKS variant as well.[9] Immunohistochemical analysis for the latency-associated nuclear antigen (also called latent nuclear antigen) is a sensitive and specific marker to establish HHV8 infection.[16] Both endothelial markers (CD31 and CD34) and lymphatic markers (podoplanin, also called D2-40) are expressed in KS and its histological variants like LLKS. With the expression of both endothelial and lymphatic markers, the histogenetic origin of KS is still debated.[1]

Although LLKS has been incorporated as a subtype in a recently published microscopic study regarding intra-oral KS in South Africa,[11] LLKS is a rare variant of KS in the US. We present the first case study, collected from 3 institutions, on the clinical and histological features of this rare variant of KS in the oral cavity. We report clinical and histological presentations of 5 cases of intra-oral LLKS along with the immunohistochemical expression of lymphatic marker D2-40. Pathologists should be familiar with LLKS in order to recognize that this rare histological variant is within the spectrum of KS.

## CASE SERIES

### Case 1

A 45-year-old male patient presented with a diffuse erythematous swelling of the right palate and tuberosity area that felt 'boggy' on palpation (Figure 1*A*). His medical history was significant for fatigue, night sweats, and chronic sinus problems. The HIV status of patient was unknown. A biopsy of the erythematous area showed mucosa lined by parakeratinized stratified squamous epithelium. Immediately underneath the epithelium, there were numerous dilated, anastomosing vascular spaces arranged in an edematous fluid-filled background in the lamina propria (Figure 1*B* and *C*). The delicate strand-like architecture of some of the anastomosing vessels protruded like papillary projections into the larger dilated spaces. The vascular spaces were lined by endothelial cells with bland morphology and vesicular nuclei. Very few of the vascular spaces contained erythrocytes. Most of the vascular channels were either empty or contained fluid. There was a prominent inflammatory infiltrate, predominantly lymphoplasmacytic in the fibrous stroma. Underneath the superficial anastomosing blood vessels, there was a small cellular focus of spindle cells in the deeper portion of the specimen (Figure 1*D* and *E*). However, there was minimal erythrocyte extravasation and no obvious mitotic cells. Except the focal area of spindle cells, the tissue was remarkably similar to inflamed granulation tissue. Immunohistochemical studies for HHV8 (Leica Microsystems, Buffalo Grove, IL, USA) and D2-40 (Covance, Princeton, NJ, USA) were performed and the results revealed positive staining for HHV8 (result not shown) and D2-40 (Figure 1*F*). A diagnosis of KS was therefore rendered on the basis of the positive HHV8 immunostaining in the nuclei of the lesional cells. The patient was then referred to an oncologist for evaluation of his HIV status and further treatment. The patient was found to be seropositive for HIV and received treatment for AIDS. The palatal lesion was reported to be resolved at the 6-month follow-up appointment.

### Case 2

A 45-year-old white male patient, who was HIV seropositive, had periodontal disease and a nodular mass of the maxillary alveolar ridge and palate. He was referred to an oral surgeon for tooth extraction and a biopsy of the mass to confirm the clinical provisional diagnosis