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Vascular Origin of Kaposi's Sarcoma

Expression of Leukocyte Adhesion Molecule-1, Thrombomodulin, and Tissue Factor

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We studied seven cases of Kaposi's sarcomas (KS) obtained from patients with AIDS and one KS from a patient without HIV infection. Antigen expression was studied by immunocytochemistry and mRNA expression by in situ hybridisation. The markers tested were endothelial leukocyte adhesion molecule-1, thrombomodulin, and tissue factor. In all tumors (AIDS and non-AIDS associated) these markers reacted positive, indicating transcription and translation of these genes in KS. The synthesis and expression of tissue factor and thrombomodulin suggests that KS is a tumor that has tissue factor-mediated thrombin formation under the control of thrombomodulin. The expression of thrombomodulin and endothelial leukocyte adhesion molecule-1 provides evidence for the vascular origin of KS. (Am J Pathol 1994, 144:51–59)

It is generally believed that Kaposi's Sarcoma (KS) cells are of mesenchymal origin, but it is not clear whether they are derived from endothelial or smooth muscle cells.[1,2] Expression of smooth muscle cell α-actin[3] has been shown in cultured AIDS-associated KS-derived cells. The endothelial cell origin has been supported by histological studies on KS of different stages. von Willebrand factor has been demonstrated in the cells lining the vascular spaces, but it is variably expressed by the spindle cell (SC) component of KS.[4] The vascular component of KS expresses also other endothelial cell antigens, such as E 92, HCl, and weakly OKM5, whereas the SC component of KS expresses strongly E 92 and OKM5, but only weakly HCl.[4] This provides strong evidence for the endothelial cell origin of KS, but points also to the inter- and intratumoral phenotypic heterogeneity of KS. The presence of other endothelial cell antigens, such as BW 200,[5] E431,[6] and CD 34[7] has also been interpreted as suggestive of an endothelial cell origin of KS.

Moloney murine sarcoma virus 349 carrying the *mos* oncogene induces KS-like tumors in neonatal Balb/c mice.[8] The authors suggested that the SC of the tumors are poorly differentiated endothelial cells.[8] Furthermore, mice transgenic for the tat gene of HIV develop KS-like skin tumors.[9] Endothelial cells transformed by the SV40 T antigen cause KS-like tumors in nude mice.[10] The animal studies together with the histological results point to the endothelial cell nature of KS. However, the failure of human KS-derived cells to induce tumors in nude mice[11] and the multifocal presentation of clinical KS suggest that the cell of origin is not genetically transformed. Rather, these tumors might arise from abnormal regulation of growth factor release/response induced by an infectious agent.[12–14] In support of this hypothesis it has been shown that tat protein of HIV-1 stimulates growth of cells derived from KS[15] and that the conditioned supernatant of activated T cells contains cytokines promoting growth of KS cells in culture and inducing normal vascular cells to acquire features of the KS cell phenotype.[16]

Endothelial leukocyte adhesion molecule-1 (ELAM-1) and thrombomodulin are endothelial cell markers and have been studied to investigate the cellular origin of KS. ELAM-1 is an endothelial cell ad-

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hesion molecule expressed by cytokine-stimulated endothelial cells.[17–21] ELAM-1 binds memory T cells independent of T cell activation.

Thrombomodulin is an endothelial cell transmembrane receptor involved in regulation of the anticoagulant protein C pathway.[22–24] Recently, it became apparent that thrombomodulin is not specific for vascular endothelial cells. It is also expressed by lymphatic endothelial cells, syncytiotrophoblast cells, and malignant endothelial cells.[25] It has been shown that cultured vascular smooth muscle cells express in a cAMP-dependent mechanism thrombomodulin,[26] whereas smooth muscle cells of the vessel wall do not.[26] Therefore, thrombomodulin and ELAM-1 were studied as markers for the vascular origin of KS. In addition, thrombomodulin (also termed fetomodulin) has been described on the parietal endoderm in mouse embryos before synthesis of developing blood vessels.[27] Because KS is associated with a strong mitogenic and proliferative effect on endothelial cells,[16] we assumed that vascular origin of proliferating KS cells might be associated with thrombomodulin expression.

In addition, we sought an explanation as to why in contrast to other malignancies thrombosis is not more frequently associated with KS, even in the presence of infectious disease, and other risk factors for thrombosis. Local expression of thrombomodulin could provide means for shifting thrombin activity toward the anticoagulant protein C pathway.

Another marker of endothelial cell activation, expressed by stimulated endothelium only, is the factor VII/VIIa receptor, triggering the extrinsic pathway of coagulation.[28] Tissue factor and thrombomodulin have not only functionally opposing activities but also enabled us to study the functional state of the endothelium in proximity to the KS, ie, the endothelial cells lining the vascular spaces of KS and the endothelial cells of normal vessels in close proximity to KS.

The study of KS indicated that ELAM-1, thrombomodulin, and tissue factor are transcribed (*in situ* hybridisation) and translated (immunocytochemistry) by spindlelike KS cells, endothelium lining the vascular spaces of KS, and in some normal vascular endothelium close to the KS. The expression of ELAM-1 and thrombomodulin further supports (but does not prove) the endothelial cell origin of KS.

Materials and Methods

Tissue

Cutaneous punch biopsies were performed on six patients with AIDS and KS, two patients with AIDS but without KS, two control patients without AIDS or KS, and one patient with KS but without AIDS. Punch biopsies were performed after obtaining informed consent to obtain a biopsy for histological documentation of KS. For further description of the patients clinical and routine histological data see

Table 1. *Patient Characteristics*

Case	Age	HIV	CDC stage prior OI	Immunological parameters	KS/Mitsuyasu staging	Prior KS treatment
1	39	+	III/–	CD4: 75/μl 4/8: 0.15	+/IA	None
2	43	+	IV/C1/PCP	CD4: 60 4/8: 0.14	+/IA	None
3	35	+	IV/C1/candida esophagitis	CD4: 76/μl 4/8: 0.15	+/IIA	None
4	23	+	III/–	CD4: 200/μl 4/8: 0.1	+/IIA	IFN-α
5	40	+	IV/C1/PCP	CD4: 20/μl 4/8: 0	+/IIA	None
6	35	+	IV C1/PCP	CD4: 220/μl 4/8: 0.2	+/IVB	Cyclophosphamide Vinblastine Bleomycine
7	26	+	III/–	CD4: 486/μl 4/8: 0.3	None	None
8	38	+	III/–	CD4: 216/μl 4/8: 0.6	None	None
9	89	–	–	Not determined	—	—
10	82	–	–	Not determined	—	—
11	Non HIV	KS				

OI, opportunistic infection; PCP, pneumocystis carinii pneumonia; 4/8, CD 4/8 ratio.
Patients no. 7 and 8 were HIV infected without KS, patients no. 9 and 10 served as healthy controls (operated for hip fractures).
HIV status was confirmed by repeated ELISA, immunofluorescence, and Western blot.

Table 1. The tissue was snap-frozen in a mixture of isopentane and dry ice and stored at −80 C until use.

Immunohistochemistry

The monoclonal antibodies used in this study have been published elsewhere (ELAM-1,[29] thrombomodulin,[30] and tissue factor).[31]

Four-micrometer thick cryostat sections were cut and fixed in acetone at 4 C. Sections were incubated with unconjugated primary antibody (see above) at previously determined appropriate dilutions in a moist chamber for 60 minutes at room temperature. Biotinylated sheep antibody to mouse immunoglobulin was used as second antibody, followed by incubation with streptavidin-biotinylated horseradish peroxidase complex. Each incubation step was followed by washing sections for 15 minutes in phosphate-buffered saline at room temperature. Peroxidase activity was visualized using aminoethylcarbazol as chromogen. On control sections, primary antibody was substituted by phosphate-buffered saline or normal mouse serum.

In each case the tumor exhibited the typical histopathological feature of KS. Some biopsies of cutaneous lesions showed dermal tumors containing a variable mixture of SC and irregular vascular spaces linked to bland-appearing endothelial-like cells, typical of the plaque state of KS.[32,33] Biopsies of other cutaneous lesions showed intertwining fascicles of SC commingled with extravasated erythrocytes and only occasional vascular spaces, consistent with the nodule state of KS.

One KS specimen, histologically undistinguishable from AIDS-associated KS, was derived from a non-HIV-infected patient. This patient showed no signs of immunodeficiency and no history of opportunistic infections.

In Situ *Hybridization*

The cDNA clones for ELAM-1,[34] thrombomodulin,[35] and tissue factor[36] have been published elsewhere.

T7-ELAM-1 was subcloned from human ELAM-1.[34] In brief, a 670-bp insert, spanning the region from bp 1332 to 2002 and containing a transmembrane region and the receptor repeat area was cut with *Bam*HI and *Hin*cII and cloned into the *Sma*I/*Ban*HI site of pSPT18. After linearizing T7-ELAM-1 with *Bam*HI antisense RNA can be generated. The sp6 promotor allows the production of sense RNA after linearizing with *Eco*RI.

T7 thrombomodulin was subcloned from the human thrombomodulin clone puc HTM 12.[35] A 611-bp insert spanning the region from bp 1531 to 2142 was cut out with *Kpn*I and *Eco*RI and cloned into the *Kpn*I/*Eco*RI site of pSPT 18. The insert was tested by searches of the database bank at the EMBL and SwissProt using Fasta. After linearizing T7-thrombomodulin with *Bam*HI antisense, RNA can be generated. The SP6 promotor allows production of sense RNA.

T7 tissue factor was subcloned from human tissue factor.[36] In brief, a 718-bp insert, spanning the region from bp 98 to bp 816 (extracellular domain) was cut with *Sma*I and *Eco*RI and cloned into the *Sma*I/*Eco*RI site of pSPT19. After linearizing T7-tissue factor with *Bam*HI, antisense RNA can be generated from the SP6 promotor. The T7 promotor allows the generation of sense RNA after cutting with *Eco*RI. All riboprobes were first tested in Northern blots. Sense probe did not give any signals, whereas antisense recognized the correct mRNA size on Northern blots. In all tissues tested sense served as negative control.

In vitro transcription reactions were conducted as described in the Boehringer-Mannheim protocol using digoxigenin-UTP for the production of riboprobes for *in situ* hybridization.

Cryostat sections of skin biopsies were placed on glass slides that had previously been coated with a solution of 100 µg/ml poly-L-lysine. Slides were fixed in freshly prepared 4% neutral buffered paraformaldehyde and acetylated in freshly added acetic anhydride (0 to 25%) with 0.1 M triethanolamine, pH 8.0. Finally sections were rinsed in PBS and dehydrated sequentially in graded alcohols.

Briefly, sections were prehybridized at room temperature for 10 minutes in a solution containing 50% deionized formamide, 4× SSC, 1× Denhardt's, 500 µg/ml salmon sperm DNA, 250 µg/ml yeast tRNA, 100 µg/ml poly (A) RNA, 10% dextran sulfate (molecular weight 500,000), and 100 mM dithiothreitol. Each section was then hybridized with 20 µl prehybridization solution containing 1 ng/µl digoxigenin-labeled antisense or sense (as control) riboprobe for 12 hours at 37 C. After hybridization slides were subsequently washed at room temperature for 10 minutes in 1× SSC, 30 minutes in 0.5× SSC and 30 minutes in 0.1× SSC. Subsequently, the slides were rinsed in 100 mM Tris-HCl (pH 7.4), 150 mM NaCl

for 2 to 3 minutes. Color development was performed as proposed by Boehringer Mannheim.

The result of *in situ* hybridization studies and immunohistology was evaluated by two of the authors (RW and RN).

Results

Immunohistochemistry

In normal skin all vascular endothelial cells were consistently positive for thrombomodulin and negative for ELAM-1 and tissue factor (Figure 1). This is consistent with the phenotypic appearance of cultured endothelial cells. In skin of HIV-infected patients without KS (Figure 2) all vascular endothelial cells were positive for thrombomodulin. In contrast to normal skin endothelial cells, some endothelial cells of normal vessels were positive for ELAM-1 and tissue factor in skin of HIV-infected patients without KS. The positivity was spotted, ie, within a vessel some endothelial cells were negative, others positive for the markers tested. Typically, ELAM-1 and tissue factor-positive endothelial cells were in

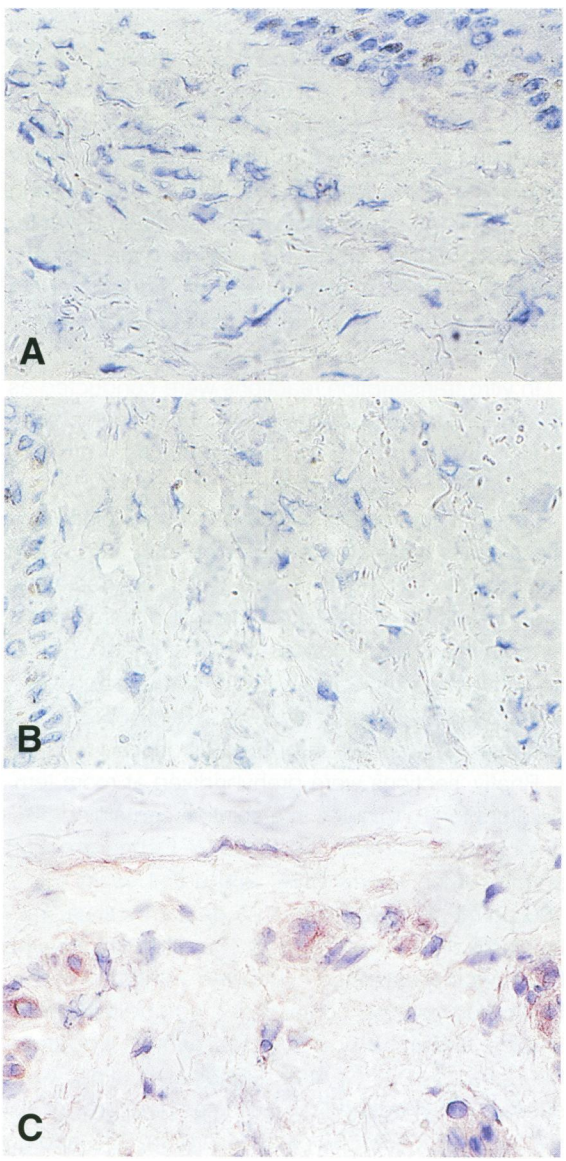

Figure 1. *A skin biopsy from normal skin of a healthy volunteer. Note that ELAM-1* (A) *and tissue factor* (B) *are not expressed by endothelial cells, whereas thrombomodulin* (C) *is strongly expressed by all endothelial cells. Immunocytochemistry, ×280.*

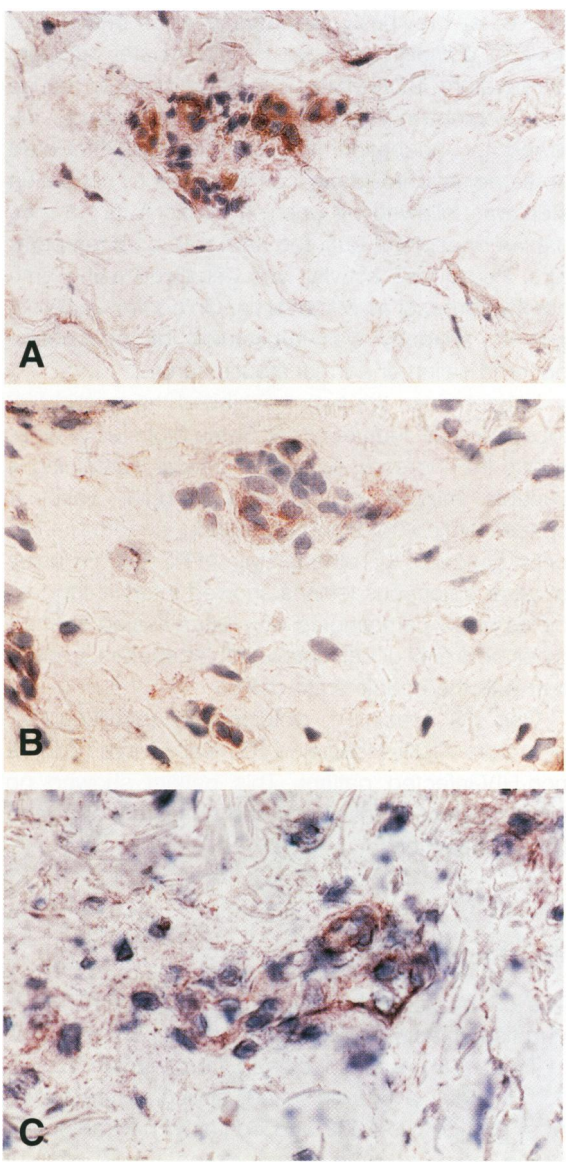

Figure 2. *A skin biopsy from normal skin of a HIV-infected patient (patient 8) without KS. Note the expression of ELAM-1* (A) *and tissue factor* (B) *in occasional endothelial cells in proximity to mononuclear cells. Small vessels with scattered perivascular mononuclear cells are depicted. Thrombomodulin* (C) *is positive in all endothelial cells. Immunocytochemistry. ×280.*

close proximity to infiltrating inflammatory cells (Figure 2). This result was interpreted as an indication of cutaneous endothelial cell activation in AIDS (Table 2).

Thrombomodulin expression was restricted to vascular endothelium. In normal skin tissue factor was also localized on extravascular cells but not endothelial cells (data not shown).

When KS were studied (Figure 3), we compared the expression of ELAM-1, thrombomodulin, and tissue factor in cells lining the vascular spaces and SC of KS. In all KS studied, vascular spaces and SC were positive for ELAM-1, thrombomodulin, and tissue factor. There was only a slight difference in the strength of tissue factor expression, vascular spaces stained weaker than SC, on the contrary vascular spaces stained stronger for thrombomodulin than SC. ELAM-1 was similar on both (Figure 3, Table 2).

We also studied vascular endothelial cells of normal vessels close to KS. A striking feature was the frequent positivity of endothelial cells for ELAM-1 and tissue factor. This was much more frequent than in the skin of HIV-infected patients without KS. In addition, the positivity of endothelial cells for ELAM-1 was associated with occasional adherence of inflammatory cells (Table 2). This was interpreted as consistent with the hypothesis of endothelial cell activation by KS.

In Situ *Hybridization*

To study whether expression of the markers studied is due to transcription by KS, we performed *in situ* hybridization. The specificity of the riboprobes was tested in Northern blots of mRNA isolated from KS. Sense probes did not react with the RNA isolated from whole tumors, whereas antisense riboprobes recognized the correct band for ELAM-1, thrombomodulin, and tissue factor (data not shown). However, Northern blots on mRNA derived from whole tumor only indicates transcription of these genes within the tumor but does not characterize the cells transcribing the genes studied. Therefore, we performed *in situ* hybridization.

In situ hybridization revealed-positivity of KS for ELAM-1, thrombomodulin, and tissue factor (Figure 4). Comparison of sections with conventionally stained serial cryostat sections supported that in KS the SC and the vascular spaces both reacted positive. No reaction was seen when a sense probe was used as control (Figure 5).

Because KS cells do not have biological properties of transformed cells, we speculated that KS of different origins might have similar properties. To test whether this is true we studied a KS lesion from one patient with KS without AIDS-associated KS. The KS of this non-HIV-infected patient reacted by *in situ* hybridization and immunohistochemistry similar to KS derived from an HIV-infected patient. As shown in Figure 6 (*in situ* hybridization) ELAM-1, thrombomodulin, and tissue factor mRNA were expressed by KS cells from a non-AIDS patient.

Discussion

It has been suggested that KS (at least in its early stages) can be viewed as a hyperplastic state of a focus of activated vessel wall-derived cells, which may regress or progress depending on the immune status of the patient and on whether the initial stimulus persists.[1] It also became clear that SC of KS in culture require T cell-conditioned medium to grow.[1,2,13–16] It has been shown that inflammatory cytokines produced by activated T cells and found increased in HIV-1-infected individuals promote growth of KS cells and induce normal endothelial cells to acquire features of the KS cell phenotype.[16] KS cells in culture also release growth factors and cytokines themselves,[12] which in turn could possibly activate endothelial cells.

To look at the cross-talk between KS cells and normal endothelial cells, we studied the expression of endothelial cell markers by spindle KS cells (SC),

Table 2. *Expression of ELAM-1, Tissue Factor and Thrombomodulin*

	Normal skin EC	Normal skin of HIV patient EC	KS-HIV			KS		
			EC	SC	VC	EC	SC	VC
ELAM-1	–	1+	1+	2+	2+	1+	2+	2+
TF	–	1+	1+	2+	2+	1+	2+	2+
TM	2+	2+	1+	1+	1+	1+	1+	1+

The expression of ELAM-1, tissue factor (TF), and thrombomodulin (TM) as determined by immunocytochemistry was graded by two of the investigators from negative (–) to 2+ (strongly positive).

EC, endothelial cells; SC, spindle cells; VC, cells lining the vascular spaces; KS-HIV, biopsy from a KS of a HIV-infected patient. KS, biopsy from a KS of a non-HIV-infected patient.

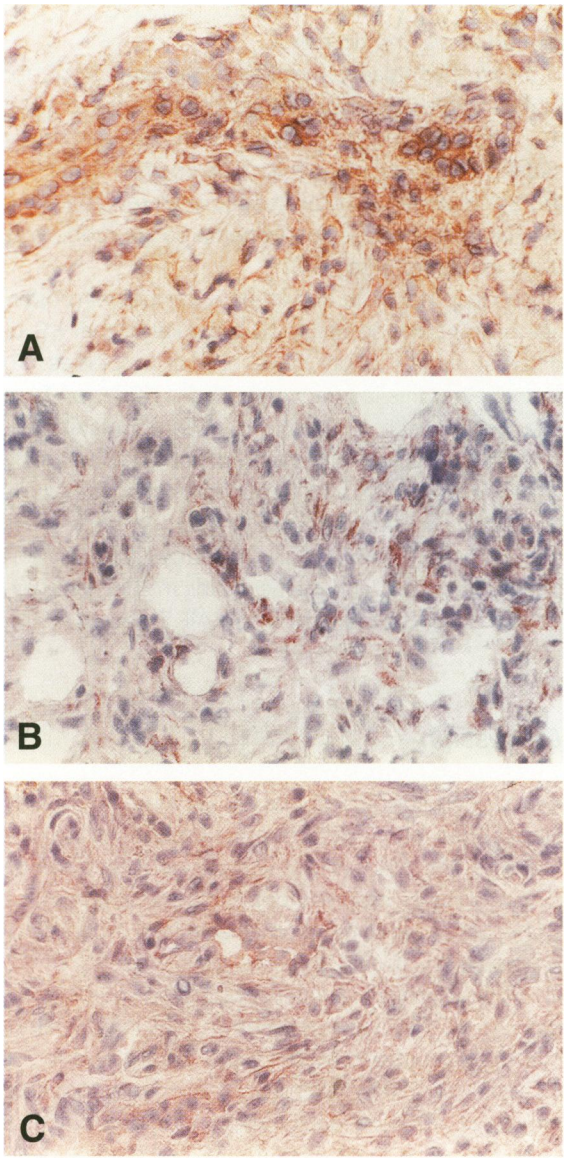

Figure 3. *A skin biopsy of a KS from a HIV-infected patient (patient 6). ELAM-1* (**A**), *tissue factor* (**B**), *and thrombomodulin* (**C**) *are positive in SC and cells lining the vascular spaces. Immunocytochemistry, ×240.*

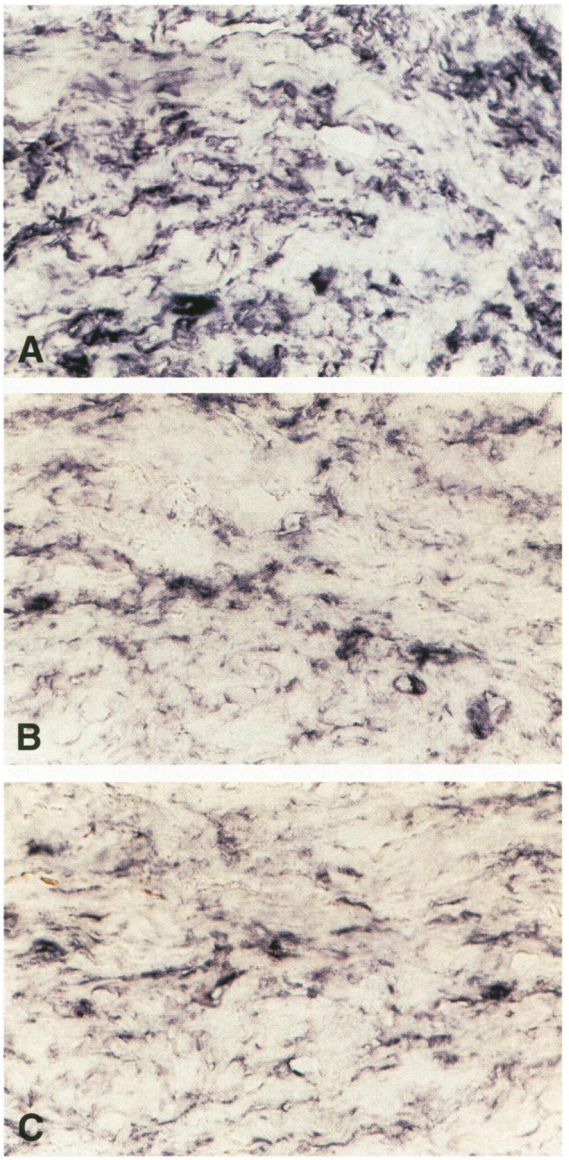

Figure 4. *A skin biopsy of a KS from a HIV-infected patient (patient 6). ELAM-1* (**A**), *tissue factor* (**B**), *and thrombomodulin* (**C**) *are expressed in sc and cells lining the vascular spaces. Nonradioactive* in situ *hybridization, ×240.*

normal endothelial cells in surrounding vessels, and endothelial cells lining the vascular spaces of KS (Table 2).

We selected with ELAM-1 and tissue factor two genes not expressed by quiescent endothelial cells, but expressed by cytokine-stimulated endothelial cells.[37–39] Thus, we used KS as a model to look at the activation of endothelial cells in a tumor model in addition to further support the view of an endothelial cell origin of KS. The expression of thrombomodulin strongly suggests the origin of KS to be endothelial cells, because thrombomodulin can only be found in vascular or lymphatic endothelial cells within the vascular tree.[24,26] The expression of ELAM-1 by SC and vascular spaces of AIDS-KS and non-AIDS-KS further supports this notion, because ELAM-1 is a marker of activated endothelium.[17–19] ELAM-1 expression also provides a mechanism by which T cells can be recruited,[20,21] needed to provide essential growth factors.[16] The cells lining the vascular spaces are as positive for stimulation of endothelial cells in this tumor. However, it remains speculation of whether ELAM-1 recrutes T cells or whether the presence of T cells induces ELAM-1 expression. Furthermore, does the morphological demonstration of ELAM-1

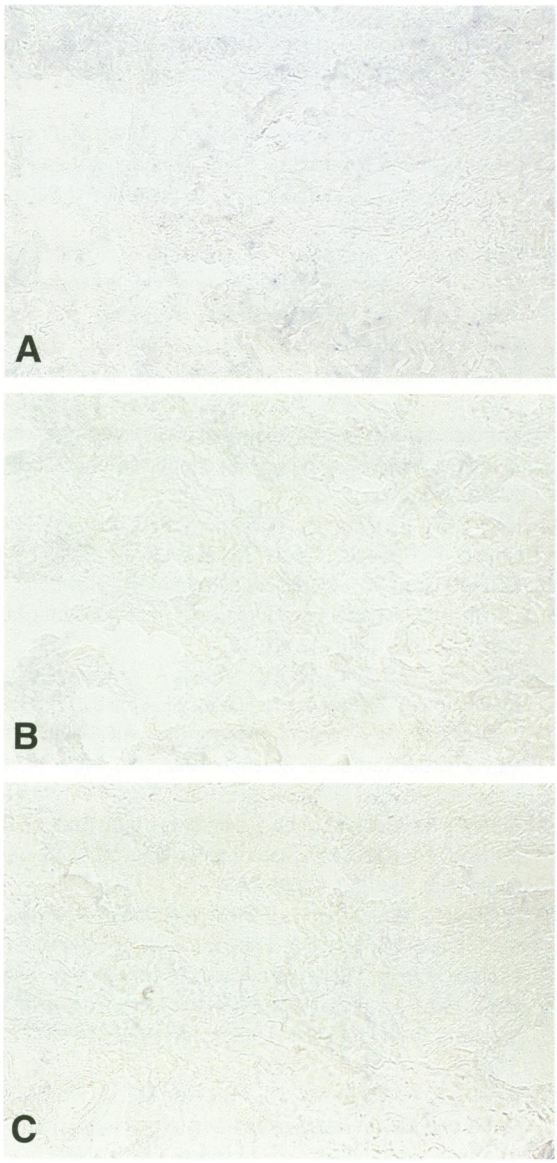

Figure 5. *A skin biopsy of a KS from a HIV-infected patient (patient 6). ELAM-1* (**A**), *tissue factor* (**B**), *and thrombomodulin* (**C**) *are negative when a sense probe was used for nonradioactive* in situ *hybridization,* ×*240.*

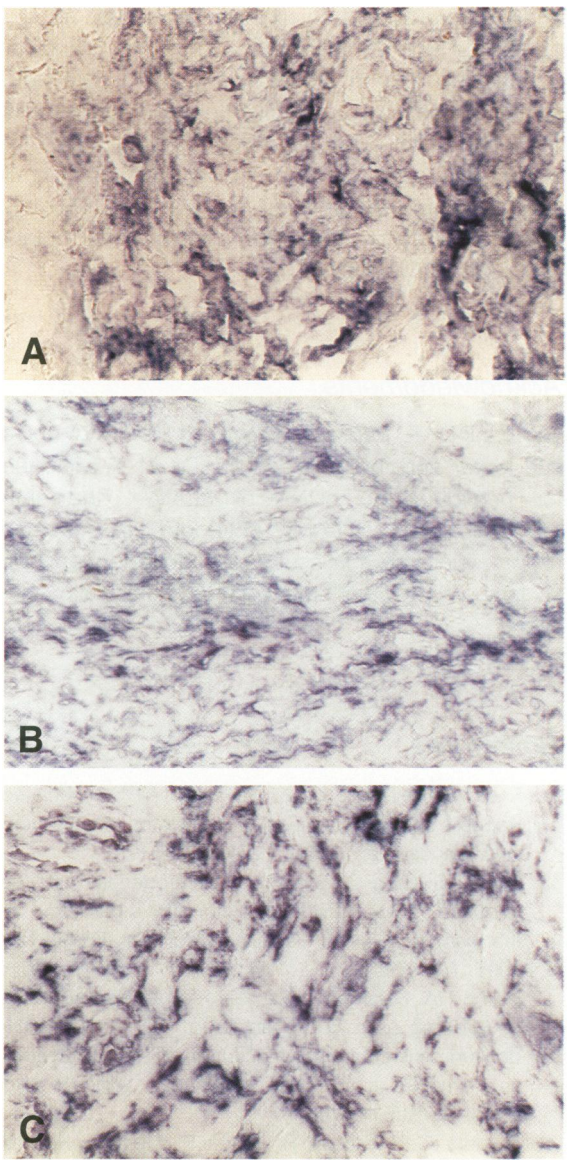

Figure 6. *A skin biopsy from a non-HIV-infected patient with KS (patient 11). ELAM-1* (**A**), *tissue factor* (**B**), *and thrombomodulin* (**C**) *are expressed in sc and cells lining the vascular spaces. Nonradioactive* in situ *hybridization,* ×*240.*

expression and corresponding adhesion of inflammatory cells not directly prove that T cell products are responsible for KS growth *in vivo*. However, *in vitro* data[16] are consistent with this hypothesis, because T cell products not only support KS growth, but also induce normal vascular cells to acquire SC like features.

A selective defect of tissue factor expression has been shown in monocytes from AIDS patients.[40] The expression of tissue factor antigen and mRNA by KS suggests that this defect is cell specific. From other tumors it is known that presumably by expressing tissue factor they contribute to the high incidence of thrombotic disorders in cancer patients. This has not been a distinguished feature in patients with KS, despite the presence of infectious disease as another risk factor for thrombosis. A possible explanation is that KS cells do not only express the procoagulant tissue factor, but also the anticoagulant receptor thrombomodulin. Coexpression of thrombomodulin and tissue factor let us to speculate, that thrombin formation by the tissue factor-triggered pathway is under control of thrombomodulin.

Therefore, we conclude that: 1) KS cells are probably derived from endothelial cells; 2) KS cells

and endothelial cells lining the vascular spaces express ELAM-1; 3) KS cells and normal vascular endothelial cells in close vicinity of KS are activated, suggesting cross-talk between tumor cells and endothelial cells; 4) endothelial cell activation markers are also expressed in HIV infection without KS to a lesser degree than in KS; and 5) KS cells express receptors for procoagulant and anticoagulant active ligands.

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