Microscopic diversity in oral Kaposi sarcoma

Belinda K. Bunn, BDS, MDent, FC Path(SA) Oral Path,[a] Marianne de Vasconcelos Carvalho, DDS, MSc,[b] Melanie Louw, MBChB, MMed,[c] Pablo A. Vargas, DDS, MSc, PhD,[b] and Willie F. van Heerden, BChD, MChD, FC Path(SA) Oral Path, PhD, DSc,[a] Pretoria, South Africa; and Campinas, Brazil
University of Pretoria and State University of Campinas

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. A total of 135 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 histologic review, each case was placed into 1 of 7 categories based on the predominant pattern of growth. These histologic divisions included lesions designated as solid, lymphangioma-like, telangiectatic, desmoplastic, lymphangiectatic, ecchymotic, and anaplastic. The presence of coexistent pathology was identified in 25 cases, largely represented by superimposed candidiasis. Concomitant cytomegalovirus and non-necrotizing granulomatous inflammation were also observed. Although 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 mimickers. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:241-248)

Kaposi sarcoma (KS) is a multicentric vasoproliferative lesion characterized by clinical and histologic heterogeneity. KS is classified as a vascular neoplasm of intermediate-grade malignant potential that rarely metastasizes.[1] The spectrum of biological behavior depends on the epidemiologic 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 morphologic 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 etiologic 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 in part because of the presence of overwhelming coexistent 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 con-

Statement of Clinical Relevance

Oral Kaposi sarcoma may be the first sign of underlying immune dysfunction. The 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 mimickers.

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[a]Oral Pathologist, Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria, South Africa.
[b]Oral Pathologist, Department of Oral Diagnosis, Piracicaba Dental School, State University of Campinas, Brazil.
[c]Pathologist, Department of Anatomical Pathology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa.
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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 3B10	Novocastra Laboratories	Newcastle upon Tyne	UK	1:100
D2-40	D2-40	DakoCytomation	Glostrup	Denmark	1:100

currently 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 coexistent infectious pathology was also investigated. Awareness of such histologic diversity facilitates distinction of OKS from possible mimics, allowing for accurate, timely diagnosis and optimal patient management.

MATERIAL 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 extraoral sites and cases with diagnostic ambiguity were omitted from the study. The routine hematoxylin and eosin–stained sections were retrospectively analyzed by 2 independent examiners both separately and jointly so as to characterize the morphologic features. Morphology alone was diagnostic of KS in most cases. 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 1 of 7 morphologic variants according to the predominant growth pattern, which constituted more than 50% 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, 4 NS
Lymphangioma-like KS	23	21-70 (36)	14F, 8M, 1 NS
Telangiectatic KS	22	18-58 (34)	14F, 7M, 1 NS
Desmoplastic KS	14	22-57 (38)	4F, 10M
Lymphangiectatic KS	12	10-45 (30)	6F, 5M, 1 NS
Ecchymotic KS	3	16-27 (22)	1F, 2M
Anaplastic KS	2	35-50 (43)	1F, 1M

F, female; *M,* male; *NS,* not stated.

RESULTS

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 1, *A*). Lesions were multifocal, with surgical accessibility dictating the site of biopsy. There were no significant differences in gender distribution (F:M = 1.1:1.0), with a peak incidence recorded in the third and fourth decades (mean = 34 years).

Solid KS (n = 59; 44%) represented the most frequent morphologic 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 1, *B*). 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 1, *C*). Dense bands of chronically inflamed fibrous connective tissue separated the cellular nodules in multinodular lesions (Figure 1, *D*). 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 2, *A*). The lymphatic channels contained lymphatic fluid and admixed red blood cells. The loose