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Human Immunodeficiency Virus-Associated Oral Kaposi's Sarcoma

A Heterogeneous Cell Population Dominated by Spindle-Shaped Endothelial Cells

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Cell lineage and cell function antigens were studied immunohistochemically in human immunodeficiency virus-associated oral Kaposi's sarcoma to provide insight into tumor pathogenesis. All tumors were composed predominantly of spindle cells that expressed endothelium-associated antigens, CD34 and CD36 (factor VIII-related antigen was expressed by considerably fewer numbers of tumor cells). Infrequently, spindle tumor cells also expressed actin. Factor XIIIa positive spindle and dendritic stromal cells comprised up to 9% of the tumor cell population. Other spindle and dendritic cells expressing macrophage-associated antigen, CD68, accounted for up to 15% of the tumor cells. Mast cells occurred frequently within and around tumors. Leukocyte function antigen (CD18) was expressed by approximately 13% of tumor cells, and its ligand, intercellular adhesion molecule (ICAM), was expressed by some tumor-associated capillaries (which also expressed endothelial leukocyte adhesion molecule, ELAM) and occasional stromal cells. Staining for proliferating cell nuclear antigen was noted in both interstitial and vascular lining cells. All tumors were non-reactive for human Papillomavirus antigen and HIV p24 antigen. Oral KS is a heterogeneous cellular proliferation composed predominantly of endothelial or endothelium-related spindle cells. Other spindle/dendritic (XIIIa-positive and CD68-positive) cells and mast cells are also present and may contribute to tumor development. ICAM and ELAM expression within tumors may assist infiltration of macrophages and other inflammatory cells into these lesions. (Am J Pathol 1993, 143:240–249)

Kaposi's sarcoma (KS), when seen in association with human immunodeficiency virus (HIV) infection, is an aggressive disease with a poor prognosis. Its cause is unknown and its pathogenesis continues to be elusive. Recent evidence has supported the notion that, at least in its early stages, KS may represent a focal hyperplasia, possibly activated by virus or virus product.[1]

Infectious organisms, especially viruses, have been suspected as initiating agents of KS for many years. Attempts to identify antigens and DNA transcripts of cytomegalovirus, hepatitis B virus, herpes 6 virus, and Epstein–Barr virus in KS have not been fruitful.[2] HIV has been implicated because the HIV *tat* gene appears to be responsible for KS-like cutaneous lesions in transgenic mice,[3] and because a *tat* gene product promotes KS cell growth in tissue culture.[4] The *tat* gene itself has not been demonstrated in the tumor spindle cells, indicating that if HIV is involved, its role would be indirect. Recently, the reports of human Papillomavirus (HPV) DNA sequences[5] and antigens[6] in some KS lesions has raised the question of HPV involvement in the development of this tumor.

The discovery of the HIV-associated skin infection, bacillary angiomatosis, which resembles Kaposi's sarcoma clinically and histologically, has given reason to search also for a bacterial etiology.[7,8] However, unlike bacillary angiomatosis, which is caused by

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Rochalimaea henselae, no bacterium has, as yet, been linked to KS.

Tissue culture studies of KS-derived cells have shown that they produce numerous cytokines, such as interleukin-1, transforming growth factor-β, fibroblast growth factor, and oncostatin M, that are likely to be important in cell proliferation, angiogenesis, and chemotaxis.[1,9–12] It has been hypothesized that these cytokines could mediate a self-sustaining autocrine growth response.[1,13] The tumor cytokine network is believed to be linked to HIV infection through the products of virus-infected lymphoid or accessory cells. These products (*tat* proteins and others) would provide significant initiating and sustaining influences on tumor progression.[4]

It has been convincingly demonstrated through immunophenotyping studies that the dominant cell of KS is differentiated toward the endothelial cell.[14–18] It has also been shown, primarily through tissue culture, that KS cells may be differentiated toward a vessel-associated smooth muscle cell.[19,20]

Recently, it was shown that factor XIIIa-positive dendrocytes are found in significant numbers in KS lesions,[21,22] although this population may be proportionally reduced in late stages.[23] HIV RNA transcripts were subsequently demonstrated in these cells, suggesting that these dendrocytes may play a significant part in tumor development.[24] It is not clear whether this cell and/or other HIV-infected cells (CD4 positive lymphocytes, macrophages) are directly responsible for initiating and sustaining this process.

The cytokine pool that seems to be present in KS suggests that dendrocytes and possibly other proinflammatory cells may be operative in this lesion. To expand what is known about the pathogenetic events of KS, we 1) determined the proportions of various cell populations present in specimens of small (early) and large (advanced) oral KS lesions, using lineage-specific antibodies; 2) determined where the greatest cell cycle activity lies, using antibody to proliferating cell nuclear antigen; and 3) evaluated oral KS for expression of HPV common antigen and HIV p24 antigen.

Materials and Methods

The source of tissue for this study was from oral KS biopsies of HIV-positive patients seen at the Stomatology Clinical Center of the University of California in San Francisco. Eighteen formalin-fixed, paraffin-embedded KS biopsy specimens that appeared well-fixed microscopically and had sufficient amounts of tissue for multiple sections were selected for immunohistochemical staining. Of these 18 specimens, 12 were small, and presumably early, lesions that were contained within the margins of the biopsy. These were well-delineated lesions composed of spindle-shaped cells lining inconspicuous vascular channels. The larger, and presumably advanced, lesions were composed of spindle-shaped cells lining slit-like and bizarre vascular channels that extended well beyond biopsy margins.

Antibodies to factor VIII-related antigen (VIII), XIIIa, CD34, CD68 (KP1), muscle-specific actin, proliferating cell nuclear antigen (PCNA), and HPV common antigen (Table 1) were used in a standard avidin-biotin peroxidase technique (Vectastain, Elite, Vector Labs, Burlingame, CA). Sections from the same cases were also stained with toluidine blue to aid in the identification of mast cells. An avidin/biotin blocking step was used in the immunohistochemical procedure to rule out the possibility of nonspecific staining of endogenous biotin in mast cells.

An additional 11 frozen biopsy specimens of advanced (8) and small (3) lesions were sectioned and immunohistochemically stained with a similar standard avidin-biotin peroxidase technique. Antibodies to CD18 (leukocyte function antigen, LFA), CD36 (OKM5), intercellular adhesion molecule

Table 1. *Antibodies*

Antibody	Source	Dilution	Specificity
Factor VIII	Dako	1:40	Endothelial cell
Factor XIIIa	Calbiochem	1:800	Dendrocytes
CD18 (LFA)	Dako	1:50	Leukocytes
CD34 (HPCA-1)	Becton-Dickinson	1:40	Endothelial cells
CD36 (OKM5)	Ortho	1:100	Endothelial cells and dendritic cells
CD68 (KP1)	Dako	1:50	Macrophages
actin (HHF)	BioGenix	1:50	Smooth muscle
PCNA (PC10)	Dako	1:10	Cell cycle antigen
HPV	Dako	1:2000	Papillomavirus
p24	Dako	1:10	HIV
ICAM	R & D Systems	1:10,000	Endothelial cells and others
ELAM	R & D Systems	1:10,000	Endothelial cells

(ICAM-1), and endothelial leukocyte adhesion molecule (ELAM) were used with these sections.

The avidin-biotin peroxidase technique was also used to test for the presence of HIV p24 antigen on paraffin and frozen KS sections. The antibody was a monoclonal mouse anti-HIV (Kal-1) which reacts with the p24 protein in cells infected with HIV type 1 on both formalin-fixed, paraffin-embedded tissue sections and frozen tissue sections. For formalin-fixed, paraffin-embedded specimens, the sections were pretreated with 4 mg/ml pepsin in 0.01 N HCl for 20 minutes at 37 C. Positive control was a human T-cell line, HUT 78 (generously donated by Dr. Jay A. Levy, University of California, San Francisco) which has been infected with HIV and expresses HIV p24.[25,26]

A 10 × 10 ocular graticule outlining an area of 0.064 mm^2 was used at a magnification of ×400 to assist in the counting of cells. For each antibody, the number of positively stained cells and the total number of cells were determined in five fields, the numbers averaged, and percentages derived. Lymphocytes and neutrophils were excluded from the counts. PCNA-positive cell counts were compared with counts of mitotic figures in five fields. The source of material for the mitotic figure counting was from specimens of 31 small and 89 large oral KS tumors in the oral pathology archives. The 18 cases that were the subject of this study came from that pool.

Results

Spindle and dendritic cells expressing factor XIIIa were found in all KS lesions (Figures 1 and 2). Their proportion ranged from 1% of the tumor cell population to 9% (Table 2). There was no appreciable difference between small and advanced lesions. Distribution of XIIIa-positive cells was variable, with some lesions showing a uniform scattering and others exhibiting a patchy heterogeneous pattern. Mitotic figures did not express factor XIIIa. Many other spindle cells between the vascular spaces were XIIIa-negative. Dendrocytes surrounding the tumor focus were invariably positive for XIIIa, especially cells located in the lamina propria.

A majority of cells in both small and large KS lesions expressed CD34 (Figures 3 and 4). These cells lined obvious vascular spaces and otherwise inapparent slits in the small lesions. Occasional spindle-shaped stromal cells appeared to be CD34-positive, although it could not be determined whether this was due to tangential sectioning of an endothelial cell. With rare exception, mitotic figures were nonreactive. CD34 immunoreactivity was seen in all endothelial cells of surrounding vascular channels and some submucosal spindle cells. Anti-VIII generally stained fewer tumor cells than anti-CD34. VIII reactivity was usually seen in well-defined capillaries.

From 4% to 15% of the tumor cells within small and large lesions expressed CD68 (KP1) (Figure 5). Morphologically these cells were round, spindle-shaped, or dendritic and were randomly distributed. Some CD68-positive cells contained hyaline globules and hemosiderin, although most did not. Hemosiderin-associated CD68-positive cells were also noted frequently in surrounding connective tissue. Mitotic figures were CD68-negative. Based on their distribution within tumors and surrounding tissue, cells stained with anti-CD68 appeared to

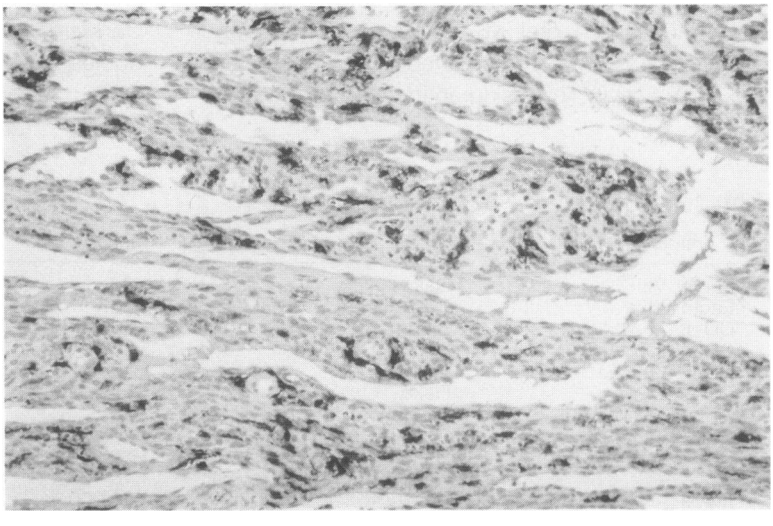

Figure 1. *Advanced oral HIV-associated KS stained with anti-factor XIIIa antibody. Numerous positively stained dendritic cells are evident in the stroma between atypical vascular channels (hematoxylin counterstain, ×40).*

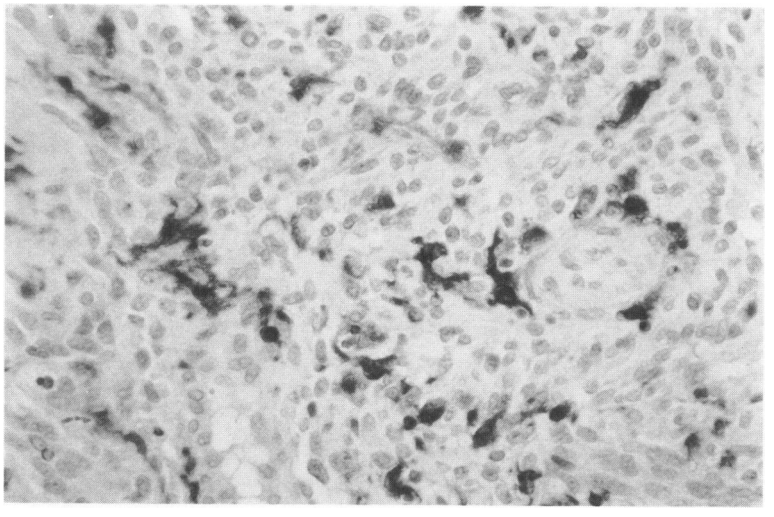

Figure 2. *Small oral KS showing XIIIa-positive dendritic cells among spindle tumor cells (hematoxylin counterstain, ×250).*

represent a different population from those stained with anti-XIIIa. A few of the CD68-positive cells appeared to be mast cells.

Actin expression was found in periendothelial cells of supporting blood vessels. There was also evidence of occasional intratumor actin-positive spindle cells. Positive cells often appeared to be lining newly formed or rudimentary capillaries within the tumors.

Nuclear PCNA staining was noted in all KS lesions studied. The distribution of positive cells was relatively uniform throughout the tumors. Both interstitial spindle cells and vascular lining cells expressed PCNA immunoreactivity. Neither cell type appeared to have more positive cells than the other. The intensity of nuclear staining varied from one cell to another, presumably due to the relatively long half life of this antigen in cycling cells. In small lesions, an average of 17% of tumor cells were PCNA-positive, and in larger lesions the average was 24%. The number of cells expressing PCNA generally correlated with mitotic counts. In one advanced lesion with abundant mitotic figures, more than 70% of the tumor cells expressed PCNA.

Cells in mitosis were usually located in the stromal areas, although occasional mitoses were noted in cells lining vascular channels. Mitotic figures were infrequently seen in the 31 small, early lesions (8 of /31, 26%): 5 lesions had a single mitosis in five high-power fields, 1 lesion had three, 1 lesion had eight, and 1 had 12. In the 89 larger, advanced lesions, more mitotic figures were found (55 of 90, 61%): 25 had one mitosis, 12 had two, 6 had three, 5 had four, 2 had five, 2 had six, 1 had seven, 1 had nine, and 1 had 14 mitotic figures in five high-power fields.

Neither HPV common antigen nor HIV p24 immunoreactivity could be detected in any of the KS lesions. However, anti-HPV antibody did stain submucosal dendrocytes in the lamina propria overlying several of the lesions. This was interpreted as cross-reactivity.

Table 2. *Proportion of Total Cells Expressing Various Cell Lineage and Cell Function Antigens in Kaposi's Sarcoma Lesions*

	Small Lesions		Large Lesions	
Antibody/Stain	P/T*	Mean % (range)	P/T	Mean % (range)
VIII	37/377	11 (9–14)	29/385	8 (5–12)
XIIIa	17/286	6 (1–9)	19/283	7 (5–8)
CD18	53/272	19 (15–22)	45/360	13 (8–22)
CD34	166/272	60 (47–83)	230/300	77 (48–89)
CD36	260/310	84 (80–88)	270/315	85 (70–95)
CD68	21/300	7 (4–9)	32/314	10 (6–15)
Actin	3/310	1 (0–3)	8/325	2 (0–3)
PCNA	58/343	17 (6–38)	89/367	24 (11–70)
HPV	0		0	
p24	0		0	
ICAM	20/260	8 (5–10)	33/294	11 (6–15)
ELAM	13/300	4 (4–5)	26/285	9 (5–13)
Toluidine blue	3/276	1 (0–2)	7/331	2 (0–5)

* P/T, mean number of positive cells/mean of total cells in 0.064 mm^2.

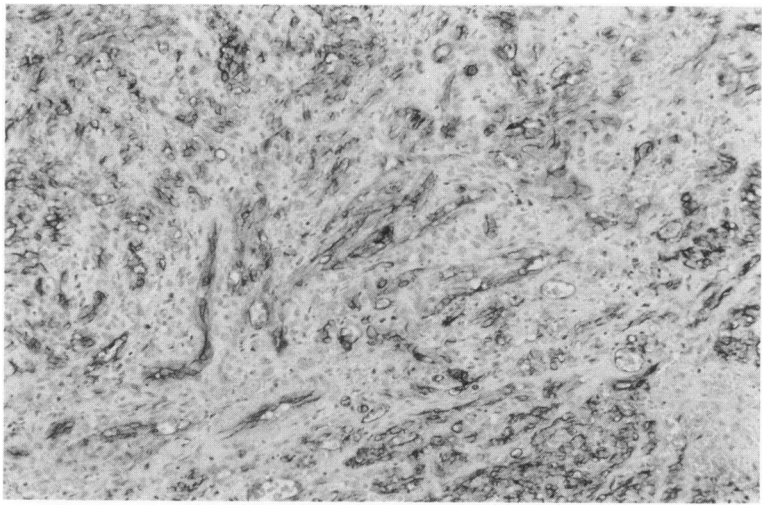

Figure 3. *Small oral KS stained with anti-CD34 antibody. All vascular channels appear to be stained; most stromal cells are non-reactive (hematoxylin counterstain, ×100).*

Frozen sections of oral KS lesions stained for CD18 (LFA) revealed a relatively uniform distribution (about 13% of total tumor cells) of positive oval, spindle, and dendritic cells (Figure 6). Both ICAM (Figure 7) and ELAM (Figure 8) were expressed by a small population of cells within the KS lesions. ICAM- and ELAM-positive cells appeared to represent the same endothelial cell population. Most positively stained vessels had well-defined lumens, but in many the lumens were poorly developed. Additionally, there were occasional ICAM-positive stromal cells. Generally, more cells expressed ICAM than ELAM. CD36 (OKM5) staining was evident on most (more than 85%) of the tumor spindle cells. Because of the extensive staining with this antibody, it was not possible to identify OKM5-positive dendritic cells. Endothelial cells lining larger vascular channels were typically non-reactive for CD36.

Mast cells were revealed by their metachromatic granules after staining with toluidine blue. These cells were found in all specimens, but in widely varying numbers and locations. Mast cells appeared to be randomly scattered within tumors in numbers ranging from 0 to 25 per high-power field. They were admixed with tumor cells, especially in the early lesions, and they were found in the surrounding connective tissue. Their shapes ranged from oval to spindle to dendritic.

Discussion

Modest differences were noted between small and large lesions in numbers of cells expressing CD34, CD68, and PCNA. This suggests that there may be shifts in cellular populations in various stages of KS development.

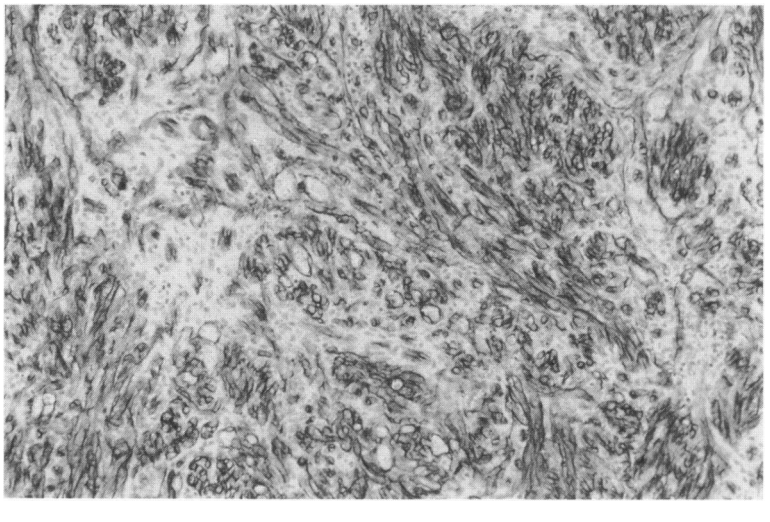

Figure 4. *Advanced oral KS showing CD34 staining of most tumor cells. Some stromal cells are non-reactive (hematoxylin counterstain, ×100).*

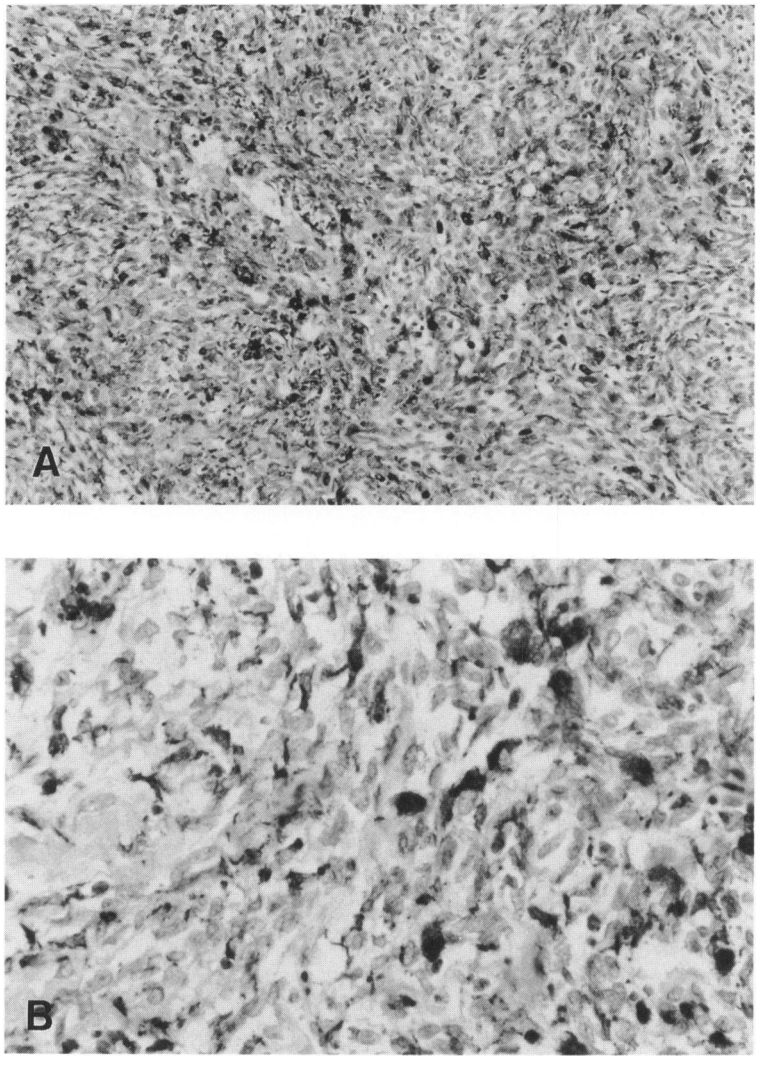

Figure 5. *Advanced oral KS stained with anti-CD68 antibody (KP1).* A: *All dark cells are immunoreactive (hematoxylin counterstain, ×100.* B: *High magnification shows CD68-positive dendritic cells (hematoxylin, ×250).*

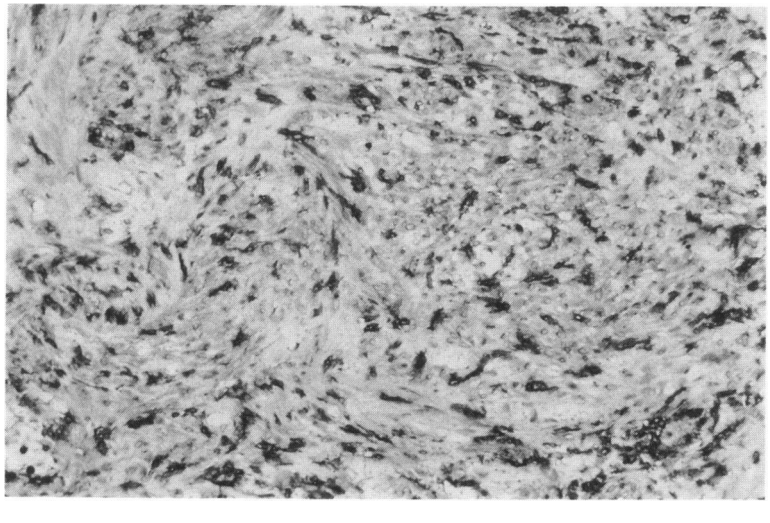

Figure 6. *Frozen section of advanced oral KS stained with anti-CD18 antibody. Positively stained cells are found evenly distributed in a spindle cell stroma (hematoxylin counterstain, ×100).*

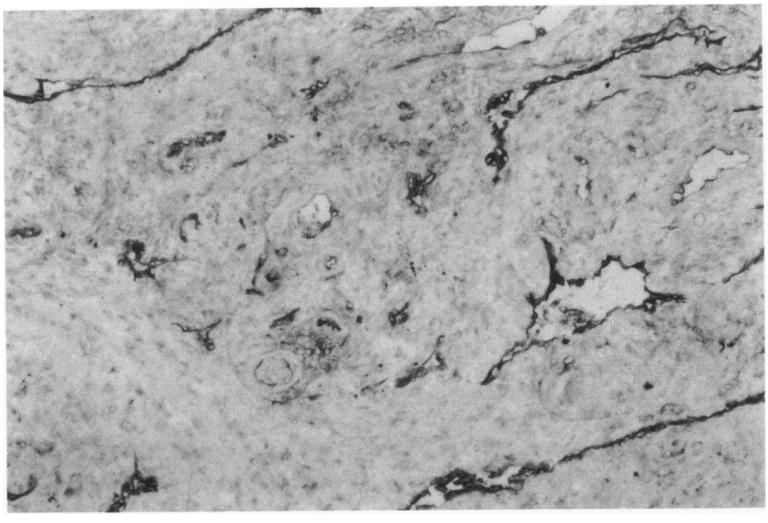

Figure 7. *Frozen section of advanced oral KS stained with anti-ICAM antibody. Well developed vessels stain prominently. Many cells in the stroma are less intensely stained (hematoxylin counterstain, ×100).*

CD34 is an antibody to hematopoietic progenitor cells, blood vascular endothelium,[27–29] and some macrophages.[30] Anti-CD34 antibody stained a majority of cells in the oral KS lesions. All cells lining vascular spaces were CD34 positive, as were many, but not all, of the interstitial spindle cells, supporting the belief that the primary proliferating cell in KS is the blood vascular endothelial cell. In early spindle-cell lesions, which were particularly subtle in hematoxylin and eosin-stained sections because of their poorly developed vascular channels, anti-CD34 prominently marked the tumor spindle cells, a feature that may be of diagnostic value for incipient KS. Because antibody to factor VIII-related antigen stained predominantly well developed capillaries, it seemed to mark well-differentiated endothelial cells, many of which were likely supporting vessels of the tumors. The staining pattern was similar to that seen with ICAM/ELAM staining.

Anti-CD36 antibody, OKM5 clone, has been used in the identification of a macrophage-related dendritic cell population found predominantly in perivascular connective tissue of the dermis and submucosa.[31,32] Because OKM5 also identifies endothelial cells, we included it in this study to see whether this antigen is expressed in spindle endothelial cell and dendritic cell populations in KS.[33] OKM5 appeared to label the same population of cells as those identified by anti-CD34. Because of the intense staining associated with OKM5 and the insufficient cellular detail in frozen sections, the presence of positively stained dendritic cells could not be determined. For the same reasons, the number of negative-staining spindle cells was partially obscured, making counts of positive cells artificially high. Although antibodies to CD34 and CD36 appeared to stain the vast majority of tumor cells, significant numbers of nonreactive cells were present

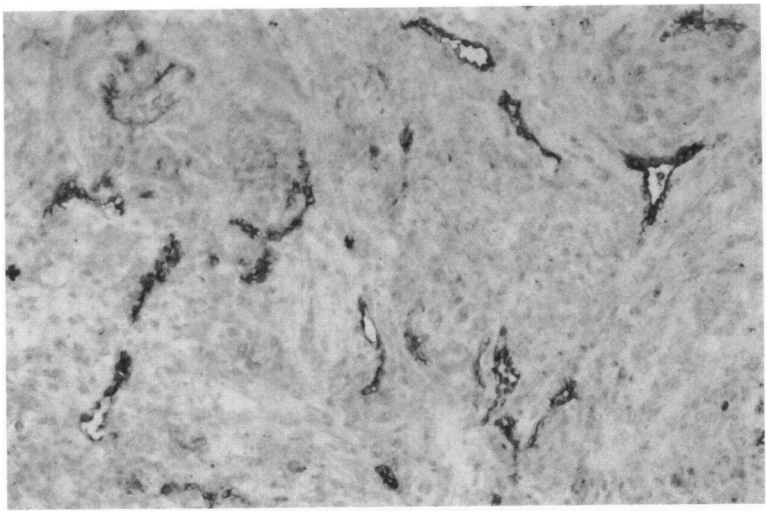

Figure 8. *Frozen section from the same KS lesion illustrated in figure 7, but stained with anti-ELAM antibody. Immunoreactivity is limited to well developed vessels (hematoxylin counterstain, ×100).*

within the tumors. It is interesting to note that CD34 and CD36 antigens may be found on both endothelial cells and macrophages. While this suggests that the prevalent spindle cells in KS may be related to macrophages, KS factor VIII immunoreactivity (though capricious), would suggest otherwise.

Factor XIIIa-positive dendrocytes are normally found in abundance in dermis and submucosa, particularly in association with blood vessels.[34,35] In this position it is believed that they are able to monitor the microenvironment and release cytokines, such as tumor necrosis factor. This relationship of dendritic cell to endothelial cell in normal tissue (as has also been described with OKM5-positive dendrocytes) may be analogous to what is seen in KS. We found factor XIIIa-positive dendrocytes in intimate relationship with endothelial cells in both early and late lesions. The numbers of XIIIa-positive cells found (less 10% of the total tumor cells), and their intratumor distribution, suggest that they play a role in the various stages of development of oral KS, but that they are not themselves neoplastic.[36] These cells, which are believed to be involved in accessory cell activities such as presentation of antigens and control of lymphocyte trafficking, may be releasing angiogenic factors or other cytokines that sustain tumor growth. That the XIIIa-positive dendrocytes were also evident in connective tissue surrounding tumors may be indicative of a reactive function in this site, since these cells are also believed to have a role in fibroplasia.

The finding of significant numbers of cells positive for CD68 (monocyte/macrophage associated antigen) in oral KS suggests a role similar to that we suspect of the dendrocytes. Only a small percentage of CD68-positive cells seem to be involved in the phagocytosis of hemosiderin and red blood cells (hyaline globules) and a few appeared to be mast cells; the remainder, especially the unusual dendritic $CD68^+$ cells, may have a role in tumor progression. The appearance of CD68-positive cells, and possibly XIIIa-positive cells as well may be due to chemotactic cytokines released by other cells.

Stains with anti-CD18 (LFA) antibody confirmed the presence of intratumor cells expressing LFAs. The leukocytes in these cases probably represented dendrocytes, macrophages, and other infiltrating inflammatory cells. ICAM, the ligand for LFA, is normally present (at low levels) on endothelial cells, macrophages, dendrocytes, and other cells. Its expression in KS likely provided the mechanism by which the LFA-positive cells infiltrated into tumor tissue.[37] ELAM, a cytokine-induced endothelial cell molecule that mediates adhesion of leukocytes, probably produced a similar response.[38] Expression of the functional markers ICAM and ELAM by KS cells supports the notion that tumor-produced cytokines have a regulatory effect on chemotaxis and tumor development (autocrine growth). It is not clear why only a small percentage of intratumor cells express these markers. The ICAM/ELAM-positive cells may represent a functional subset of the CD34/CD36 population that is more responsive to cytokine stimulation. This would reflect different levels of cellular differentiation within KS. Alternatively, the ICAM/ELAM-positive cells could represent a clone of endothelial cells that is different from other tumor endothelial cells.

The mast cell infiltrates in these lesions added more evidence of the cellular heterogeneity of these tumors. These cells may contribute to the growth of these tumors through the release of proinflammatory and/or angiogenic cytokines, or they may simply represent resident cells caught up among the proliferating tumor cells.

The formation of rudimentary actin-positive capillary-like structures and the occasional individual cell staining suggested that some tumor cells were differentiated toward the myocyte or pericyte.[19,20,39] It could not be determined whether the actin-positive cells were part of the same population that was CD34-positive.

The relatively high level of PCNA staining belies the observed low mitotic index associated with these lesions.[40] PCNA expression was seen in both the endothelial and stromal compartments. Double staining will be needed to assess which populations are expressing PCNA.

Use of polyclonal antibody to HPV common antigen and monoclonal antibody to HIV p24 antigen did not provide support for direct HPV or HIV infection in KS. However, detection systems with greater sensitivity may yet provide substantial evidence of a causative agent in KS.

From this study, the following concluding observations are made: Oral KS consists of a heterogenous population of cells that is dominated by CD34/CD36-positive blood vascular endothelial cells. Significant numbers of factor XIIIa-positive and CD68-positive spindle/dendritic cells and small numbers of mast cells are present in oral KS. Functional endothelial markers, ICAM and ELAM, are expressed by a subpopulation of tumor cells. Although mitotic figures are comparatively sparse and are found predominantly in stromal cells and less frequently in lining cells, significant numbers of vascular lining and stromal cells are in cell cycle in oral

KS. Small numbers of KS tumor cells express muscle-specific actins.

These observations show that HIV-associated oral KS is a proliferation of blood vascular endothelial cells that express various levels of endothelial-related lineage-specific and functional antigens. We believe that tumor development is mediated, in part, by inflammatory cells and cytokines. Pertinent inflammatory cytokines may be increased because of local production or possibly because of systemic elevation.[41,42] ICAM and ELAM expression by tumor cells may provide a mechanism for leukocyte infiltration. Angiogenic factors (fibroblast growth factor and others) may be produced by tumor cells themselves and infiltrating dendritic cells, such as dendrocytes and macrophages, and would contribute to tumor growth.

Acknowledgments

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