

## 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.<sup>1</sup> 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.<sup>1</sup>

In all 4 clinical forms of KS, the lesions go through similar histological evolution. The lesion progressively evolves from patch to plaque to nodular stages.<sup>2</sup> 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.<sup>1</sup> The causative organism of KS is human herpesvirus 8 (HHV8), which was originally described by Chang et al. in 1994.<sup>3</sup>

In 1957, Ronchese and Kern described patients previously diagnosed with classic KS, who later developed fluid-containing bullae on their lower extremities.<sup>4</sup> 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.<sup>5</sup>

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.<sup>6,7</sup> The aggressive behavior of KS in this instance led to debate about the possibility

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### 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.

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.<sup>8</sup>

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.<sup>8</sup> Also, a recent series of 4 cases reported by Ramirez et al. and a review by Davis and Scott report similar findings.<sup>9,10</sup> 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.<sup>11-14</sup> This variant accounts for less than 5% of KS cases in 1 reported series.<sup>15</sup> 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.<sup>8,10,14</sup> However, in their article studying microscopic patterns of intra-oral LLKS, Bunn et al. report LLKS occurring more frequently in females.<sup>11</sup>

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 lymphangioma, hemangioma, and low-grade angiosarcoma.<sup>9</sup> Similar to conventional KS, the identification of HHV8 in lesional tissue is diagnostic for the LLKS variant as well.<sup>9</sup> Immunohistochemical analysis for the latency-associated nuclear antigen (also called latent nuclear antigen) is a sensitive and specific marker to establish HHV8 infection.<sup>16</sup> 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.<sup>1</sup>

Although LLKS has been incorporated as a subtype in a recently published microscopic study regarding intra-oral KS in South Africa,<sup>11</sup> 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 1A). 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 1B 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 1D 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 1F). 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

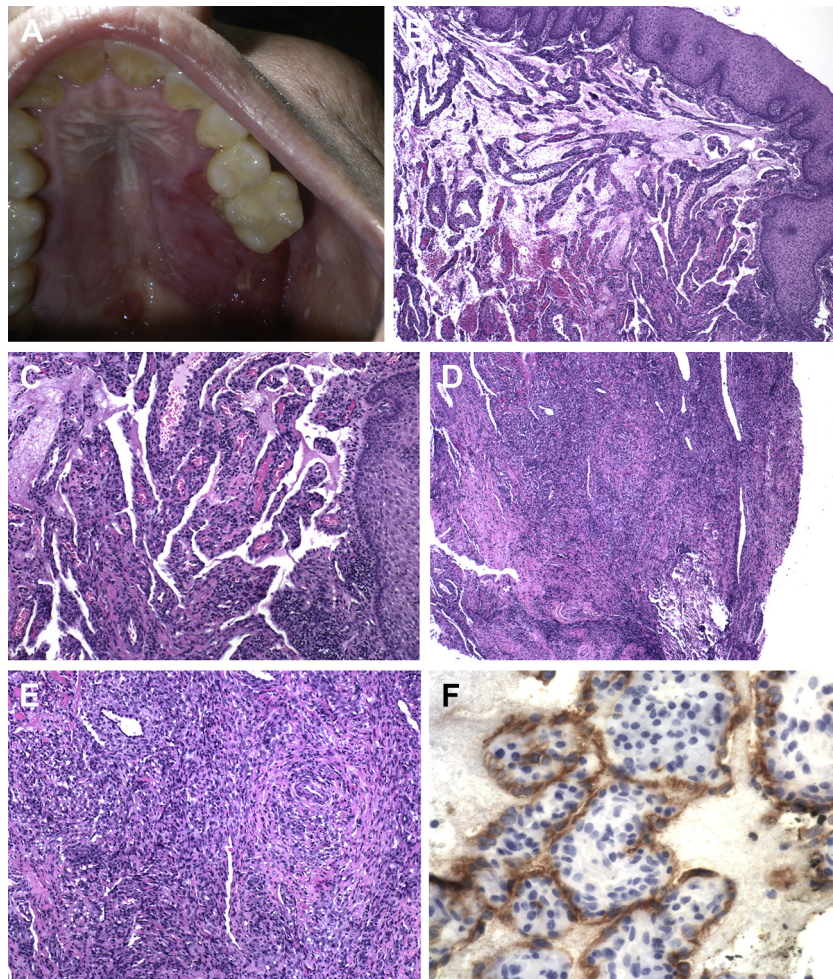


Fig. 1. Clinical, histological, and immunohistochemical features of case 1. (A) Intra-oral photograph shows the mirror image of an erythematous swelling in right maxillary tuberosity and palate area. (B) The characteristic anastomosing vessels impart a lymphangioma-like appearance (hematoxylin-eosin stain, original magnification  $\times 4$ ). (C) Prominent papillary tufting is seen (hematoxylin-eosin stain, original magnification  $\times 10$ ). (D) A focal area of spindle cells is seen in the deeper aspect of the specimen (hematoxylin-eosin stain, original magnification  $\times 4$ ). (E) An absence of prominent extravasation of erythrocytes and any obvious mitotic figures is noted (hematoxylin-eosin stain, original magnification  $\times 10$ ). (F) Immunohistochemical studies for podoplanin (D2-40) demonstrate cytoplasmic staining in the cells lining the vascular spaces (anti-D2-40 stain, original magnification  $\times 20$ ).

of KS. Histopathological analysis of the biopsy specimen revealed markedly dilated anastomosing vascular spaces lined by endothelial cells with a bland morphology in the lamina propria (Figure 2). The smaller vessels had a papillary architecture. Spindled cells, mitotic activity, and extravasation of erythrocytes were not seen. Immunohistochemistry showed positive staining for HHV8 in the lesional cells, and a diagnosis of LLKS was established. The positive immunostaining for D2-40 was observed only in the endothelial cells lining the lymphatic spaces and was less intense than in the other cases.

### Case 3

A thin, but otherwise healthy appearing 37-year-old African American male presented with “granulation tissue” of the right and left retromolar areas. Both the

right and left retromolar lesions were excised and were diagnosed histologically as chronically inflamed granulation tissue. Seven months later the patient presented with swollen, necrotic appearing tissue in the same locations. A panoramic radiograph demonstrated mandibular bone loss beneath the soft tissue swellings. His HIV status was unknown at the time of biopsy. The second biopsy specimens showed focal areas of granulation tissue similar to the first biopsy specimen. In addition, there were areas showing large anastomosing vascular channels lined by endothelial cells with a bland cytomorphology (Figure 3A and B). However, the majority of the specimen showed very closely arranged vascular spaces (Figure 3C). There was also a focal area of spindle cells, which had occasional mitoses. A plasmacytic infiltrate was noted. An immunohistochemical



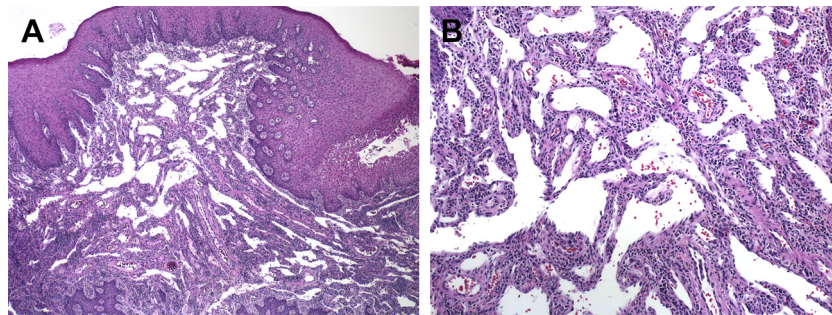


Fig. 2. Histological features of case 2. (A) Anastomosing, irregularly shaped vascular spaces are seen in the lamina propria. A spindle cell component is absent (hematoxylin-eosin stain, original magnification  $\times 4$ ). (B) A predominantly plasmacytic infiltrate is noted. No mitotic figures are seen (hematoxylin-eosin stain, original magnification  $\times 10$ ).

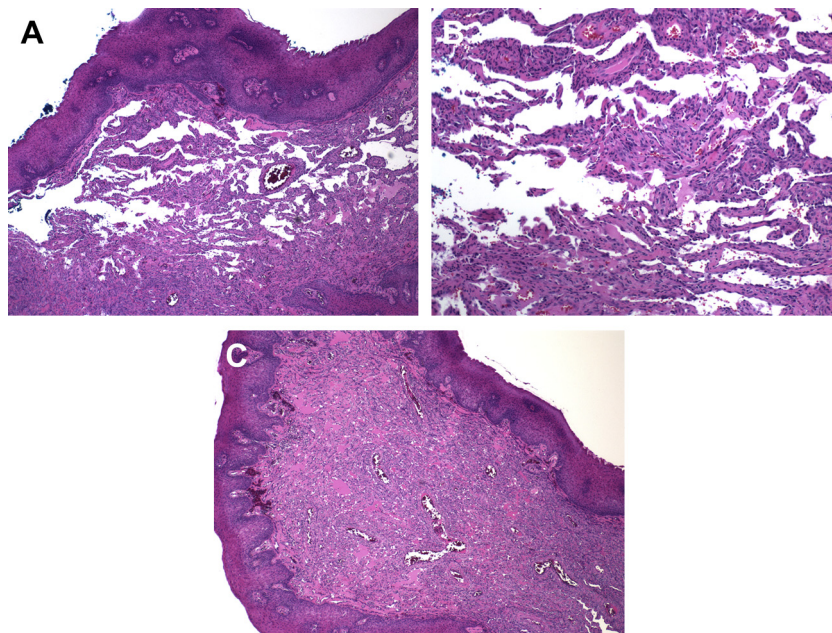


Fig. 3. Histological features of case 3. (A) Dilated vascular spaces arranged in anastomosing patterns are seen prominently in the lamina propria (hematoxylin-eosin stain, original magnification  $\times 4$ ). (B) Prominent papillary tufting is noted (hematoxylin-eosin stain, original magnification  $\times 10$ ). (C) Predominant areas showed closely arranged vascular spaces, simulating a spindle cell architecture (hematoxylin-eosin stain, original magnification  $\times 4$ ).

stain for HHV8 was performed and it showed positive nuclear staining which confirmed the diagnosis of KS. D2-40 immunostaining also showed the presence of the protein in the endothelial cells lining the vascular spaces.

#### Case 4

A 54-year-old male presented with a purple mass extending to involve the posterior hard palate, soft palate, and oropharynx. He first noticed the mass 7 months ago. He had been HIV-positive for approximately 2 decades and had been placed on highly active anti-retroviral therapy (HAART) therapy. At the time of presentation, he was not on HAART therapy and his CD4 count was reported to be 97. An incisional biopsy of the palatal lesion showed numerous dilated vascular

spaces (Figure 4). In addition, this specimen demonstrated a prominent papillary epithelial hyperplasia. An immunohistochemical study for HHV8 showed positive nuclear staining in the lesional cells and confirmed the diagnosis of KS. Immunohistochemical results for D2-40 also demonstrated positive staining in the endothelial cells.

#### Case 5

A 35-year-old Caucasian male patient, whose HIV status was unknown, presented with bilateral purplish nodular lesions in the palate extending from the soft palate posteriorly to the premolar areas anteriorly and extending almost to the midline. An incisional biopsy of the affected area was performed and histological analysis

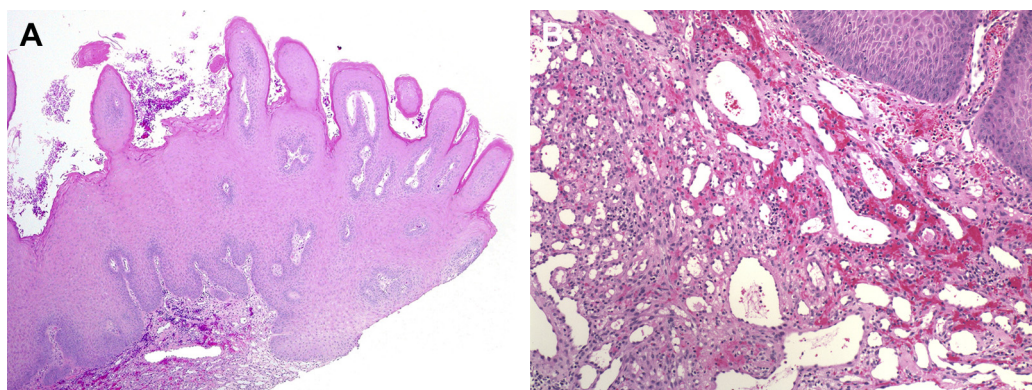


Fig. 4. Histological features of case 4. (A) A prominent papillary epithelial hyperplasia is seen in the surface of the specimen (hematoxylin-eosin stain, original magnification  $\times 4$ ). (B) Dilated vascular spaces without spindle cells are seen in the lamina propria (hematoxylin-eosin stain, original magnification  $\times 10$ ).

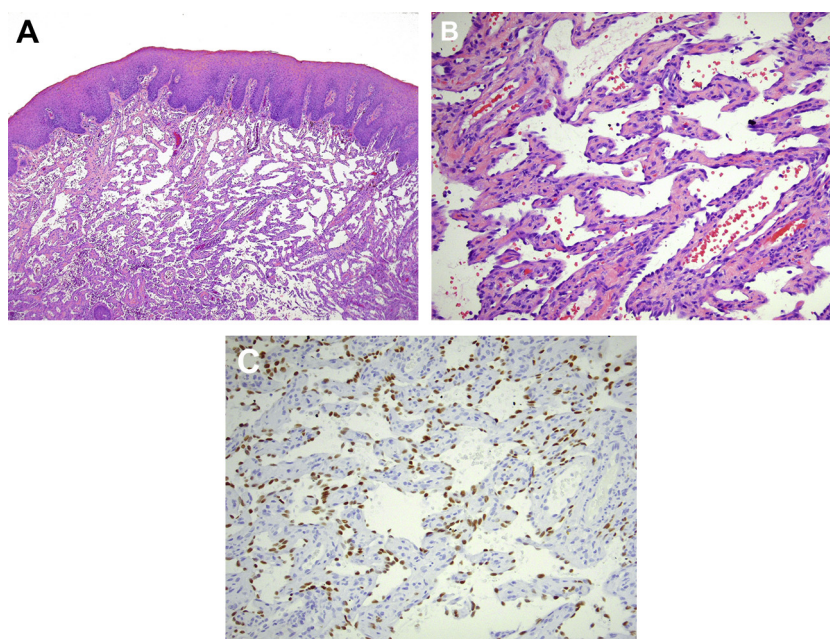


Fig. 5. Histological and immunohistochemical features of case 5. (A) The characteristic appearance of LLKS is seen predominantly with no focal areas of spindle cells (hematoxylin-eosin stain, original magnification  $\times 4$ ). (B) A bland cytomorphology without any pleomorphism or mitotic figures is observed (hematoxylin-eosin stain, original magnification  $\times 10$ ). (C) Immunohistochemistry for HHV8 demonstrates positive staining of nuclei, especially in cells lining the vascular spaces (anti-HHV8 stain, original magnification  $\times 20$ ).

revealed anastomosing dilated vascular spaces without a spindle cell component or significant erythrocyte extravasation (Figure 5A). Mitotic activity was sparse and no significant inflammatory component was seen (Figure 5B). A positive immunohistochemical reaction in the nuclei of the endothelial cells for HHV8 established the diagnosis of KS (Figure 5C). D2-40 immunostaining was also performed and observed to be positive in the endothelial cells lining the lymphatic spaces. Following the diagnosis of KS, the patient underwent additional tests and was reported to be seropositive for HIV.

## DISCUSSION

LLKS has been described in endemic KS, AIDS-associated KS, and classic KS.<sup>8-10</sup> All our intra-oral cases were AIDS-associated KS. Clinically, LLKS has been described as bullous or cystic lesions as well as red or purple patches, plaques, or nodules on the skin. In all our 5 intra-oral cases, the lesions were described as erythematous swellings or nodular mass lesions.

The unusual histological pattern in the LLKS variant makes it essential for pathologists to be aware of this pattern to avoid misdiagnosis. It typically presents as



ectatic, irregularly shaped vascular spaces that are present in the lamina propria right underneath the epithelium. The characteristic presentation is the anastomosing, interconnecting vessels that sometimes project like papillary tufts.<sup>1,17</sup> The vascular structures are lined by banal endothelial cells, which have either plump and round or flat and elongated nuclei. The endothelial cells do not show cytologic atypia or mitotic activity. The location of the lesion right underneath the epithelium, the absence of erythrocytes in many vessels, and the papillary strand-like architecture imparts a lymphatic vessel appearance to the lesion. A predominantly lymphoplasmacytic infiltrate has often been described in these lesions and is also seen in our intra-oral cases 1, 2, and 3. In a recent retrospective article studying 23 cases of intra-oral LLKS, Bunn et al. report that the classic features of KS were present in most cases facilitating diagnosis.<sup>11</sup> However, the spindle cell component with prominent extravasation of blood cells that typically characterizes KS was not present in most of our cases. Therefore, recognizing this lymphangioma-like pattern as a variant of KS helps to avoid misdiagnosis, especially in patients whose HIV status is unknown, such as in our cases 1, 3, and 5.

The development of bullous lesions or lymphangioma-like areas in KS is peculiar, and whether the lesional cells in these areas are neoplastic in nature has been a subject of debate. Ronchese and Kern attributed these areas to lymphangiectasia, secondary to obstruction by the neoplasm.<sup>4</sup> Gange and Jones contended that these bullous lesions were primarily a neoplastic process and not a secondary edematous change.<sup>17</sup> Recent studies also demonstrated the presence of HHV8 in the cells lining the lymphangioma-like areas, which supports a neoplastic theory.<sup>9,18,19</sup> In all our 5 intra-oral cases, the immunohistochemical staining for HHV8 had shown positive staining in the cells in the lymphangioma-like areas. This finding also supports the neoplastic nature of the lymphangioma-like areas in KS.

Although the histogenetic origin for KS cells has been debated, recently it has been shown that KS cells expressed lymphatic markers in addition to the pan-endothelial markers CD31 and CD34.<sup>20-22</sup> Podoplanin (D2-40) is a membrane protein that has been reported to be expressed in lymphatic endothelial cells and also in KS lesional cells.<sup>20,24</sup> Our results showed positive cytoplasmic and membranous staining in the lesional cells in all our 5 cases, similar to the results reported by Grayson and Pantanowitz.<sup>23</sup> The positive immunoreactivity for podoplanin in our series supports the hypothesis of a possible lymphatic origin or lymphatic differentiation in KS.

Another histological variant of KS that could also present with bullous skin lesions was recently described by Pantanowitz and Duke as lymphangiectatic KS.<sup>15</sup>

The histological features of this lesion vary significantly from LLKS. It presents as thin-walled dilated lymphatic vessels present at the periphery of the lesion close to the epithelium and in between lesional KS cells. The vascular spaces in lymphangiectatic KS are not irregularly shaped and do not have the characteristic anastomosing pattern with papillary tuft-like projections.<sup>23</sup>

## CONCLUSION

LLKS is a rare histological variant of KS that occurs most often in the skin of the extremities. We report 5 intra-oral cases demonstrating this histological pattern in which the typical KS features (spindle cell proliferation with erythrocyte extravasation) are not evident. It is important for pathologists to recognize this unusual variant of KS, especially when the characteristic spindle cell component of KS is not present or the HIV status of the patient is not known.

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