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AIDS-Related Kaposi's Sarcoma Displays Differential Expression of Endothelial Surface Antigens

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The authors studied 11 cases of Kaposi's sarcoma (KS) in patients with the acquired immunodeficiency syndrome (AIDS) for their reactivity with two monoclonal antibodies (B721 and E431) that recognize endothelial cell surface antigens. Reactivity of these antibodies with KS was compared with the reactivity of other known endothelial markers (F8rAg, Ia, HCL-1). Staining was done with avidin–biotin–alkaline phosphatase immunohistochemistry on acetone-fixed frozen sections. In all samples of tumor both the spindle cell component and the vascular lining cells stained with both B721 and E431. In general, the spindle cells stained less intensely than did the vascular lining cells. There was both intratumor and intertumor variability. B721 and E431 are proposed as two additional markers for KS, and it is suggested that their reactivity with the tumor supports the hypothesis that KS is derived from vascular endothelium. The possibility is also raised that the variability of staining for vascular markers could have diagnostic possibilities, and further studies for investigation of this hypothesis are suggested. (Am J Pathol 1988, 130:244–251)

ALTHOUGH Kaposi's sarcoma (KS) is a significant finding in patients with the acquired immunodeficiency syndrome (AIDS), the etiology, pathogenesis, and histogenesis of this tumor are still unsettled. Most work done on the tumor has utilized the techniques of histopathology, including enzyme histochemistry and immunohistology. These studies have led to conflicting theories as to the histogenesis and biology of KS.

The prevailing theory of histogenesis is that KS is derived from vascular endothelium.[1,2] This hypothesis is based on the fact that Factor VIII-related antigen (F8rAg) is expressed by KS, although its expression is variable. The spindle cell component of KS, in particular, has been reported to have variable to absent expression of this marker.[3–5]

This variable and apparently unreliable expression of F8rAg has led to an alternate theory of histogenesis, that KS is derived from lymphatic endothelium.[6] Recent studies to test this hypothesis examined enzymatic markers, antibodies to F8rAg, Dr/Ia antigens, and macrophage/endothelial antigens (M/E).[7] These studies failed to show any reaction of the tumor with antibodies to Ia antigen or M/E antigen and only weak staining in a minority of cases with antibody to F8rAg, consistent with reactions on lymphatic endothelium. The enzymatic phenotype was also more typical of lymphatic endothelium.

Additional data in support of the vascular endothelial origin of KS have recently been reported by Rutgers et al.[8] The authors described three monoclonal antibodies (E92, OKM5, HCL-1) that all react with normal vascular, but not lymphatic, endothelium and react with the vascular lining cells of KS. In addition, two of the three antibodies (E92, OKM5)

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react with the spindle cell component of the tumor. The third antibody (HCL-1) showed variable and weak reactivity with the spindle cells. These observations led the authors to conclude that KS was indeed a vascular endothelial tumor.

In this report, we provide additional evidence for a vascular origin for both the vascular lining cell and the spindle cell component of KS. We recently described one antibody, B721, which reacts with endothelium arteriolar smooth muscle and activated lymphocytes.[9,10] In this paper we report a second monoclonal antibody, E431, which also reacts with vascular endothelium. We studied 11 cases of KS in patients with AIDS and compared the reactivity of B721 and E431 with known markers for this tumor.

Materials and Methods

Biopsy Specimens

Cutaneous 4- or 6-mm punch biopsies of KS[9] were obtained from patients with AIDS after appropriate informed consent. An excisional lymph node biopsy was obtained for histologic diagnosis, and a portion of the node was submitted for this study. One specimen of cutaneous KS was obtained at postmortem examination. The tissues were immediately covered with OCT, snap-frozen in liquid nitrogen-cooled isopentane as previously described,[9] and stored at −80 C.

Polyclonal and Monoclonal Antibodies

B721 is an IgG_{2a}-K murine monoclonal antibody raised against the human B-cell lymphoblastoid cell line RPM1-8392. It reacts with all vascular endothelium except for the renal glomeruli and the sinusoids of the liver and spleen and reacts with the smooth muscle of vessel walls in arterioles and venules.[9] It also reacts with activated, but not resting, peripheral blood lymphocytes.[10] This includes most activated B cells and CD8 cells and a subset of activated CD4 cells. It does not react with lymphocytes in either the T-cell or B-cell domains of normal lymph nodes. The antibody recognizes a 75,000-dalton antigen.[11]

E431 is an IgM-K murine monoclonal antibody. It was raised against first-trimester chorionic villi. In brief, BALB/c mice were immunized with 0.5-g (wet weight) isolated first-term chorionic villi obtained from elective pregnancy terminations. The mice were boosted at 2-week intervals. The final intravenous immunization was performed with solubilized (Triton x-100) chorionic villi. The spleen was harvested 3 days after the intravenous immunization, and the spleen cells were fused to the SP-2 murine myeloma line. Hybridomas were selected in HAT media (hypoxanthine–aminopterin–thymidine), and clones were screened by immufluorescence against frozen sections of first-trimester and term placenta. E431 was found to react only with chorionic villus vessels. The hybridoma was subcloned by limiting dilution. The antibody isotype was determined by radial immunodiffusion (Meloy Laboratories). No cross-reaction was found with any of the IgG isotypes. The antibody was screened by enzyme-linked immunochemistry against all major adult tissues.

Other antibodies used included W6/32, which recognizes an HLA A,B,C framework determinant,[12] L243, which recognizes a framework determinant on the DR/Ia antigen,[13] HCL-1, which was the generous gift of Dr. David Posnett,[14] and a polyclonal affinity-purified antibody to F8rAg (Accurate Scientific, Westbury, NY; antibody concentration, 1 mg/ml). W6/32 and L243 were obtained as cell lines from the American Tissue Type Collection (ATCC, Rockville, Md)

Immunohistochemical Staining

Tissues were cut at 4 μ and immediately fixed in −20 C acetone for 10 seconds. The slides were rehydrated with appropriate blocking serum (1% horse serum for monoclonal antibodies, 1% goat serum for polyclonal F8rAg). The slides were incubated with 60 μl of primary antibody for 30 minutes at 37 C. All monoclonal antibodies were used as undiluted hybridoma supernatants. The polyclonal anti-F8rAg antibody was used at a dilution of 1 : 10. The slides were then incubated with a 1 : 200 dilution of biotinylated horse anti-mouse Ig (monoclonal antibodies) or a 1 : 200 dilution of biotinylated goat anti-rabbit Ig (polyclonal antibody) for 30 minutes at room temperature. This was followed by incubation with the avidin–biotin–alkaline phosphatase complex (ABC-AP, Vector Laboratories, Inc., Burlingame, Calif) for 30 minutes at room temperature. Each incubation was preceeded by a 10-minute wash in phosphate-buffered saline (PBS). The slides were washed a final time in 0.1 M Tris buffer, pH8.2. The blue reaction product was developed for 20 minutes at room temperature in the dark with the use of AP substrate III (Vector) containing 10 mM levamisole and 1 mM phenylalaninamide, a partial inhibitor of intestinal alkaline phosphatase.[15] The slides were counterstained with nuclear fast red and eosin, dehydrated in alcohol, cleared in Histoclear (National Diagnostics, Manville, NJ), mounted in Permount, and examined and photographed on a Zeiss II photomicroscope. Controls included isotype appropriate irrelevant

monoclonal antibodies, an irrelevant affinity-purified polyclonal antiserum used at the same antibody concentration, MOPC-11 (IgG) and MOPC-104 (IgM) myeloma proteins, sections incubated with no primary antibody (either PBS or 1% normal serum was used in place of antibody), and sections incubated with ABC-AP alone. In addition, W6/32 and HCL-1 were used as positive controls.

Results

Immunohistochemical Distribution of E431 Reactivity

E431 was found to react strongly and consistently with the endothelium of arterioles, capillaries, and venules in all major organs (Figure 1). The antibody also reacted with the endocardium, and the endothelium of the cartoid arteries and jugular veins.

In the skin, E431 stained arterioles and venules in the dermis. There was no staining apparent on dermal lymphatics (Figure 1A). Dermal lymphatics were identified as endothelium-lined vessels lacking smooth muscle and unreactive with B721, L243 (DR), and αF8rAg.

On lymphoid organs, E431 was reactive with the splenic sinusoids. On lymph nodes E431 reacted consistently with blood vessel endothelium and sporadically with the lining cells of the lymphatic sinuses. The reactivity appeared strongest on large macrophage-like cells in these sinuses (Figure 1D). Control sections of lymph node stained with B721 confirmed that this antibody is unreactive with lymphatic sinus endothelium (Figure 2).

Because the distribution of reactivity of E431 corresponds to some of the reactivities reported for F8rAg, we attempted to block the binding of E431 with polyclonal antibody to F8rAg. No blocking of E431 reactivity could be detected in a variety of tissues preincubated with polyclonal anti-F8rAg.

Histopathology of KS

Sections of all histologic samples showed typical features of KS. The skin biopsies showed nodules of spindle cells containing irregular vascular slits and occasionally larger vessels along the periphery. The sections of the lymph node showed mutiple foci of tumor composed of primarily spindle cells with few vascular spaces, which replaced approximately one half of the node.

Immunohistochemistry of KS

Sections of KS showed variability of staining for both B721 and E431, both within a single biopsy and between biopsies (Table 1, Figure 3). In general, both the vascular lining cell and the spindle cell component of the tumor reacted with both antibodies. The reaction of E431 was more uniform, with all of the vascular lining cells reacting strongly and the spindle cell component reacting only slightly less intensely. B721 showed staining of the vascular lining cells and slightly weaker staining of the spindle cells. In at least two sections there was an occasional focus of spindle cells which were barely reactive with B721 adjacent to a more strongly reacting focus of tumor. For both E431 and B721, reaction on adjacent apparently "normal" vessels appeared stronger than on either the vascular or spindle cell component of KS.

The staining pattern of the other markers was consistent with previous observations. HCL-1 reacted strongly with the vascular lining cells of KS but was only weakly reactive or nonreactive with the spindle cell component. F8rAg and Dr/Ia antigen showed variable staining on both the spindle cell and vascular lining cell of KS, although we detected greater reactivity with these markers than has been previously reported in some studies.

Although there was intratumor and intertumor variability, the majority of KS samples in the studies were $B721^+$, $E431^+$, Dr/Ia^+, and $F8rAg^+$. Both the vascular lining cells and spindle cells displayed this phenotype. In general, the vascular lining cells appeared to have a slightly greater reactivity than the spindle cells.

Discussion

We have demonstrated the reactivity of KS with two additional monoclonal antibodies directed against vascular endothelial cell antigens. Although we must raise the same caveat expressed by Rutgers et al,[8] namely, that we can not absolutely exclude reactivity of one of these antibodies (B721) with lymphatic endothelium under all conditions, our studies to date have shown no such cross-reactivity, with any structure that by morphologic or immunochemical criteria is clearly of lymphatic origin.[7,16] We also find no evidence of E431 reacting with dermal lymphatic vessels. These vessels were also unreactive with antibodies to HLA-DR, and F8rAg and weakly reactive with W6/32 (HLA-A, B, and C). This reaction pattern has been previously reported to define lymphatic endothelium.[16] The occasional reaction seen with lymph node sinus lining cells may mean that the antigen recognized by E431 can be expressed at low levels on some populations of lymphatic sinus cells. Such weak and/or variable expression of vascular antigens on lymphatic endothelium has been previously re-

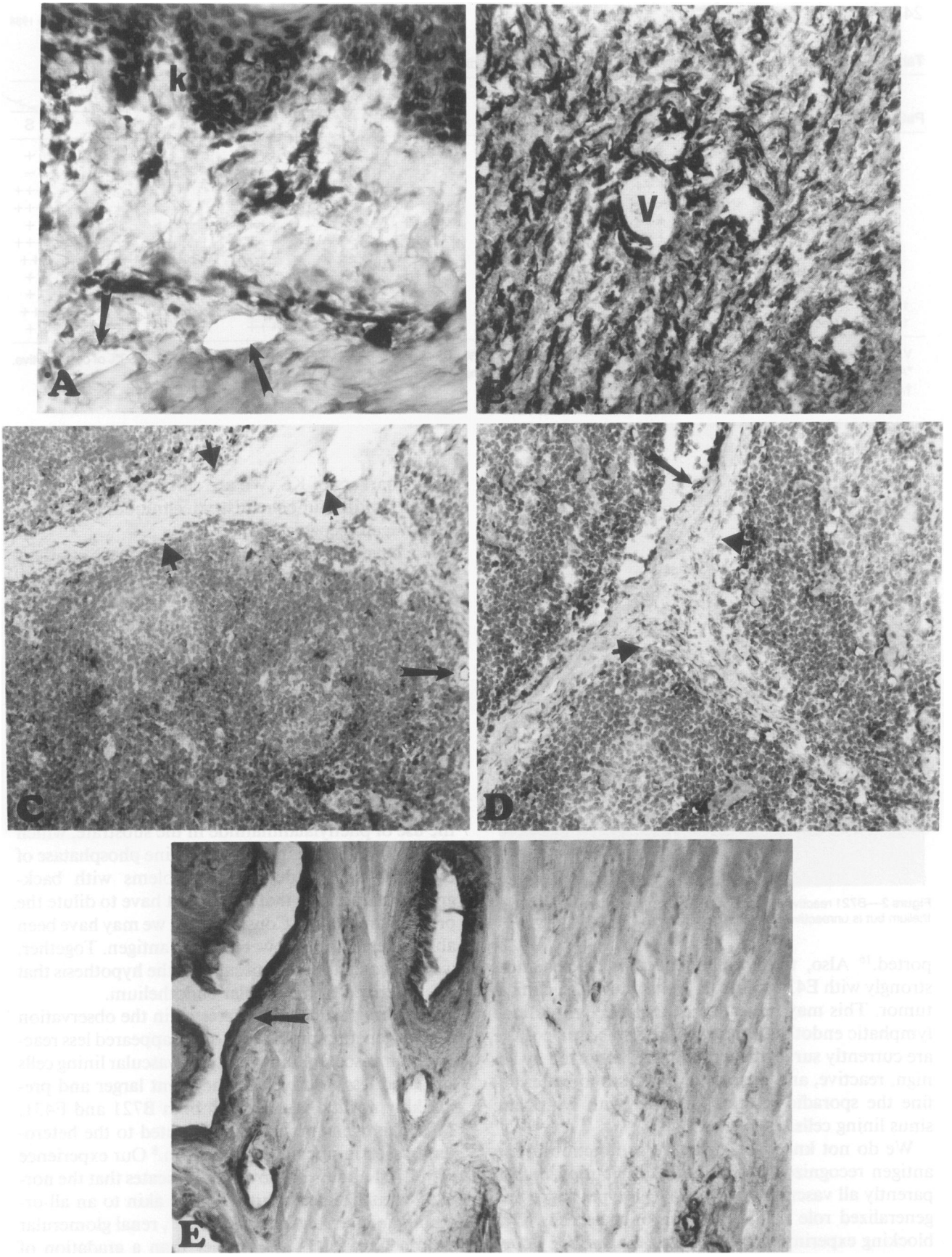

Figure 1—E431 reactivity on normal adult tissues. Sections of all major organs were stained with E431 by a standard immunoperoxidase procedure (identical to that described in Materials and Methods, except that peroxidase was substituted for alkaline phosphatase and the substrate was 3-amino-9-ethylcarbazole, *AEC*). The antibody reacted with the endothelium of arterioles, capillaries and venules, as well as the hepatic and splenic sinusoids. **A**—Normal skin. E431 reacted with the vascular endothelium of the small dermal blood vessels. The same staining pattern was observed with B721 and αF8rAg. The keratinocytes (*k*) are negative. Dermal lymphatic vessles were unreactive (*arrow*). These structures were also negative for HLA-Dr, and F8rAg, but weakly positive for HLA-A, B, and C. This phenotype has been previously reported for lymphatic endothelium. **B**—Spleen. Both larger vessels (*V*) as well as the splenic sinusoids show strong reactivity. **C**—Lymph node. On most lymph nodes E431 reacted only with the vascular endothelium of the capillaries and arterioles (*arrow*). The capsular sinus and afferent lymphatics are unreactive (*arrow heads*). **D**—On two of ten lymph nodes examined scattered staining of the capsular sinus was noted. One portion of the capsular sinus is positive (*arrow*), and other portions of the sinus along the fibrous septa are negative (*arrowheads*). **E**—Heart. The endocardium (*arrow*) and myocardial vessels are positive; the myocardium is unreactive.

Table 1—Reactivity of Kaposi's Sarcoma With Monoclonal Antibodies to Endothelial Surface Antigens

Patient	Type of lesion*	F8rAg		B721		E431		HCL-1		Ia	
		V	S	V	S	V	S	V	S	V	S
1	Nodule	+++	+++	+++	+++	+++	+++	+++	+++	+++	+
2	Plaque	++	++	+++	++	+++	+++	+++	+	+++	−
3	Plaque	+++	+++	+++	+++	+++	+++	+++	+	+	+++
4	Plaque	+++	+++	+++	+++	++	+	+++	−	+++	+++
5	Plaque	+++	+++	+++	+++	+++	+++	+++	++	++	+
6	Nodule	+++	+++	+++	+++	+++	+++	+++	++	+++	+++
7	Nodule	+++	+++	+++	++	+++	+++	+++	+	+++	++
8	Nodule	+++	+++	+++	+++	+++	++	+++	++	+++	+
9	Nodule	+++	++	+++	+++	+++	+++	+++	+	++	+
10	Focal	+++	+++	+++	+++	+++	+++	+++	+	+++	++
11	Nodule†	+++	+++	+++	+	+++	+++	+++	−	+++	+

V, vascular lining cell; S, spindle cell. −, no or only rare positive cell; +, <25% of cells positive; ++, 25–50% of cells positive; +++, >50% of cells positive.
*All specimens were skin lesions except for Case 10, which was a lymph node biopsy.
†Autopsy case.

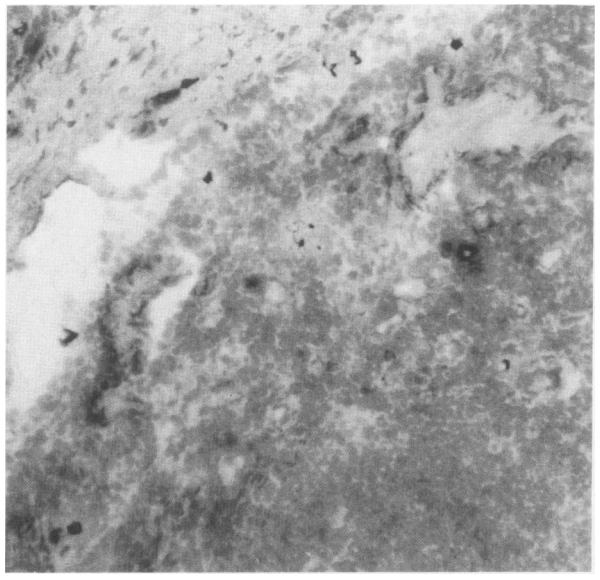

Figure 2—B721 reactivity on lymph nodes. B721 reacts with vascular endothelium but is unreactive with the lymphatic sinus.

ported.[16] Also, the lymph node that reacted most strongly with E431 was from a site draining a clinical tumor. This may indicate that reactive lymph node lymphatic endothelium can express this antigen. We are currently surveying lymph nodes involved by benign, reactive, and neoplastic processes to better define the sporadic reaction of E431 with lymphatic sinus lining cells.

We do not know the structure or function of the antigen recognized by E431. Its distribution on apparently all vascular endothelial cell types suggests a generalized role in the function of these cells. Our blocking experiments suggest that the antibody does not recognize F8rAg, and its distribution on adult tissues and KS suggests that it is not similar to the other markers of KS. We are currently employing a number of immunochemistry techniques to identify the antigen recognized by E431.

We have also confirmed the observations of others that both F8rAg and Ia/Dr antigen are expressed by both the spindle cell and vascular lining cell component of KS. In contrast to some other studies, we detected somewhat more reactivity with both of these markers on the tumor. Although this may reflect different concentrations and/or affinities of our reagents, we believe that our choice of immunohistochemical technique also contributed to these observation. ABC-alkaline phosphatase has been reported to be more sensitive than PAP, two-step techniques or even the ABC-peroxidase technique.[17] Also, the use of phenylalaninamide in the substrate, which slightly inhibits the intestinal alkaline phosphatase of the ABC-AP,[15,18] decreased problems with background staining, so that we did not have to dilute the primary antibodies. Consequently, we may have been able to detect much lower levels of antigen. Together, we believe that these data support the hypothesis that KS is derived from vascular endothelium.

We were particularly interested in the observation that, in general, spindle cells of KS appeared less reactive than vascular lining cells, and vascular lining cells appeared less reactive than adjacent larger and presumably normal vessels, with both B721 and E431. This heterogenity has been attributed to the heterogenity seen in normal endothelium.[8] Our experience with B721 and E431, however, indicates that the normal vascular heterogenity is more akin to an all-or-nothing pattern (eg, aorta is $B721^+$, renal glomerular endothelium is $B721^-$), rather than a gradation of reactivity. This suggests that the variability seen in KS may be due to other factors.

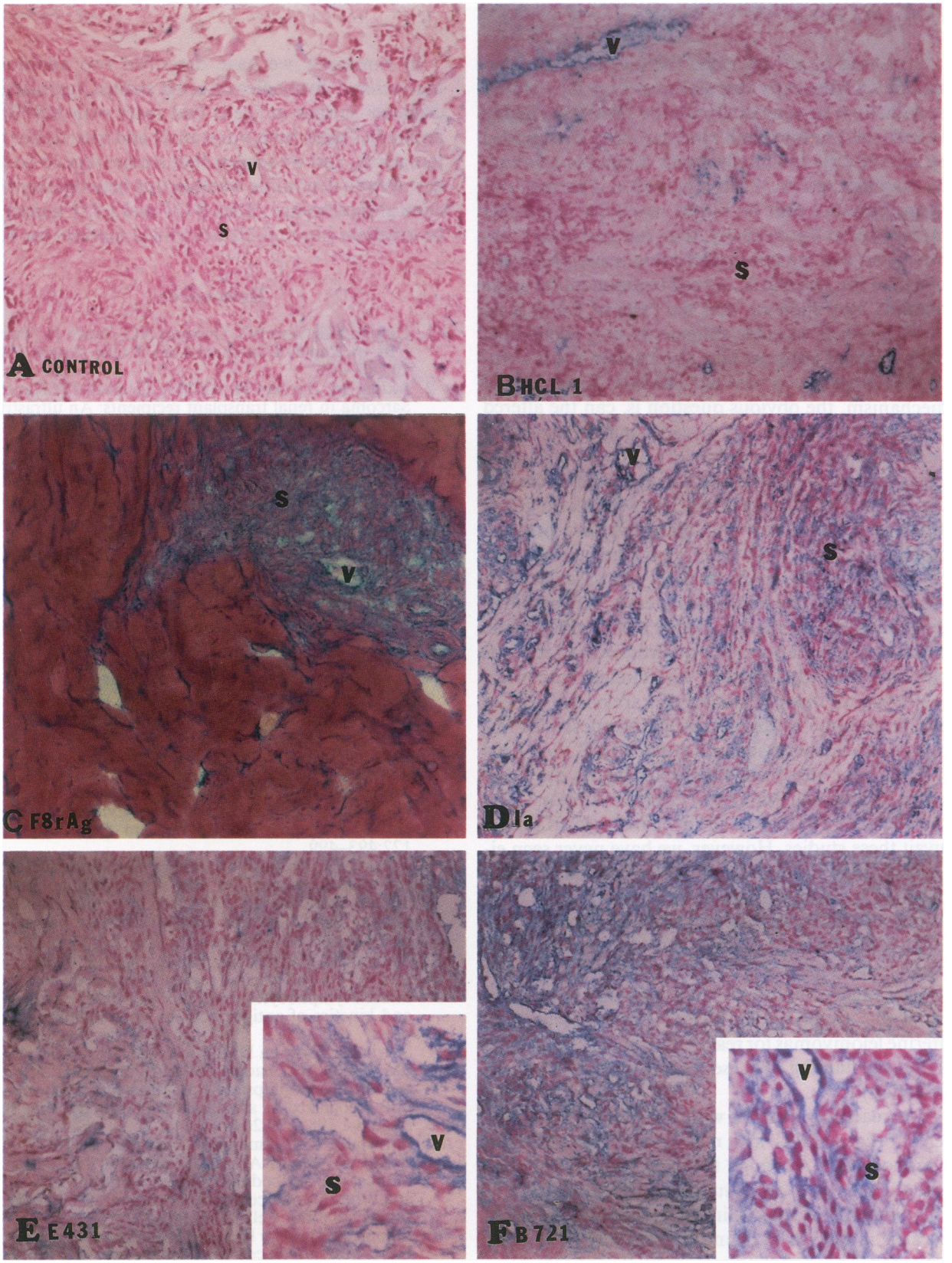

Figure 3—Distribution of endothelial surface antigens on KS. Four of the antibodies directed against endothelial surface antigens (F8rAg, Ia, E431, B721) reacted with both the vascular lining cells (*v*) and the spindle cell (*s*) of KS. In general, the vascular cells were more strongly reactive than were the spindle cells. There was both intratumor and intertumor variability for all markers. **A**—Negative control. Irrelevant primary antibody. (×100) **B**—HCL-1. In agreement with previous observations, HCL-1 reactivity was confined to the vascular lining cells with little or no reactivity seen on the spindle cells. (×100) **C**—F8rAg. (×100) **D**—L-234 (Ia). (×100) **E**—E431. Reactivity was more uniform with this antibody than with the other markers. (×100) **Inset**—Note positive staining of spindle cells. (×250) **F**—B721. (×100) **Inset**—Note positive staining of spindle cells. (×250) Alkaline phosphatase immunochemistry, Vector-blue substrate, nuclear fast red, and eosin counterstains.

Beckstead et al[7] described the histologic progression of KS from early vascular spaces lined by plump endothelium to neovascularization producing highly vascularized lesions with vascular cores surrounded by spindle cells and finally sheets of spindle cells with few vascular spaces. If this progression is correct, and if one assumes that decreased reactivity is a direct measure of antigen density, then our and others' observations that the spindle cell component is less reactive than the vascular lining cell component for some markers may indicate that the cells of KS express lower levels of vascular antigens as they proliferate. Such a loss of antigens may also explain the intertumor heterogenity of vascular markers. Regardless of mechanism, the obvious question is, can the altered reactivity of the tumor for vascular markers be correlated with its biologic behavior? Such a correlation exists, for instance, in transitional cell carcinoma of the bladder, where loss of reactivity for blood group antigens is correlated with aggressive and invasive biologic behavior.[19] To determine whether a similar correlation can be made with KS and vascular antigens, we must study many more cases with sensitive dilution techniques to see whether the reactivity of the different components can be quantitated and to compare this antibody reactivity with clinical outcome.

We believe that B721 and E431 are both excellent additions to the battery of markers proposed for immunohistochemical identification of KS. We have not yet been able to test these antibodies on either other spindle cell tumors or vascular tumors. The specificity of B721 and E431 as markers for KS must await these studies. However, we have never seen either antibody stain fibroblasts and would be very surprised if these antibodies reacted with a dermatofibroma or similar spindle cell proliferation. Because B721 reacts with the smooth muscle of small arterioles,[9] examination of smooth muscle neoplasms will be particularly important in determining the specificity of this antibody. We have examined sections of uterine leiomyomas for reactivity with B721 and have found no staining of these lesions (unpublished observation).

The reactivity of B721 with KS is of particular interest because B721 also reacts with most activated lymphocytes.[10] Although the expression of lymphocyte antigens on endothelium is well documented,[20,21] B721 may be of some clinical significance in AIDS because it appears to define serologically a subset of activated $T4^+$ lymphoblasts.[10] AIDS patients have decreased and abnormal T4 cells.[22-24] Whether it is merely coincidental that these patients also develop an aggressive $B721^+$ tumor will require further studies to define the role of the 721 antigen.

In summary, we have described two additional monoclonal antibodies directed against vascular endothelial surface antigens that react with KS. Both antibodies show both intratumor and intertumor heterogenity, and we suggest that studies should be undertaken to determine whether this heterogenity is of clinical significance. Both B721 and E431 appear to be excellent immunohistochemical markers for KS.

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