Microscopic diversity in oral Kaposi sarcoma

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ABSTRACT

Kaposi sarcoma is the most common HIV-associated neoplasm, frequently presenting with oral mucosal involvement. This retrospective study aimed to assess

and highlight the histomorphological spectrum of oral Kaposi sarcoma. One hundred and thirty-five cases diagnosed between 1990 and 2011 were retrieved from the archives of the Oral and Dental Hospital of the University of Pretoria, South Africa. Following histological review, each case was placed into one of seven categories based on the predominant pattern of growth. These histological divisions included lesions designated as solid, lymphangioma-like, telangiectatic, desmoplastic, lymphangiectatic, ecchymotic and anaplastic. The presence of co-existent pathology was identified in 25 cases, largely represented by superimposed candidiasis. Concomitant cytomegalovirus and non-necrotizing granulomatous inflammation were also observed. Whilst the prognostic significance of these variants is yet to be determined, the appreciation and recognition of such morphologic diversity remains essential in distinguishing these lesions from possible mimics.

STATEMENT OF CLINICAL RELEVANCE

Oral Kaposi sarcoma may be the first sign of underlying immune dysfunction. The myriad of microscopic growth patterns encountered in oral Kaposi sarcoma are highlighted and characterized here in an attempt to facilitate the diagnosis with distinction from possible histopathological mimics.

Kaposi sarcoma (KS) is a multicentric vasoproliferative lesion characterized by clinical and histological heterogeneity. KS is classified as a vascular neoplasm of intermediate grade malignant potential which rarely metastasizes.[1] The spectrum of biological behavior depends on the epidemiological form of disease.[2,3] The earliest classic form of KS as first described by Moritz Kaposi in 1872 runs a protracted yet indolent course.[4,5] Iatrogenic KS (transplantation associated) occurs in patients on

immunosuppressive therapy and expresses borderline to intermediate behavioral qualities. Endemic (African) KS and epidemic (HIV/AIDS associated) KS are far more aggressive, fulminant forms of disease with potentially fatal consequences.[6] Despite distinct pathogenetic mechanisms, all forms share the fundamental clinical and morphological features that typify KS.[2,3] The true malignant potential of KS remains contentious with most lesions demonstrating attributes of reactive, hyperplastic processes while the more clinically advanced and infiltrative lesions display qualities of a frankly malignant nature.[7]

Human herpes virus-8 (HHV-8) is implicated as the etiological agent in all forms of disease, yet, infection alone is inadequate for KS initiation and progression. Underlying immune suppression is generally a prerequisite for development of KS.[3,8,9] Epidemic KS arising in the context of the HIV/AIDS pandemic remains the most frequent clinical form of disease characterized by the greatest malevolence and poorest prognosis. This is due in part to the presence of overwhelming co-existent neoplastic and infectious disease. Disseminated KS in the untreated HIV-positive patient heralds progression to AIDS with many of these patients failing to survive beyond 6-months.[8] More than two thirds of the global HIV-infected population resides in poverty-stricken regions of sub-Saharan Africa, with an estimated 5.6 million sufferers in South Africa alone.[10] Epidemic KS thus constitutes the bulk of our surgical cases with almost no cases of the endemic type identified. Oral mucosal lesions of epidemic KS occur concurrently with cutaneous lesions in 71% of patients. The oral cavity represents the initial site of KS in up to 22% of cases, often being the first clinical indication of HIV infection in previously undiagnosed individuals.[5,11] Furthermore, oral Kaposi sarcoma (OKS) is prognostically significant

in antiretroviral naive patients, portending far greater mortality than KS in untreated patients with cutaneous lesions only.[12-14]

The microscopic features of KS are for the most part easy to recognize; nevertheless, the increasing number of morphologic variants as reported in cutaneous KS potentially presents a diagnostic obstacle for the histopathologist. Confounding this further in epidemic cases of KS is the presence of parallel pathology, often due to disseminated infections, occurring concomitantly in KS biopsy specimens. The aim of this study was to describe the multitude of growth patterns encountered in a series of OKS lesions, including documentation of a newly recognized microscopic variant which we have termed desmoplastic KS (DKS). The presence of co-existent infectious pathology was also investigated. Awareness of such histological diversity facilitates distinction of OKS from possible mimics, allowing for accurate, timely diagnosis and optimal patient management.

MATERIALS AND METHODS

All cases diagnosed histologically as OKS between 1990 and 2011 were retrieved from the departmental archives of the Oral and Dental Hospital of the University of Pretoria, South Africa. KS from extra-oral sites and cases with diagnostic ambiguity were omitted from the study. The routine hematoxylin and eosin-stained sections were retrospectively analyzed by two independent examiners both separately and jointly in order to characterize the morphological features. Morphology alone was diagnostic of KS in the majority of cases.

Table I. Confirmatory immunohistochemical staining

Antibody	*Clone*	*Manufacturer*	*City*	*Country*	*Dilution*
CD31	JC70A	Dako	Glostrup	Denmark	1:200
CD34	QBEnd 10	Dako	Glostrup	Denmark	1:50
HHV8-LNA	1	Novocastra	Newcastle upon	UK	1:100
	3B10	Laboratories	Tyne		
D2-40	D2-40	Dakocytomation	Glostrup	Denmark	1:100

Immunohistochemistry including CD31, CD34, D2-40 and HHV-8 was performed where confirmation of the diagnosis was needed (Table I). Following histopathological analysis, the cases were categorized as one of seven morphological variants according to the predominant growth pattern which constituted more than fifty percent of the total volume of lesional tissue. Clinical details pertaining to each case were recorded, based on evaluation of the histology request forms and diagnostic reports (Table II).

Table II. *Microscopic variants diagnosed in oral Kaposi sarcoma lesions*

Variant	*Cases*	*Age (mean)*	*Gender*
Solid KS	*59*	*8-58 (33)*	*30F, 25M, 4NS*
Lymphangioma-like KS	*23*	*21-70 (36)*	*14F,8M, 1NS*
Telangiectatic KS	*22*	*18-58 (34)*	*14F, 7M, 1NS*
Desmoplastic KS	*14*	*22-57 (38)*	*4F, 10M,*
Lymphangiectatic KS	*12*	*10-45 (30)*	*6F, 5M, 1NS*
Ecchymotic KS	*3*	*16-27 (22)*	*1F, 2M,*
Anaplastic KS	*2*	*35-50 (43)*	*1F, 1M*

F, female; M, male; NS, Not stated.

RESULTS

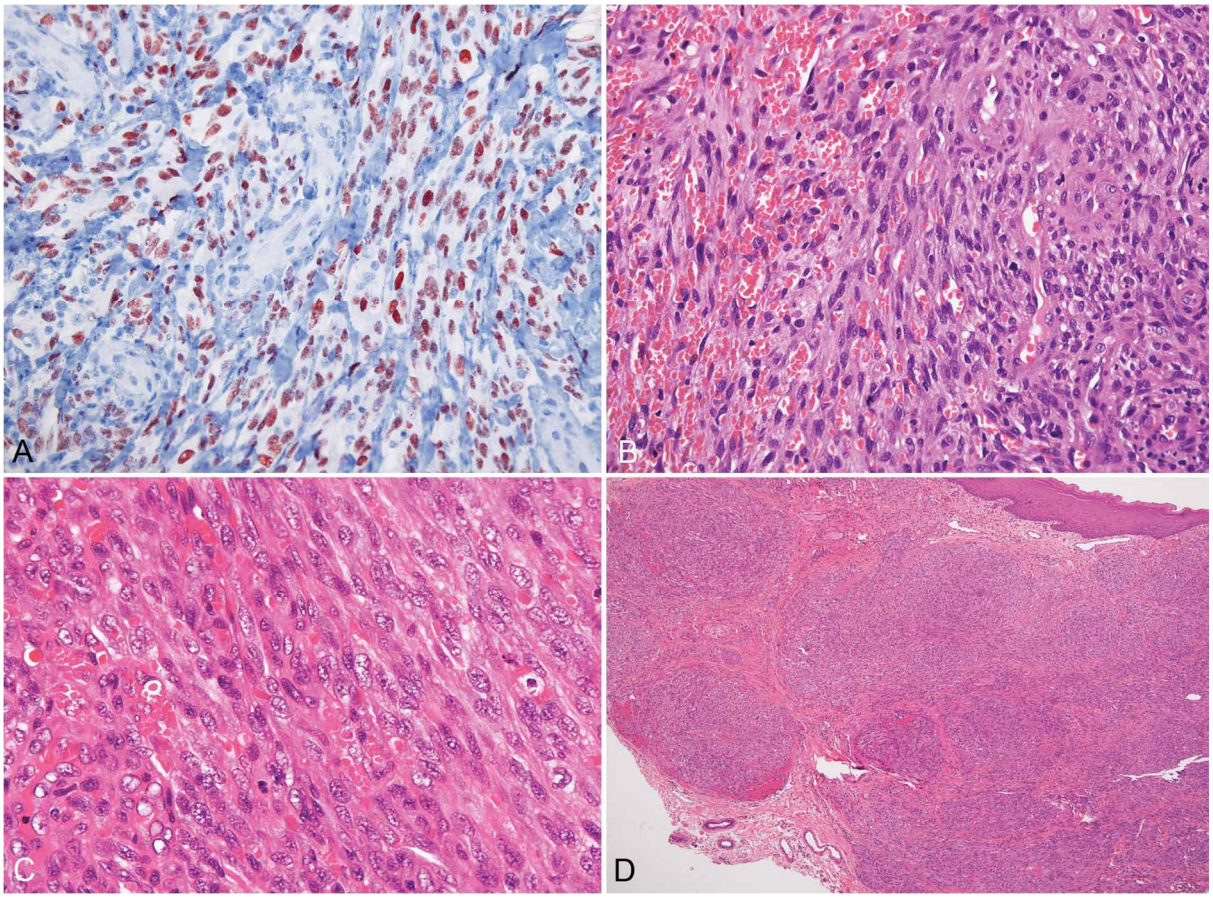

Fig. 1. **A,** Strong diffuse nuclear immunoreactivity in a case of solid KS (immunohistochemical staining with HHV, original magnification X 200). **B,** Solid KS with fascicular arrangement of spindle cells and extravasational hemorrhage (hematoxylin-eosin stain, original magnification X 200). **C,** High power magnification of solid KS showing fascicles of spindle cells, slit-like vascular channels and scattered amorphous, eosinophilic globules (hematoxylin-eosin stain, original magnification X 400). **D,** Solid KS comprising multiple lobules of spindle cells separated by fibrous bands (hematoxylin-eosin stain, original magnification X 40).

A total of 135 cases were included in this study. Most patients were clinically suspected to be HIV-positive at the time of biopsy although many had never been formally tested. HHV-8 immunohistochemistry was positive in all cases evaluated

(Figure 1A). Lesions were multifocal, with surgical accessibility dictating the site of biopsy. There were no significant differences in gender distribution (F: M = 1.1:1), with a peak incidence recorded in the third and fourth decades (mean = 34 years).

Solid KS (n=59; 44%), represented the most frequent morphological category and comprised established, exophytic, ulcerated masses with a nodular to multinodular pattern of solid, uninterrupted growth. Lesions were diffusely cellular with organized fascicles of spindle cells and occasional storiform areas (Figure 1B). The compact vascular spaces were mostly slit-like with associated hemorrhage, hemosiderin deposits, eosinophilic globules and chronic inflammation identified in the adjacent connective tissue (Figure 1C). Dense bands of chronically inflamed fibrous connective tissue separated the cellular nodules in multinodular lesions (Figure 1D). Sporadic mitoses with little evidence of atypia were noted. Plump spindle cells had an epithelioid to sieve-like appearance when cut in cross section.

Lymphangioma-like KS (LLKS) constituted the second largest OKS category (n=23; 17%), the hallmark of this variant being the presence of irregular, angulated lymphatic channels lined by flattened endothelial cells (Figure 2A). The lymphatic channels contained lymphatic fluid and admixed red blood cells. The loose intervening stroma comprised spindle cells, foci of hemorrhage and minimal collagenous connective tissue. Conspicuous nodular aggregates of plasma cells were a distinctive feature in several cases, a trait not documented in cutaneous LLKS (Figure 2B). LLKS lesions appeared to be extensive and established with evidence of infiltration and dissection of the connective tissue deep within the submucosa. The promontory sign was especially marked in these cases.

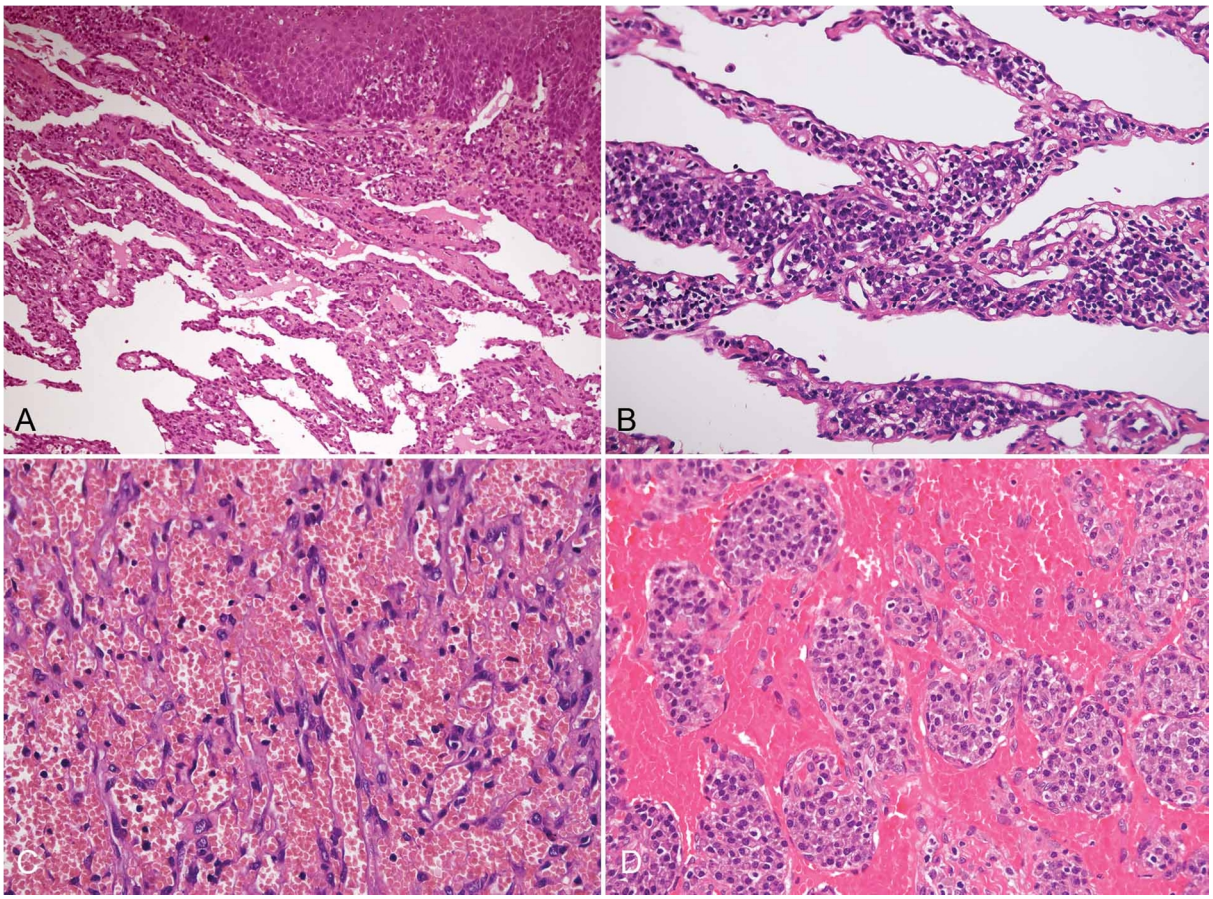

Fig. 2. **A,** The characteristic irregular, angulated lymphatic channels seen in lymphangioma-like KS (hematoxylin-eosin stain, original magnification X 100). **B,** Aggregates of plasma cells in a case of lymphangioma-like KS (hematoxylin-eosin stain, original magnification X 200). **C,** Engorged vascular spaces of telangiectatic KS (hematoxylin-eosin stain, original magnification X 200). **D,** Conspicuous nodular aggregates of plasma cells in telangiectatic KS (hematoxylin-eosin stain, original magnification X 200).

Telangiectatic KS (TKS) comprised similarly advanced, exophytic lesions with marked surface ulceration (n=22; 16%). These cases had prominent, engorged, ectatic vascular spaces and abundant extravasational hemorrhage (Figure 2C). An overall decrease in cellularity was appreciable. Hemosiderin deposits and eosinophilic globules were plentiful. Interspersed pockets of plasma cells as seen in oral LLKS were also noteworthy (Figure 2D).

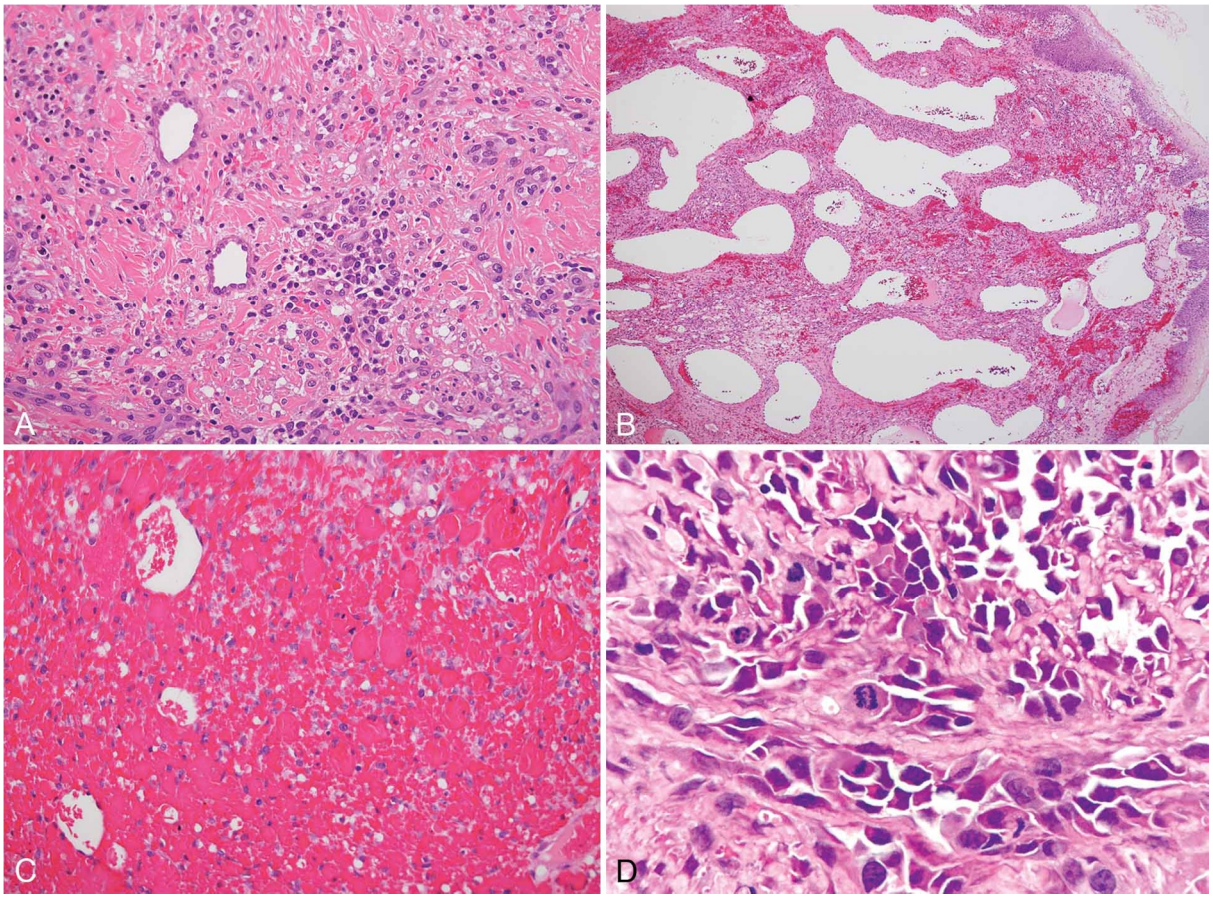

Fig. 3. **A,** Desmoplastic KS typified by abundant collagenous connective tissue which separates the cellular constituents (hematoxylin-eosin stain, original magnification X 200). **B,** Rounded, non-anastomosing vasculature identified in lymphangiectatic KS (hematoxylin-eosin stain, original magnification X 400). **C,** Ecchymotic KS is dominated by extravasational hemorrhage which at times obscures the cellular KS components (hematoxylin-eosin stain, original magnification X 200). **D,** Anaplastic KS with vascular spaces lined by pleomorphic endothelial cells exhibiting features of hobnailing and nuclear hyperchromasia. Increased numbers of mitotic figures are readily recognized (hematoxylin-eosin stain, original magnification X 400).

Fourteen (10%) of the cases in the present series showed unusual, unique histopathological features which have not been described before. These cases were designated *desmoplastic KS* (DKS). Lesions categorized as DKS demonstrated diffuse and extensive growth both laterally and vertically with deep submucosal

infiltration indicative of lesional advancement. In addition, a consistent histological finding was the presence of marked stromal desmoplasia. The lesions classified as DKS were clearly more developed than typical plaque forms. Unlike the typical nodular proliferations seen in established KS, DKS showed little circumscription and little to no surface elevation clinically. The lesional components were markedly compressed by abundant intervening fibrous connective tissue (Figure 3A). Although the lesions were all extensively infiltrative, cytological atypia was consistently absent. Tumor infiltration of skeletal muscle exhibited a tessellated pattern reminiscent of proliferative myositis in some areas. Cellular infiltration of adjacent minor salivary glands and adipose tissue was evident. Smooth muscle actin (SMA) immunohistochemical staining showed focal positivity within the stromal fibroblastic component.

The last three descriptive categories in this series were lymphangiectatic KS (n=12; 9%), ecchymotic KS (n=3; 2%) and anaplastic KS (n=2, 1.5%) (Table II). *Lymphangiectatic KS* is a well-documented cutaneous lymphedematous variant with distinctive histopathological qualities. Low power examination of lesions imparted a cribriform to “Swiss cheese”-like pattern (Figure 3B). Discrete, rounded ectatic lymphatic channels lined by prominent endothelial cells with focal hobnailing interrupted the features of conventional KS. The lymphatic spaces were completely separate and disconnected from each other with no evidence of the anastomosing, jagged architecture that exemplify LLKS. Cases assigned the diagnosis of *ecchymotic KS* (EKS) were microscopically dominated by extravasational hemorrhage which obscured the cellular KS component (Figure 3C). Conventional features were focally present in all cases which aided the final diagnosis. The two examples of *anaplastic KS* (AKS) described here, showed considerable intra-lesional

variation in morphology with no distinct pattern of predominance. There was widespread cytological atypia, pleomorphism and brisk mitotic activity. Both tumors had focal ectatic vasculature lined by cuboidal to hobnailed endothelial cells of variable size and high nuclear to cytoplasmic ratios (Figure 3D). Several angiosarcomatous regions were observed.

Parallel pathology was observed in 25 cases, predominantly as concurrent superficially invasive candidiasis. One case contained a co-existing non-necrotizing granuloma whilst an additional lesion demonstrated triple pathology in the form of cytomegalovirus and candida co-infection. Scattered plasma cells were a conspicuous microscopic finding in all of the histological variants described, however, the presence of dense plasma cell pockets in LLKS, TKS and some DKS cases constituted an additional unique feature of interest.

DISCUSSION

Contrary to the dramatic decline in the prevalence of KS observed within developed countries following introduction of successful highly active antiretroviral therapy (HAART), rates continue to surge in resource-poor regions. The impact and effects are far-reaching, being no more prevalent than in South Africa that is currently home to more HIV-infected persons than any other country.[5,7,8,10,11,15]

OKS is most prevalent in epidemic forms of disease, occurring at all stages of HIV infection. End-stage disease (AIDS) correlates strongly with a higher clinical prevalence with lesional aggression indicating immune deterioration, low CD4 cell count and increased HHV-8 viral loads.[11,15-17] The high incidence of OKS might be

related to salivary shedding of HHV-8 viral particles at distinctly higher levels compared with plasma. HHV-8 may also be harbored within the oropharyngeal epithelium, allowing for replication and further increased salivary shedding.[18,19]

Microscopic recognition of KS is seldom problematic, even in lesions with unconventional morphologies. The traditional features common to all forms of disease are almost invariably present at least focally. Incisional biopsies may, however, be non-representative displaying areas with unusual morphology thereby hampering histopathological diagnosis. KS histopathology closely mirrors the clinical evolution of lesions. Early patch stage lesions are subtle and non-specific, presenting the most frequent diagnostic challenge. Focal, superficial, sparsely cellular vascular proliferations are typical. A vague lymphoplasmacytic perivascular inflammatory infiltrate is present.[2,7,18,20,21] As lesions increase in size, becoming thicker and more plaque-like to nodular, an increase in vascularity and cellularity is noted microscopically. The proliferation of new blood vessels lacking pericytes accounts for the extravasational hemorrhage so intricately associated with KS. The hemorrhage is accompanied by deposition of hemosiderin and scattered amorphous hyaline globules within and between lesional cells. The most conspicuous change is the appearance of a spindle cell component that extends between the lesional vasculature.[2,7,18,21] The inflammatory component is a persistent constituent.[20] The so-called promontory sign is a classic feature of nodular stage KS and describes the presence of round, regular native blood vessels which protrude into the irregular, compressed lumina of lesional vessels.[2,7,18,21-23] The mucosal surface in OKS is often ulcerated with associated pyogenic membrane formation, neutrophilic inflammation and granulation tissue which blend with the underlying lesional KS component.

OKS, much like its cutaneous counterpart, presents with a multitude of histopathological patterns, some of which have been alluded to in earlier studies.[21] A similar array of morphologies was noted in this series of OKS together with recognition of a new microscopic variant in the form of DKS.

Solid KS has the conventional features encountered in nodular stage lesions and was the most common subtype in the present series. Nodular stage KS has a pyogenic granuloma-like clinical appearance. A pyogenic-granuloma-like microscopic variant of KS has been described in some cutaneous lesions.[24] The oral lesions described as solid KS were, however, much larger and did not show the lobular arrangement of capillary-sized vessels attributed to this subtype. In spite of the recognizable diagnostic features, the histological differential diagnoses would include lesions ranging from reactive and benign to distinctly malignant. Lesions bear some resemblance to nodular fasciitis, inflammatory myofibroblastic tumor and predominantly spindled and cellular fibrous histiocytoma. Solid KS also shares features with Kaposiform hemangioendothelioma and well differentiated angiosarcoma while those with compact, organized fascicles echo fibrosarcomatous growth.

LLKS is a widely accepted cutaneous variant with a striking predilection for the lower extremities arising in background lymphedema. It is a rare cutaneous form, accounting for less than 5% of the variants thus far documented.[24] LLKS is responsible for a bullous-like clinical appearance in skin lesions, a feature not evident in the oral cavity. The clinical significance of LLKS is unknown; however, lymphedematous cutaneous variants forecast a poor clinical outcome.[22,24] The prominent jagged sinusoidal lymphatic vessels discerned in LLKS may prompt consideration of various vascular and lymphatic lesions including lymphangioma,

kaposiform hemangioendothelioma, lymphangiosarcoma and well differentiated angiosarcoma.

TKS in the current series appears to be more prevalent than its infrequently documented cutaneous analogue. TKS and EKS present in much the same way clinically as the other KS variants but have microscopic features characterized by marked hemorrhage. These two variants can be distinguished from each other on the basis of their cellularity. TKS comprises large, ectatically dilated spaces which are engorged with red blood cells. There is abundant extravasational stromal hemorrhage, nevertheless, the cellular spindle cell component is still identifiable. EKS on the other hand is associated with such extensive hemorrhage that the cellular components are almost completely obscured. Focal areas showing conventional KS features are invariably present but may require serial sections for identification. In the absence of adequate clinical information or a high index of suspicion, the histological features of both TKS and EKS may be misinterpreted as submucosal hemorrhage, traumatic hemorrhage, the pooling of blood within a vascular malformation or evidence suggestive of an underlying bleeding disorder. The diagnosis of KS may easily be overlooked in these two variants if biopsy specimens are superficial or non-representative.

DKS is a novel histomorphological KS variant which we describe here for the first time. DKS lesions had a distinct predilection for occurrence within the attached mucosa of the gingiva, palate and dorsum of tongue. The histological features unique to this variant included the depth of tumor infiltration and the abundant stromal connective tissue which compressed the cellular elements in areas. This unusual morphology in the absence of recognizable KS features necessitates confirmatory immunohistochemical staining. DKS of the oral cavity shares

overlapping features to some degree with keloidal KS of the skin, the latter, however, has a tendency to clinical keloid formation, implying exophytic growth and possible traumatic origin.[7, 24] DKS may need to be distinguished from the regressive changes seen in KS associated with HAART as well as the possibility of recrudescent KS as a result of IRIS.[5,25] In this regard, DKS did not show any evidence of lesional circumscription or localization by peripheral fibrosis nor was there a history of HAART initiation in any case. DKS may be missed completely in small, superficial fibrous biopsies. The desmoplastic stromal reaction is well documented in invasive carcinomas and refers to the interaction between tumor cells and the surrounding stroma which constitutes the tumor microenvironment.[26]. The fibroblasts within the tumor stroma trans-differentiate into myofibroblasts under the influence of cytokines and growth factors produced by the invasive tumor cells. The myofibroblasts may facilitate tumor progression through paracrine signaling.[27] Myofibroblastic transformation in tumor stroma is associated with more infiltrative, proliferative neoplasms. All cases of DKS in this series expressed variable degrees of SMA positivity within the desmoplastic stromal component, a possible indication of increased clinical aggression or progression. This correlates with the extensive lateral and vertical infiltration noted histopathologically.

Two of the samples examined, were deemed to be anaplastic KS variants. AKS is a rare expression of KS, separated from other variants by its increased number of mitoses and pronounced cytological atypia. Although documented in all clinical forms of disease, anaplastic KS is particularly prevalent in epidemic disease. AKS is characterized by extensive local destruction, deep infiltration and a propensity for metastasis. The more vascular regions of AKS require microscopic distinction from angiosarcoma and hobnail hemangioendothelioma while the

predominantly cellular areas resemble malignant melanoma and spindle cell malignancies.

The diagnosis of KS, irrespective of the variant, is facilitated by recognition of focal areas showing conventional features. It is thus essential to sample lesions adequately for histopathological assessment with serial sections being of assistance where typical features are absent. Immunoreactivity for the vascular markers CD31 and CD34 and the lymphatic endothelial marker D2-40, in conjunction with nuclear HHV-8 immunopositivity, are useful for diagnostic confirmation.

The profound immune suppression that accompanies epidemic KS predisposes patients to development of disseminated systemic opportunistic infections and other neoplasms.[28] The occurrence of co-existent infections, dermatoses and neoplasms has been described in cutaneous KS and to a lesser extent in OKS.[28-33] Twenty-five cases in this series showed co-existent pathology, most commonly in the form of superficially invasive candidiasis. This is not unexpected, considering oral candidiasis represents the most frequent intra-oral manifestation of HIV, regardless of stage. Triple pathology was evident in a case of LLKS that contained endothelial cells with intranuclear cytomegalovirus (CMV) inclusions as well as invasive fungal hyphae (Figure 4). An example of DKS contained a single non-necrotizing granuloma with a sarcoid-like appearance. Limited preliminary special investigations were negative for fungal or Mycobacterial agents, not entirely ruling out an infectious origin. The co-existence of KS and granulomatous inflammation occurring at the same site has been documented in the skin.[33] The diagnosis of a sarcoid-like reaction should be made with caution following careful exclusion of a concurrent infectious process. On the contrary, non-infective granulomas may potentially represent foreign body or unusual drug reactions.[32]

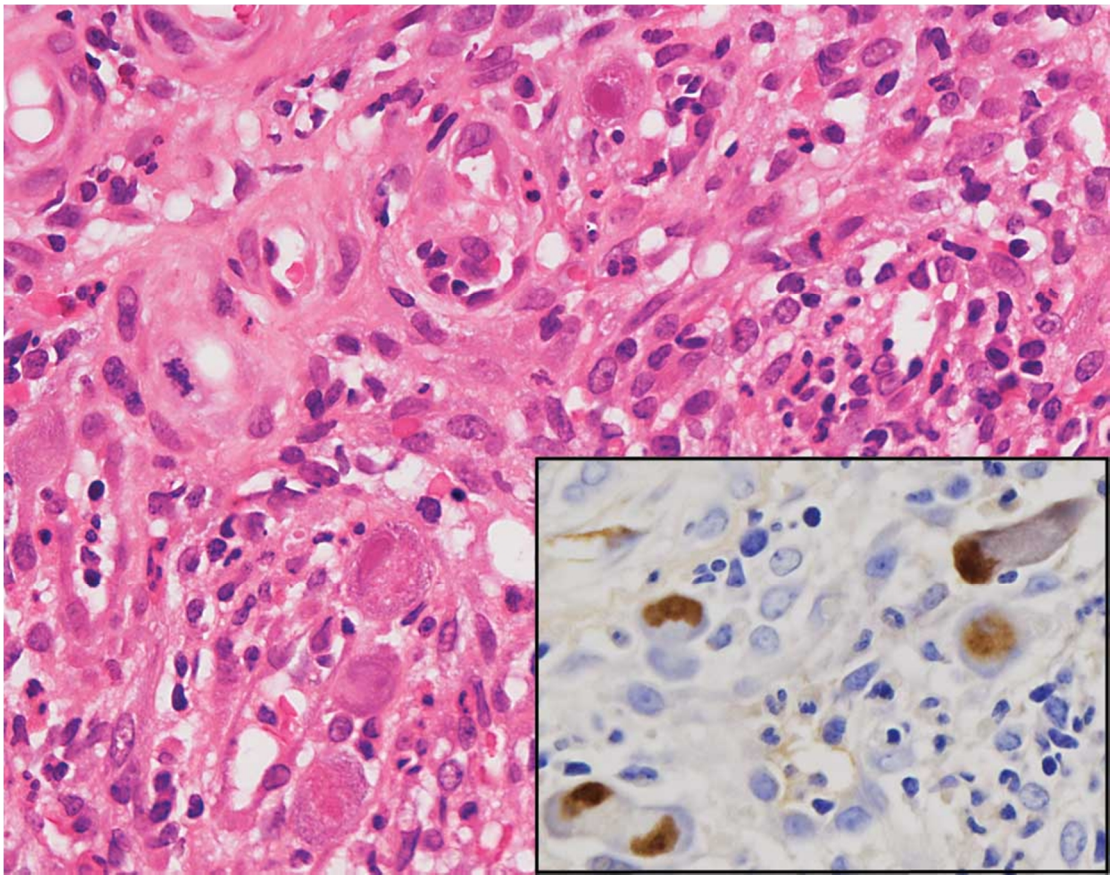

Fig. 4. Co-existent pathology is highlighted in this case of KS and CMV. Scattered prominent endothelial cells contain large intranuclear viral inclusions (hematoxylin-eosin stain, original magnification X 400). The insert demonstrates positive CMV immunoreactivity (immunohistochemical staining with CMV, original magnification X 400).

The microscopic diversity of OKS and the high prevalence of co-existent pathology provide the histopathologist with distinct diagnostic challenges often perpetuated by inadequate clinical details. Heightened awareness of the histopathological spectrum of OKS should expedite an accurate diagnosis. Moreover, the diagnosis of OKS should be diligently followed by serological investigation in instances where a patient's retroviral status is unknown. Multiple concurrent pathologic processes within the same biopsy specimen are prognostically

significant, signalling marked immune deterioration or the possibility of IRIS in patients following recent HAART induction.

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