Early Lesions of Kaposi's Sarcoma in Homosexual Men

An Ultrastructural Comparison With Other Vascular Proliferations in Skin

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An aggressive variant of Kaposi's sarcoma (KS) has appeared in young homosexual men with evidence of systemic immunosuppression. The ultrastructure in biopsy specimens from 8 KS cases in young homosexual men has been compared with that in biopsy specimens from 4 KS cases in elderly heterosexuals and with that in biopsy specimens from 23 cases of benign vascular disorders of skin. In all cases of KS the small blood vessels lacked a prominent investment of pericytes and their processes, had a fragmented and often absent basal lamina, had frequent discontinuities in the endothelial lining, and had only a few small junctional densities between endothelial cells. Some clinically aggressive cases of KS also had necrosis of individual endothelial cells and had prominent cytoplasmic processes entrapping individual collagen fibers. The benign disorders lacked these features. These differences in the structure of the small vessels may be of diagnostic value in some early cases of KS. The loss of dendritic pericytes in blood capillaries in KS might relate to the telangiectasia which is a prominent feature of the early lesions of KS. (Am J Pathol 1983, 111:62–77)

A DRAMATIC CHANGE in the epidemiology and clinical course of the vascular neoplasm called Kaposi's sarcoma (KS) has occurred in the United States since 1981. Previous to that time KS affected predominantly older men (over age 50) of Jewish, Italian, Mediterranean, or black ancestry,[1-3] particularly when it arose in otherwise apparently healthy individuals. Also KS usually appeared in the skin of the lower extremities, often bilaterally, and gradually spread centripetally, to involve lymph nodes, lung, liver, intestine, or other viscera. Since 1979 a more aggressive variant of KS has been found in young homosexual men (under age 58) predominantly in New York and California, which together account for 77% of the currently reported cases (Centers for Disease Control, personal communication). In addition to departing from the usual ethnic predisposition, this variant KS also tends to begin in a more scattered distribution on the body surface. It may begin in unusual sites, such as the skin of the shoulder or trunk, and tends to spread rapidly, to involve many other skin sites, oral mucosa, lymph nodes, and viscera. In many (15–40%) of these young patients the disease progresses rapidly, and they die of KS within 1 year, despite standard combination drug chemotherapy regimens.[4]

Although this variant KS has definitely increased in incidence in these locations of the United States, earlier studies showed that an aggressive form of KS affects African children.[5,6] Also, 20% of the cases reported by Cox and Helwig[2] occurred in patients aged 9 to 49 years, and 7 of the 11 deaths from KS in that series occurred in patients less than 45 years old at the onset of their disease. Twenty-two percent of the cases reviewed by McCarthy and Pack[1] also occurred in patients under age 40.

The chief candidate as an explanation for the very aggressive behavior of KS is the finding of profound

Supported in part by American Cancer Society Grant RD151 and by Veterans Administration research funds.

Accepted for publication November 8, 1982.

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0002-9440/83/0407-0062

immunosuppression in this young homosexual population, as indicated by associated opportunistic infections with *Pneumocystis carinii* and cytomegalovirus[4] as well as by markedly depressed ratios of helper to suppressor T lymphocytes[7-9] in peripheral blood. KS has been noted previously to be one of the earliest tumors that can appear after immunosuppression therapy in transplant recipients.[10,11] Exactly how this immunosuppression might act to favor a more aggressive form of KS is not known at present.

The histologic criteria for making a diagnosis of KS have been expounded clearly.[12,13] The lesions of KS usually begin as flat erythematous (red-purple to red-brown) macular lesions which have been called patch stage lesions.[13] These early patch lesions have been described histologically as having an angiomatous phase[12,13] in which there is a proliferation of thin-walled irregular vascular channels mainly in the reticular dermis. As the clinical lesions become thickened to form plaques and eventually tumor nodules, histologic sections show that the lesions tend to contain nodules of spindle-shaped cells, which entrap many erythrocytes. Because of the spindle shape of the cells, some authors have called this the fibroblastic phase of KS.[12] In the late stages, biopsies of KS usually present no diagnostic problems, but there can be occasional cases in which it is difficult to distinguish in a small punch biopsy between the early patch stage of KS and a variety of benign lesions such as dermatofibromas ("fibrous histiocytoma"), nonpalisading forms of granuloma annulare, insect bite reactions, pyogenic granuloma, or even stasis dermatitis. Well-developed lesions of these types usually are easily distinguished from one another, particularly in large punch or scalpel biopsies.

The present study has two objectives: 1) To determine whether or not there are ultrastructural features that correlate with the aggressive behavior of KS in young homosexual men and 2) To define those ultrastructural features that can be used to distinguish early patch stage or angiomatous lesions of KS from a variety of benign vascular growths.

Preliminary reports by others have not indicated that there are any obvious differences at the histologic level between KS in homosexual men and the more usual forms of KS.[14] In this study we carry this comparison to the ultrastructural level and observe differences with regard to the presence of necrotic endothelial cells and cellular projections into the collagen bundles in some but not all cases.

Materials and Methods

Ten biopsy specimens from 8 cases of Kaposi's sarcoma (KS) arising in young homosexual men (Table 1) were taken with the use of standard biopsy punches or scalpels for elliptical excisions. Biopsies were performed in all cases before any treatment was initiated except in Case 4, where several injections of intravenous vincristine had been given 9 weeks before biopsy. Anesthesia was provided by intracutaneous injection of lidocaine, usually with added epinephrine to help control hemostatis. The biopsy specimens were carefully divided for light microscopy and electron microscopy or histochemistry. Tissues for standard light microscopy were fixed in phosphate-

Table 1—Kaposi's Sarcoma: Clinical Data

Case	Age	Race	Sex	HP	Duration at biopsy (years)	Initial stage	Lesion thickness	Follow-up interval (years)	Therapy	Progression
1	46	W	M	+	0.1	SV	Tu	2.2	C	RP; D (KS)
2	40	W	M	+	1.0	SLV	Pl,Tu	0.5	C	RP; D (KS)
3	38	W	M	+	1.0	SL	Pl	0.6	C	R
4	40	W	M	+	0.3	S	Pl	0.5	C	St (KS); D (P)
5	29	W	M	+	0.2	SL	Ma	0.5	Vi	St
6	35	W	M	+	0.2	S	Pl	0.4	Vi	St
7	34	W	M	+	0.1	S	Pl	0.2	I	R
8	34	W	M	+	0.2	S	Ma	0.2	C	RP
9	87	W	M	–	U	S	Pl,Tu	0.2	N	St
10	62	B	M	–	4.0	S	Ma	0.3	N	St
11	72	B	F	–	1.5	S	Pl	0.3	N	SP
12	64	W	M	–	14.0	S	Pl	0.1	N	RP*

Abbreviations used: B, black; C, combination drug chemotherapy; D, died of (cause); F, female; HP, homosexual preference; I, interferon (Dr. Bijan Safai, Memorial Hospital, New York, NY); KS, Kaposi's sarcoma; L, lymph node involvement; M, male; Ma, macular lesions "patch" stage; N, none; P, *Pneumocystis carinii* pneumonia; Pl, plaque lesions; R, remission; RP, rapidly progressive; S, skin involvement; St, stable; SP, slowly progressive; Tu, tumor lesions; U, unknown; V, visceral involvement; Vi, vincristine (Velban); W, white.

* This patient had experienced recent rapid progression of lesions at the time of biopsy, although more indolent disease had been present for a long time.

Table 2—Benign Disorders: Clinical Data

Case	Age	Race	Sex	Diagnosis	Lesion duration (years)	Follow-up interval (years)	Therapy	Progression
13	63	W	M	Dermatofibroma	U	4.3	S	No
14	51	W	M	Dermatofibroma	2.0	4.3	S	No
15	58	W	M	Dermatofibroma	2.5	3.8	S	No
16	79	O	M	Dermatofibroma	U	2.7	S	No
17	59	W	M	Dermatofibroma	30.0	0.8	S	No
18	54	W	M	Dermatofibroma	0.3	1.3	S	No
19	U	W	M	Fibrous histiocytoma, atypical	4.0	0.0	S	U
20	74	B	M	Dermatofibroma	U	0.8	S	No
21	58	W	M	Dermatofibroma	U	1.8	S	No
22	37	B	M	Fibrous histiocytoma	20.0	1.8	S	No
23	64	W	M	Dermatofibroma	U	0.1	S	No
24	62	W	M	Dermatofibroma	1.0	0.0	S	U
25	62	W	M	Pyogenic granuloma	0.3	1.6	S	No
26	61	B	M	Pyogenic granuloma	0.2	2.0	S	No
27	71	W	M	Pyogenic granuloma	0.3	0.0	S	U
28	27	W	F	Pyogenic granuloma	0.2	0.1	S	R (1)
29	53	W	M	Capillary hemangioma	2.0	0.0	S	U
30	74	W	M	Hemangioendothelioma, benign	U	3.0	S	No
31	70	W	M	Stasis dermatitis	U	2.0	Bx	P
32	55	W	M	Stasis dermatitis (hypertrophic)	U	1.0	Bx	P
33	55	W	M	Stasis dermatitis	U	1.0	Bx	P
34	42	B	M	Angiokeratoma	U	0.3	S	U
35	65	W	M	Telangiectasia, post BCNU	0.1	1.0	Bx	St

Abbreviations used: B, black; Bx, biopsy; BCNU, 1,3-bis(2-chloroethyl) 1-nitrosourea; F, female; M, male; No, no recurrence or progression; O, oriental; P, persistant; R, recurrent for (number of times); S, surgical excision; St, stable; U, unknown; W, white.

buffered formalin[15] and embedded in paraffin. Sections were cut at 5 μ and were stained with hematoxylin and eosin. Tissues for electron microscopy were fixed immediately after excision by immersion in a fixative containing 2% glutaraldehyde and 2% paraformaldehyde in 0.1 M sodium cacodylate buffer, pH 7.4, with 0.6 mg/ml of calcium chloride added.[16] The tissues were cut into 1 cu mm blocks carefully with apposed razor blades to minimize distortion. The blocks were allowed to fix for 4–17 hours in this solution at room temperature for the first 4 hours and at refrigerator temperature thereafter. The tissues were rinsed in 0.1 M sodium cacodylate, fixed in 1% osmium tetroxide in veronal acetate buffer, dehydrated in graded ethanol-water solutions, and embedded in a DER736-Epon812 mixture as previously described in detail.[17] Sections were cut of each block, at 0.05–1.0 μ in thickness, and stained with toluidine blue. Regions rich in vascular channels were selected and sectioned at 30–50 nm with the use of diamond knives. The sections were stained with uranyl acetate and lead citrate and examined in a Philips EM201 transmission electron microscope.

These cases were compared with 4 cases of Kaposi's sarcoma arising in elderly heterosexual patients, 11 cases of dermatofibromas (or fibrous histiocytomas), 6 cases of pyogenic granulomas or hemangiomatous lesions, 3 cases of stasis dermatitis, and 2 cases of telangiectasia (Table 2). Biopsy specimens of these disorders were processed similarly except for the fixation of some of the benign lesions immediately after excision in phosphate-buffered formalin[15] prior to fixation in osmium and processing for electron microscopy. The quality of fixation was comparable to that obtained with glutaraldehyde, in that any differences attributable to fixation variation were slight when compared with the differences observed in the various tissues studied.

Cases 1 and 3 have been the subject of individual case reports because of their clinical presentations. The electron-microscopic results have not been reported in detail in Case 1 and not at all in Case 3.[18,19]

Results

Histology

In 5 of the 8 cases of KS arising in young homosexual men, there were both irregular endothelial-lined vascular channels as well as groups and cords of cells without distinct lumens, which permeated the interstices between collagen bundles in the reticular dermis. This produced a "dissection of collagen" appearance, which has been previously described in the classic form of KS.[20] Usually those channels with distinct lumens are lined by rather flattened endothelial cells without prominent nuclear atypia. They form anastomoses frequently with each other to produce

irregular vascular networks that wrap around collagen bundles. Entrapped erythrocytes were abundant in 7 of the 8 cases of KS in homosexuals. Hemosiderin was present in small amounts. There was a tendency for the thin-walled irregular vascular channels to penetrate the dermis along the adventitial spaces near larger thick-walled arteries and veins and to invade the adventitial dermis of sweat glands. Usually there were, in addition, small numbers of spindle-shaped cells. Plasma cells were present often as a few small clusters near the irregular vascular channels with lumens. An infiltrate of small lymphocytes was sparse and scattered among the cells of the KS tumor tissue. In 1 of the cases, the KS tumor had predominantly compact aggregates of spindle-shaped cells, among which there were numerous entrapped erythocytes. These spindle cells had nuclei that resembled those of the endothelial cells but were slightly larger. Also, the spindle cells had more abundant cytoplasm.

In 1 of the 8 cases, the lesion was very subtle and required careful scrutiny to be distinguished from stasis dermatitis, but a few regions demonstrated the characteristic spread of irregular vascular channels deep in the reticular dermis.

Mitoses generally were very sparse, with only 0–1 per 10 high-power fields (HPF) as seen with a ×40 objective lens. In only 2 cases were there up to 2 mitoses per 10 HPF. Necrotic cells were apparent in these same cases in approximately the same numbers and were recognized by nuclear pyknosis and eosinophilic condensed cytoplasm. When compared with the electron-microscopic study, light microscopic study presents some difficulty in identifying necrotic cells and distinguishing them from infiltrating lymphocytes in some instances.

The light-microscopic appearance of the 4 cases of KS in the elderly heterosexual patients is similar to that described above for KS in the homosexual patients, except that necrotic endothelial cells were not seen in the heterosexual group.

Electron Microscopy

In normal small blood capillaries in the dermis of patients with nonvascular disorders, electron micrographs demonstrated the presence of several of the important features (Figure 1) to be compared with those found in cases of Kaposi's sarcoma. The endothelium is a continuous lining. The edges of endothelial cells are attached at intercellular junctions which have an increased electron density and are readily observable. The presence of dendritic pericytes can be inferred from the cross-sectioned profiles of their processes, which are in contact the endothelial cells. The basal lamina usually is continuous and encloses both the endothelial cells and the pericytes where they abut on the collagenous tissue matrix. Fortuitous sections demonstrate pericyte nuclei. Both endothelial and pericyte nuclei have a similar appearance of partial chromatin condensation and small, usually inapparent nucleoli.

The electron-microscopic results for the various groups are presented for comparison in Table 3. Many of the ultrastructural features are shared in the KS from homosexuals and heterosexuals; they will be described together. Features observed in the homosexual group that are selectively found in that group are specifically mentioned as such. In early or patch-stage lesions of KS in both homosexuals and heterosexuals, electron micrographs confirm the endothelial nature of the majority of the cells infiltrating in the reticular dermis (Figure 2). These endothelial cells line cleftlike lumens, which may be either very thin and are probably inapparent by light microscopy (Figure 2) or more dilated. Very few lumens contain erythrocytes (presumably because of the small size of the blocks and their extraction during fixation and washing steps of specimen preparation). The cellular lining of the clefts is continuous in most areas, but focal discontinuities are easily observed (Table 3). These vary in size from slender spaces between endothelial cells less than a micrometer in width to wide discontinuities 4–5 μ in width (Figure 3). Most of the endothelial cells appear to have been viable at the time of fixation; however, a few necrotic cells are found with pyknotic nuclei and fragmentation of cytoplasm (Figure 4). Necrotic cells are evident in 5 of the 8 biopsy specimens from homosexual patients with KS and none of the 4 from elderly heterosexuals with KS (Table 3). Basal lamina is present as short fragments at the regions of contact of endothelial cells of the smallest vessels in KS with the collagenous connective tissue (Figures 2–4). Discontinuities are easily found. In the larger vessels of KS, the basal lamina tends to be continuous around the endothelial cell aggregates.

The endothelial cells have oval nuclei, generally euchromatic dispersed chromatin, and small to medium-sized nucleoli. No viral inclusions are found. The cytoplasm contains a few small, sometimes dilated, cisternae of rough endoplasmic reticulum (RER), a few mitochondria, and a small Golgi complex. While the endoplasmic reticulum is often in close proximity to mitochondria, images of RER completely encircling mitochondria that are degenerating are not found.[21] Weibel-Palade bodies[22] are found in the cytoplasm of endothelial cells in vessels

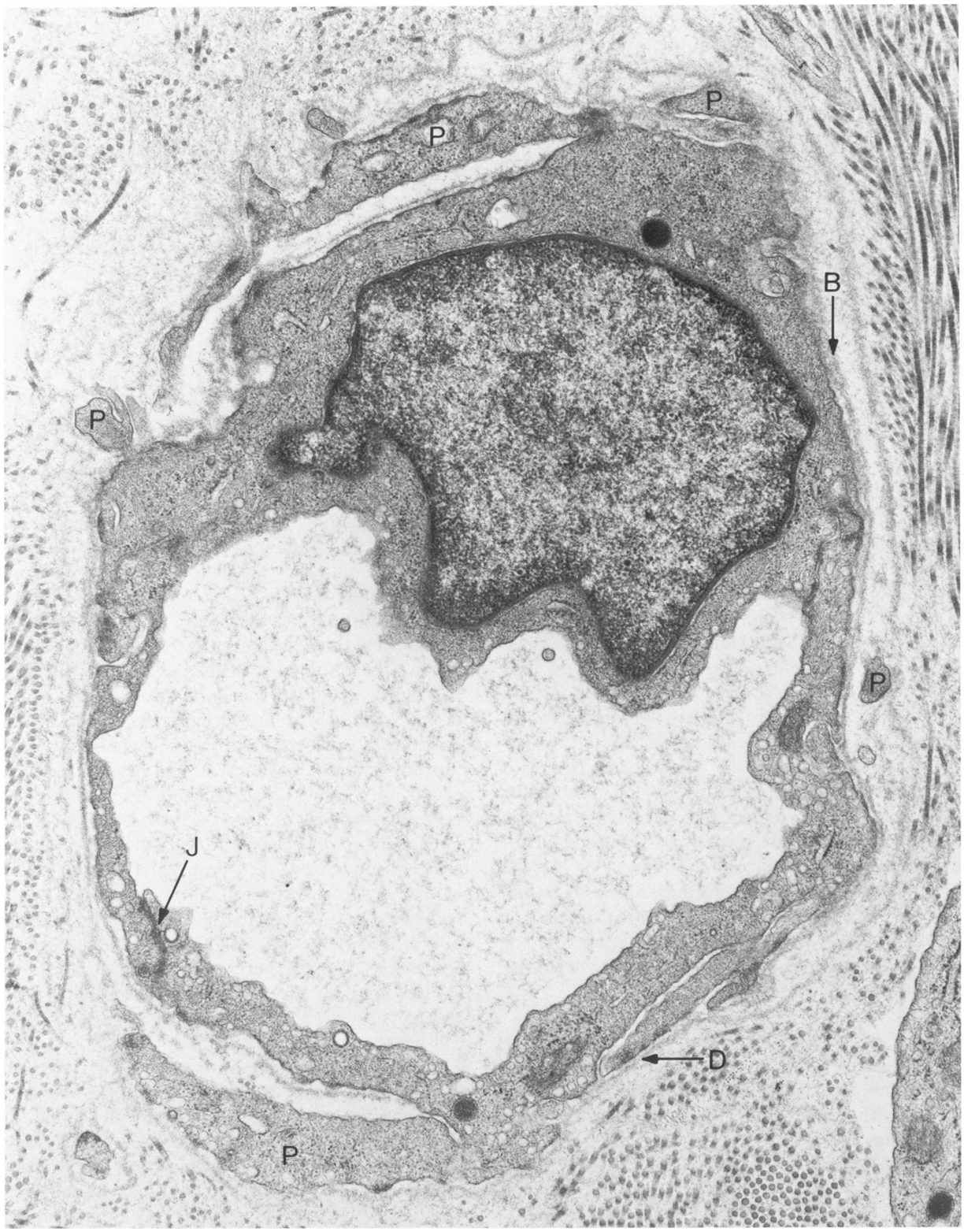

Figure 1 – Electron micrograph of a normal dermal capillary in human skin. This capillary has a continuous lining of endothelial cells, which are attached at dense intercellular junctions (*J*). Pericytes are present but usually are represented in sections by profiles of transected cytoplasmic processes, which contact the endothelium (*P*). Basal lamina encloses both endothelium and pericytes where they abut on collagenous tissue (*B*). Focal dense regions are present in the cytoplasm near the basal lamina (*D*). (× 19,600)

Table 3—Principal Ultrastructural Features

Case number	Dx	Pericyte processes*	Endothelial breaks†	Basal lamina‡	Hemorrhage	Endothelial erythrophagocytosis§	Relation to collagen‖	Necrosis¶
1	KS+	0	+ +	±	+ + + +	±	R	+ + +
2	KS+	0	+ + +	0	+	0	B	+
3	KS+	0	+ +	±	+ +	+	B,P	±
4	KS+	±	+	±	+	±	B	±
5	KS+	0	+	0	+	0	B,P	±
6	KS+	0	+ +	0	+	±	R	+
7	KS+	±	+	±	+	0	B	+
8	KS+	0	+ +	0	+ +	±	B,P	+
9	KS−	0	+	±	+ +	+	B,P	0
10	KS−	±	+	±	0	0	B,P	0
11	KS−	0	+ +	±	0	±	B	0
12	KS−	0	+	±	+	+ + +	B,P	0
13	DF	+ + +	0	+ + +	0	0	B	0
14	DF	+ + +	0	+ + +	0	0	B	0
15	DF	+ + +	0	+ + +	0	0	B	0
16	DF	+ + +	0	+ + +	0	0	B	0
17	DF	+ + +	0	+ + + +	0	0	B	0
18	DF	+ + +	0	+ + +	0	0	B	0
19	DF	+ + +	0	+ + +	0	0	B	0
20	DF	+ + +	0	+ + +	0	0	B	0
21	DF	+ + +	0	+ + +	0	0	B	0
22	FH	+ + +	0	+ + +	0	±	B	0
23	DF	+ + +	0	+ + +	0	0	B	0
24	DF	+ +	0	+ + +	0	0	B	0
25	PG	+	0	+ +	0	0	P±	0
26	PG	+ +	0	+	0	0	0	0
27	PG	+ + +	0	+	0	0	0	0
28	PG	+ + +	+	+	0	0	P±	0
29	CH	+ +	0	+	0	0	0	0
30	HE	0	0	+	0	0	0	0
31	SD	+ + +	0	+	0	0	B	0
32	SD	+ + +	0	+	0	0	B	0
33	SD	+ + +	0	+	0	0	B	0
34	AK	+ + +	0	+	0	0	0	0
35	TE	0	0	+ + +	0	0	0	0

Abbreviations used: Dx, diagnosis; KS+, Kaposi's sarcoma in homosexual man; KS−, Kaposi's sarcoma in heterosexual; DF, dermatofibroma; FH, fibrous histiocytoma; PG, pyogenic granuloma; CH, capillary hemangioma; HE, hemangioendothelioma, benign; SD, stasis dermatitis; AK, angiokeratoma; TE, telangiectasia; R, replacing collagen bundles; B, in spaces between collagen bundles; P, pseudopodlike cytoplasmic processes extend into collagen bundles (if only a very few such areas, then the P is given a ± indication).

Meaning of rating system: 0, none observed; ±, rarely observed, or present in trace amounts; +, occasionally observed or a few observed, small in size, slight in amount; + +, moderate numbers, moderate size, moderate amounts; + + +, prominent, large, wide; + + + +, abundant, very thick.

* Pericyte processes around small vessels.

† Gaps or breaks in the endothelial continuity.

‡ Basal lamina around small vessels.

§ Erythrophagocytosis by endothelial cells (not including macrophages.

‖ Position of cell cytoplasm relative to the collagen bundles (see also abbreviations).

¶ Necrosis of endothelial cells.

with distinct lumens and with an associated perithelial cell layer. They are not evident in the very thin-walled irregular vascular channels or in the solid nests of spindle cells.[23]

There are two types of filament systems that are apparent in the cytoplasm. Intermediate filaments, 10 nm in diameter, are abundant in the endoplasmic region of the cytoplasm but rarely are aggregated into distinct bundles. Microfilaments, 7 nm in diameter, are present in small bundles in the cortical region or the ectoplasm of the cell. When present, they generally are in that part of the cytoplasm near the basal lamina, rather than near the lumen. An unusual finding in two cases is the presence of microfilament bundles in the ectoplasm near the lumen. Generally the endothelial cells do not have extensively interdigitated or overlapped borders and form only small junctions of the intermediate type (70F—maculae adherentes; see McNutt and Weinstein[24]) (Figures 2 and 3). In the zone of contact of the endothelial cells with the collagenous tissue, the endothelial cells form a few dense regions of contact with the adjacent fibers.

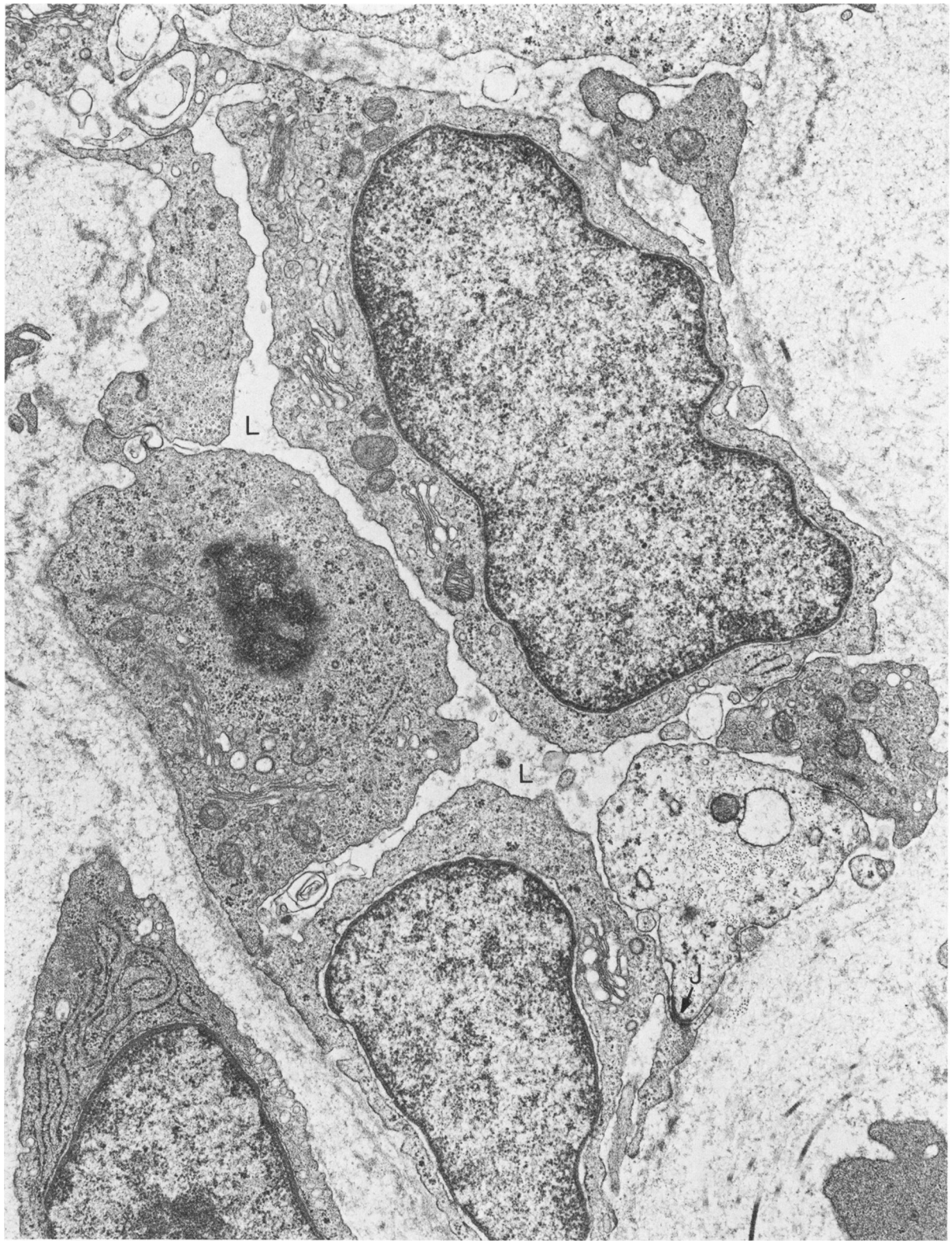

Figure 2—Kaposi's sarcoma. In this abnormal dermal vascular channel the lumen is reduced to a slit (*L*), which probably would escape recognition by light microscopy. The intercellular junctions are small and sparse (*J*). The basal lamina is fragmented. Pericyte processes are absent or greatly reduced in prominence (Case 4). (×17,900)

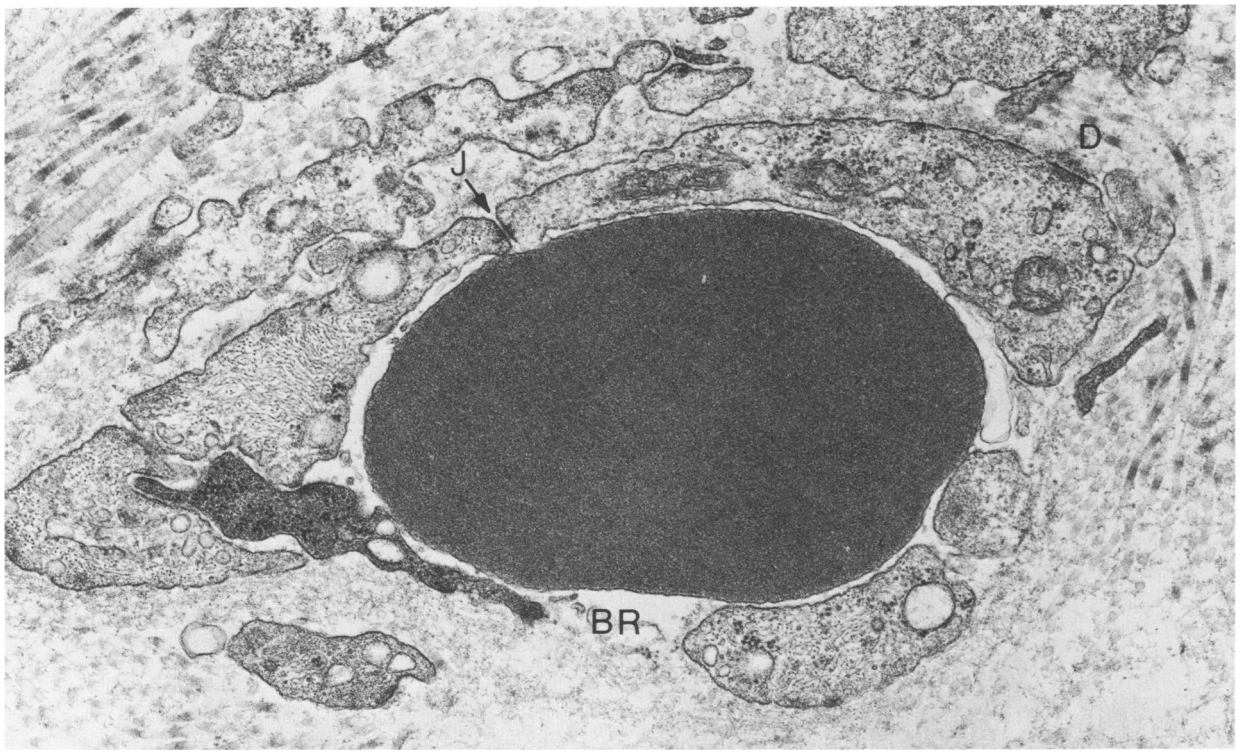

Figure 3—Kaposi's sarcoma. This capillary illustrates breaks in the continuity of the endothelium (*BR*). Basal lamina is fragmentary and is most evident near focal cytoplasmic densities (*D*). Pericyte processes are not recognized. Note the condensation of the cytoplasm of one of the endothelial cells suggesting focal cell damage. Intercellular junctions are small (*J*). An erythrocyte is in the lumen (Case 4). (×24,500)

In some of the KS lesions, there are cytoplasmic projections of endothelial and fibroblastic cells that encircle individual collagen bundles or even small groups of fibers (Figures 5 and 6). Entrapment of individual collagen fibers was most prominent in Cases 8 and 12 (Table 3). Case 8 is that of a homosexual patient and Case 12 is that of a heterosexual patient, but both had rapidly progressive disease at the time of biopsy.

Dendritic pericytes are greatly reduced in prominence in the vicinity of many of the small irregular vascular channels (Figures 2–5); however, in the lesions there are small blood vessels with intact basal lamina and pericytic cell processes. These may be residual capillaries entrapped by the tumor growth. Adjacent to the vessels are a few enlarged fibroblasts, macrophages that sometimes contain erythrocyte fragments or ferritin, and rare plasma cells.

Erythrophagocytosis by endothelial cells is rare. It is common for endothelial cells to be adjacent to erythrocytes trapped in small vascular clefts (Figure 3) but definitive erythrophagocytic inclusions are rare in endothelial cells in KS in the young homosexual men we have studied.

Necrotic cells are present as pycnotic nuclear fragments associated with cytoplasmic fragmentation (Figure 4). It is not always possible to determine the cell of origin of the necrotic fragments; but on the basis of size and location, they seemed most likely to derive from endothelial cells (Figure 4). They were most prominent in Cases 1–8 (Table 3).

Comparison With Other Vascular Growths

The histologic criteria for the diagnosis of typical dermatofibromas and pyogenic granulomas have been described clearly in standard textbooks and need not be repeated here.[12,25,26]

In electron micrographs, these growths of small blood vessels tend to have a basal lamina that is almost completely continuous and to have a prominent investment of pericytic cells and their cytoplasmic processes (Figures 7–9). The endothelial lining is continuous, and intercellular junctions of the intermediate type are moderately abundant. Dense regions of contact with the basal lamina are common. Gaps between endothelial cells and discontinuities in the basal lamina tend to occur only at the most peripheral superficial zone in pyogenic granuloma. Such discontinuities are not observed in dermatofibromas.

Lymphatic vessels in pyogenic granulomas and stasis dermatitis bear the closest resemblance in en-

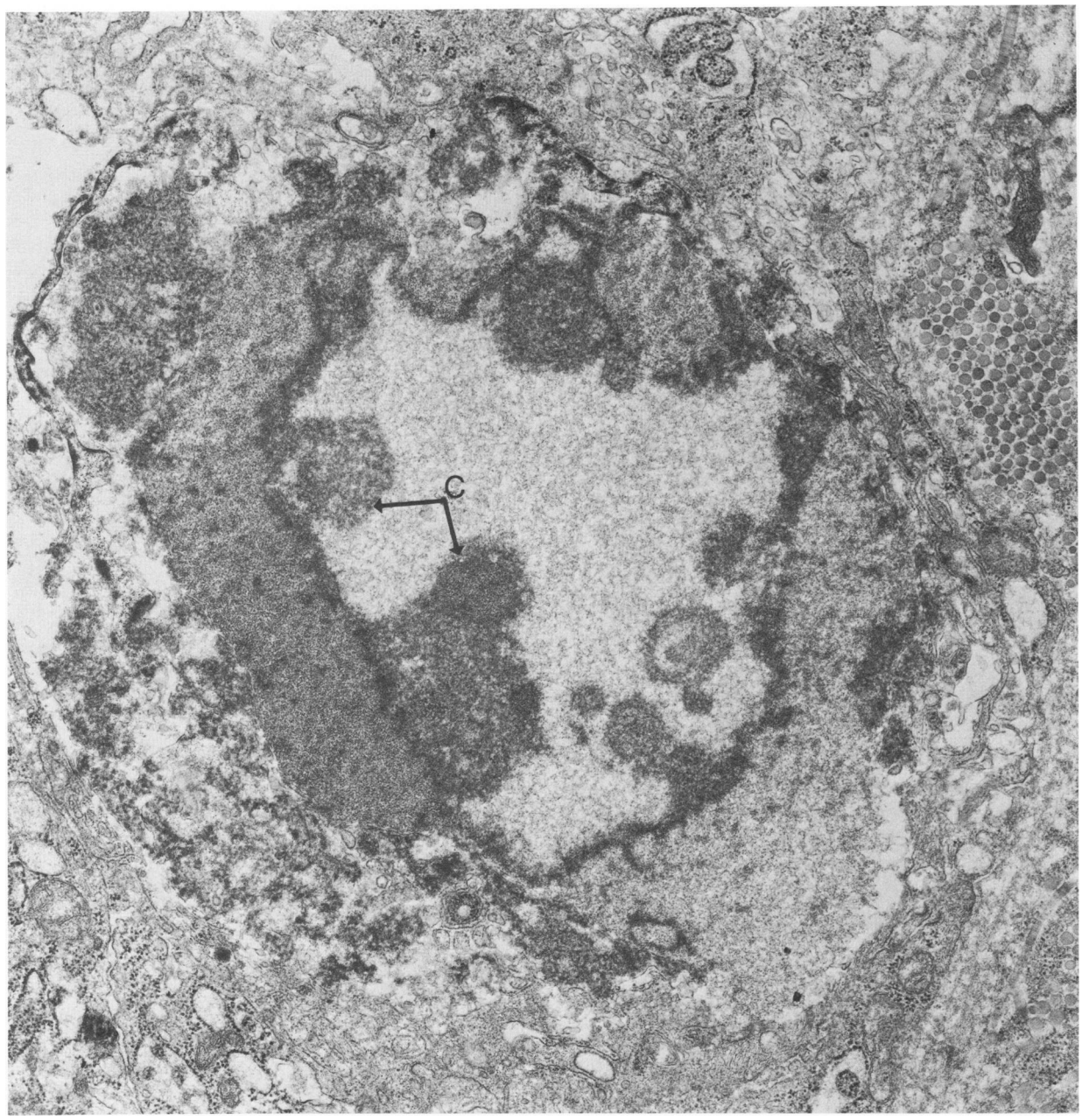

Figure 4—Kaposi's sarcoma. This necrotic cell in the tumor cell aggregates has chromatin condensation (*C*) and cytoplasmic fragmentation. The size of the cell suggests it is a necrotic endothelial cell. Such cell necrosis was observed before treatment only in rapidly progressive cases of Kaposi's sarcoma (Case 2). (× 18,500)

dothelial cells of KS (Figure 10). They both have irregular lumens and thin attenuated cytoplasm, lack a distinct basal lamina, and have few dense intercellular junctions as well as a markedly decreased to absent pericyte layer. The benign lymphatics differ from the KS vessels in that the benign lymphatics have an almost complete endothelial lining except for interendothelial gaps 1 μ or less and otherwise tend to have extensively overlapping cell borders (Figure 10). Also, necrotic endothelial cells are not found. Basal attachment densities are prominent (see Table 3).

Pericytes may be lost in telangiectasia induced by the topical application of 1,3-bis(2-chlorethyl)1-nitrourea (BCNU) to the skin, as in the treatment of cases of mycosis fungoides[27] (Figure 11). Despite the loss of pericytes, the basal lamina is prominent and focally thickened (Figure 11). The endothelium is continuous.

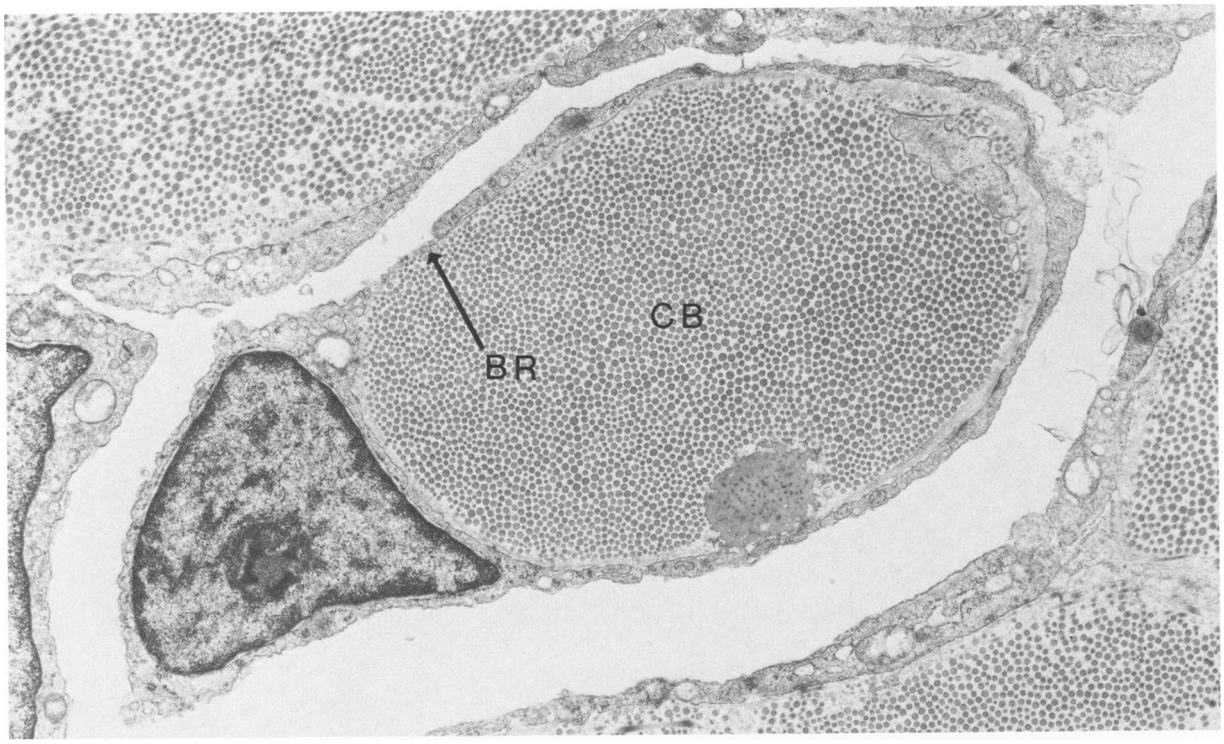

Figure 5—Kaposi's sarcoma (elderly female heterosexual). This irregular vascular channel is formed by endothelial cells, which wrap around individual collagen bundles (*CB*) (seen in cross-sections) and have breaks in continuity (*BR*). Pericytes are absent. The border of the cytoplasm with the collagen tends to be smooth (compare with Figure 6; Case 11). (× 10,600)

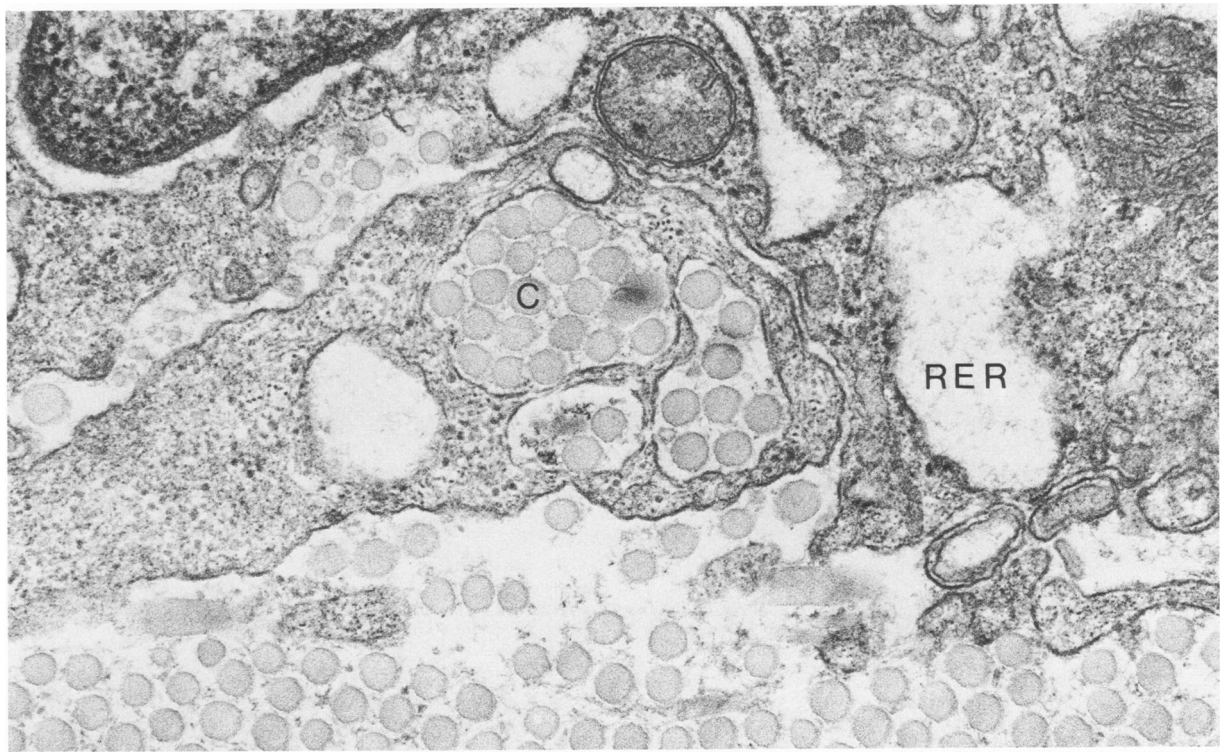

Figure 6—Kaposi's sarcoma (in young male homosexual). The border of the tumor cells with the collagen occasionally shows aggressive infiltration of the edge of collagen bundles, so that there is segregation of small groups of fibers, some of which have a small diameter, as can be seen in these cross-sectioned collagen fibers (*C*) (compare with Figure 5). Such entrapment of collagen fibers was seen only in rapidly progressing cases of Kaposi's sarcoma. Somewhat dilated cisternae of rough endoplasmic reticulum were frequent (*RER*). Basal lamina is absent (Case 8). (× 42,300)

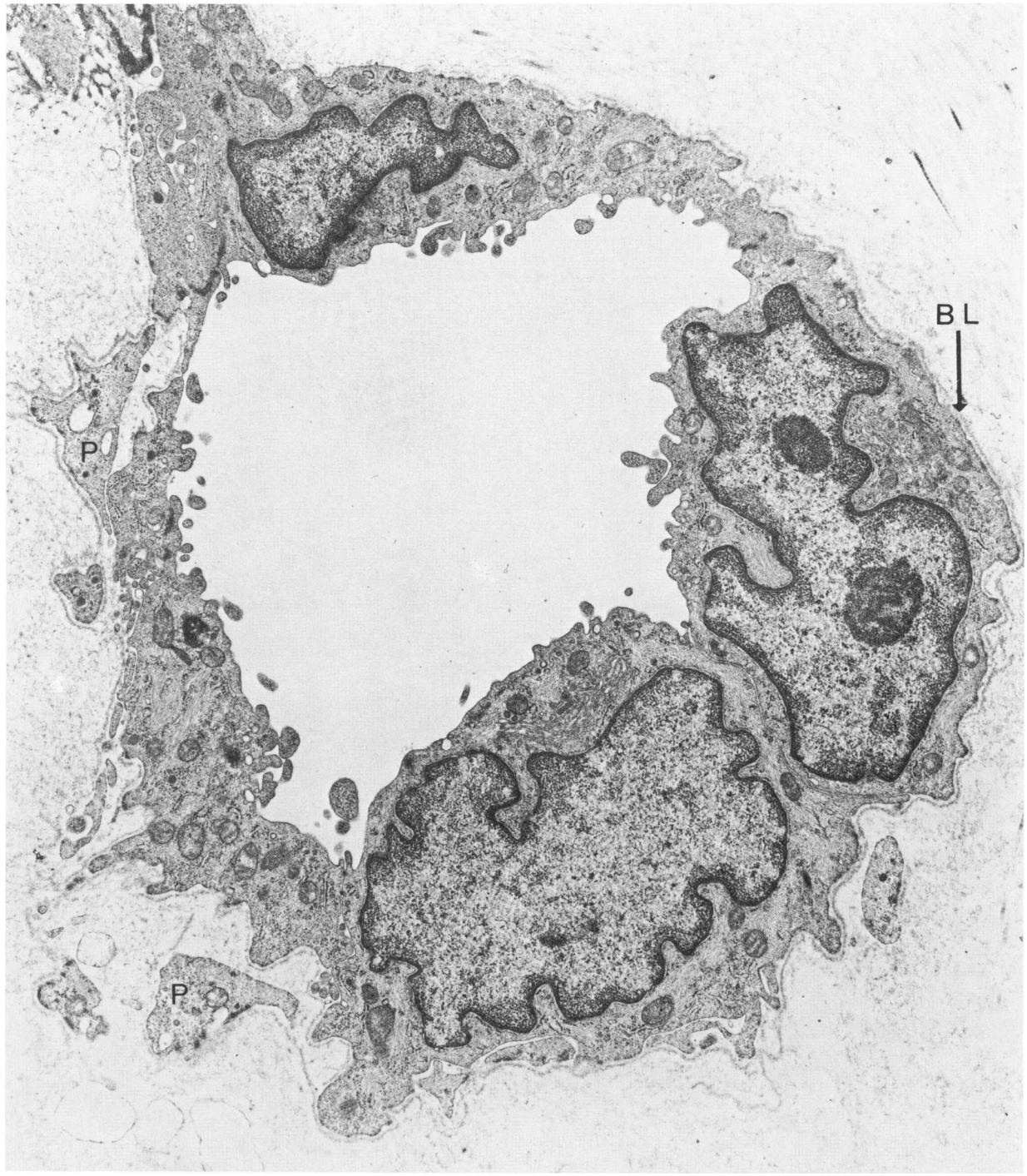

Figure 7—Dermatofibroma. Although the nuclei in this blood capillary are somewhat pleomorphic in appearance, the endothelium is continuous, as is the basal lamina (*BL*). Pericyte processes are also present (*P*) (Case 20). (×11,400)

Discussion

Previous reports on the ultrastructure of KS lesions have dealt primarily with the evaluation of the possible cell of origin of the distinctive spindle cell component in the tumor nodules in this disease. Most recent evidence favors an origin of the cells in KS from blood vascular walls rather than from Schwann cells, fibroblasts, or reticuloendothelial cells.[28-32] Other investigators have concluded that the distinctive irregular vascular networks that are typical of the early KS lesions may arise from the endothelial cells

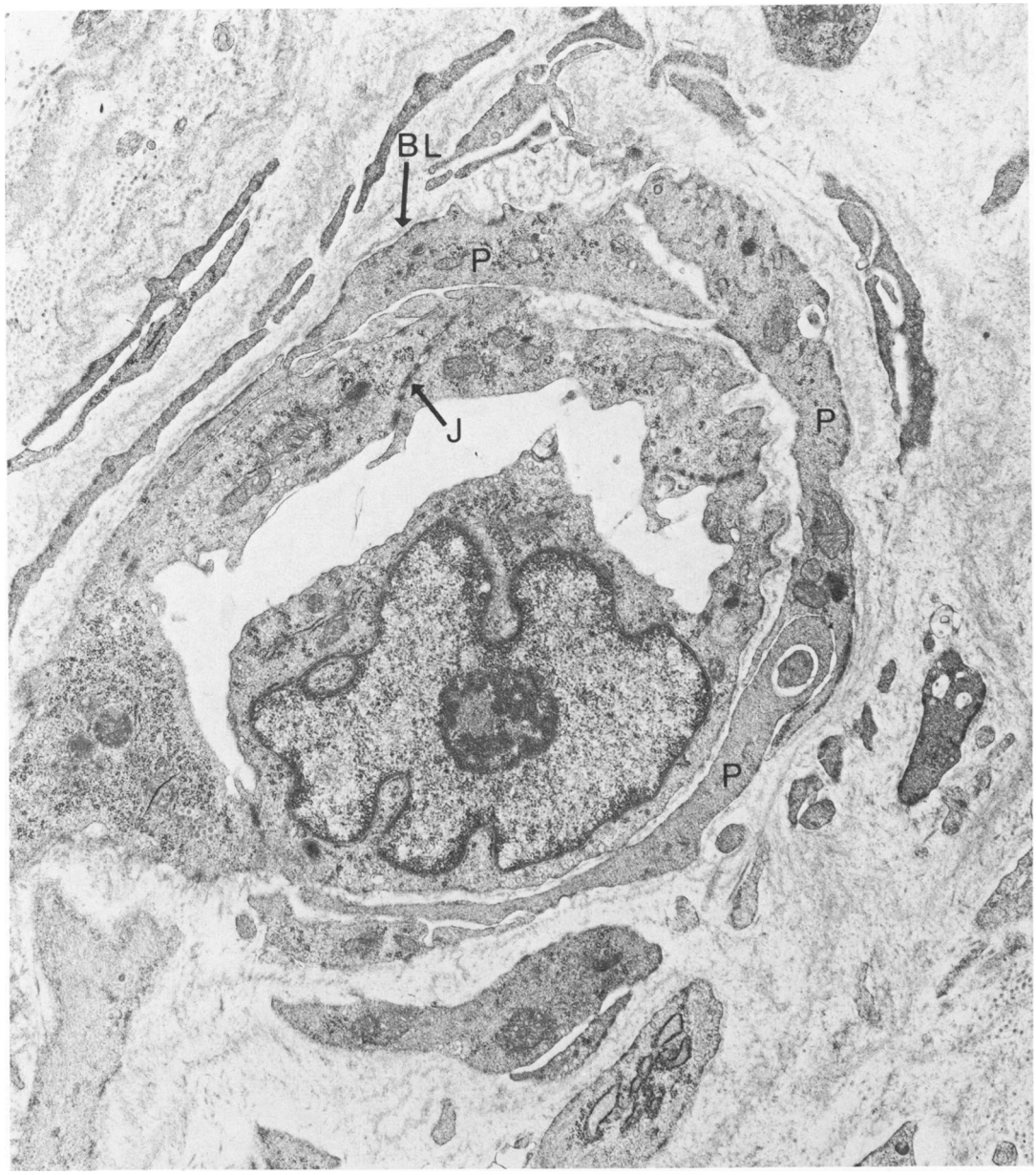

Figure 8—Stasis dermatitis, hypertrophic type. This blood capillary has a very prominent investment of pericytic cell processes (*P*) and a continuous basal lamina (*BL*). Intercellular junctional densities are prominent (*J*) (Case 32). (×11,600)

of either blood vessels or lymphatics.[33] The spindle cells have been considered to have been derived from either endothelial cells or perithelial cells or even from an angiogenic stem cell capable of differentiating into both endothelial cells and pericytes.[29,30]

In this study we have concentrated on the early angiomatous lesions of KS in an attempt to learn whether there are differences in these lesions which correlate with the aggressiveness of the behavior of the KS in terms of the rapidity of the spread of the lesions clinically. We were unable to find unequivocal ultrastructural features that correlated with the rapidity of the spread of KS. One of the inherent problems is that KS skin lesions follow varying rates of progression in both the young homosexual and the old heterosexual patients and do not allow a simple type of comparison. There was some suggestion that extensive endothelial cell projections around collagen fibers were found in some very actively spreading lesions of KS, but these were not found in all cases and were present in both homosexual and heterosexual patients. Necrotic endothelial cells were noted only in

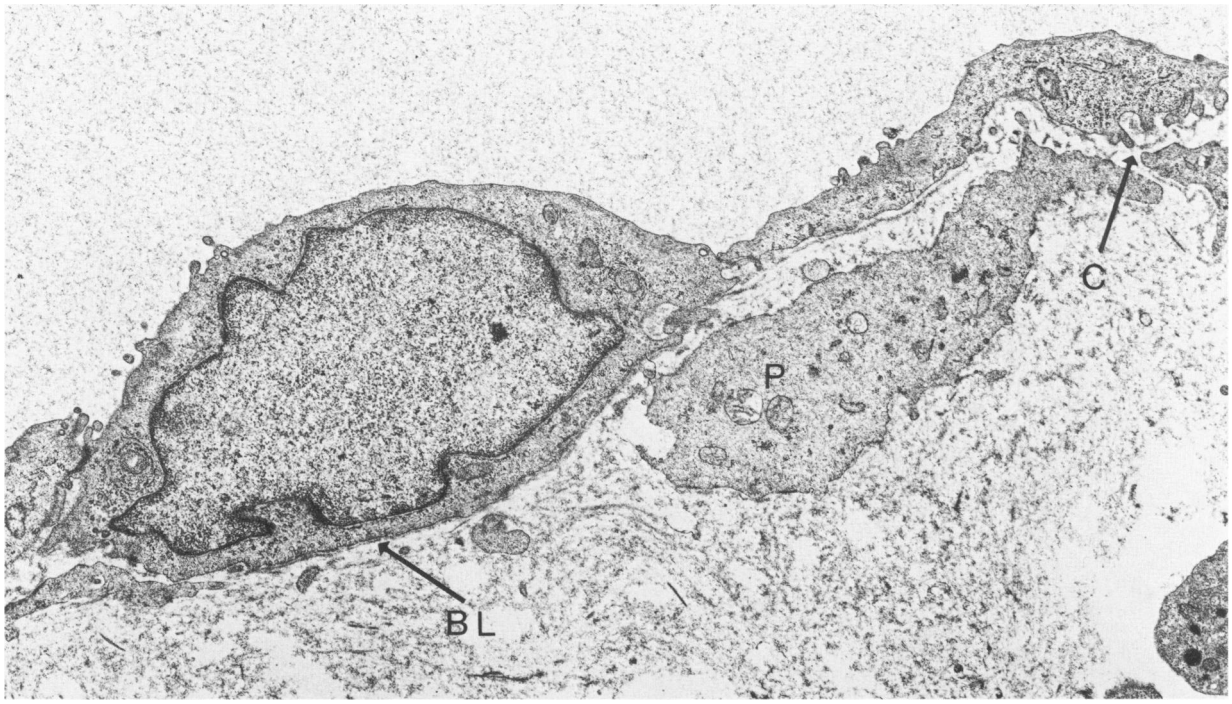

Figure 9—Pyogenic granuloma. Throughout most of their extent, the blood vessels have a continuous endothelium with only small open clefts between cells (*C*). Basal lamina (*BL*) is moderately abundant, as are pericyte cell processes (*P*) (Case 26). (×9,200)

biopsy specimens from early KS in the homosexual patients but were not a very striking finding in all cases. When all types of KS were compared with benign vascular growths, the main differences noted in KS were marked reduction in dendritic pericytes and their cytoplasmic processes in the small vessels; frequent discontinuities in the endothelial lining; striking reduction in the amount of basal lamina; endothelial cell projections enclosing collagen fibers; and necrosis of individual endothelial cells in untreated lesions. These features were demonstrated easily in routine transmission electron microscopic studies of KS biopsy specimens.

Endothelial discontinuity could be found in some

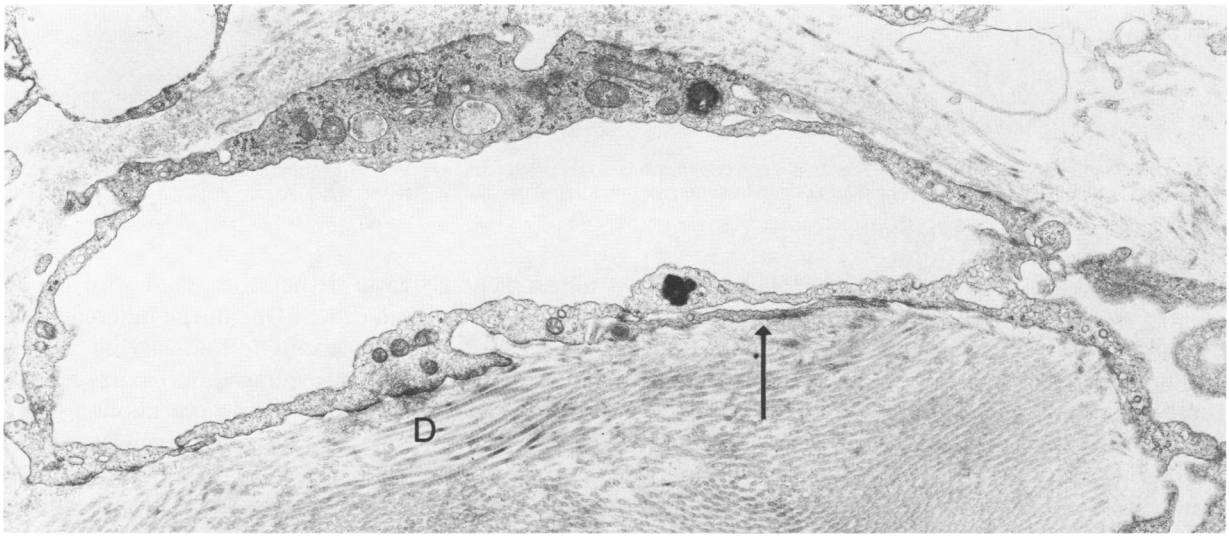

Figure 10—Stasis dermatitis. This lymphatic channel has a wall structure very similar to blood vessels in Kaposi's sarcoma. Basal lamina and pericyte processes are inapparent. Intercellular junctions are small and very sparse. However, the endothelium is continuous and has overlapping cell borders (*arrow*). Basal densities (*D*) are more prominent than in most Kaposi's blood vessels (Case 33). (×9,600)

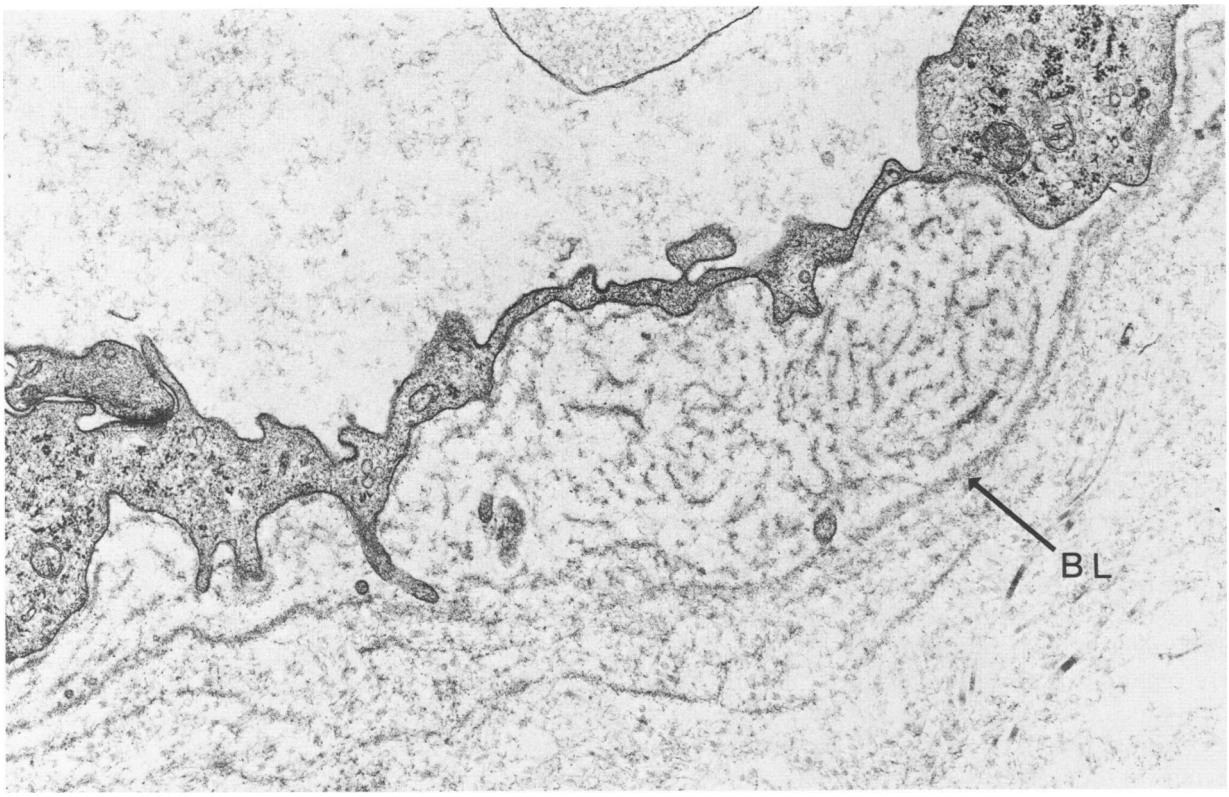

Figure 11 — Telangiectasia (secondary to topical chemotherapy). This blood capillary has lost pericytes and has a focally thickened basal lamina (*BL*), which is continuous. The endothelium is continuous (Case 38). (×21,200)

instances in benign lesions in very limited regions but was found throughout the lesion only in KS. For example, endothelial discontinuities were found where there was intense inflammation at the surface of pyogenic granulomas. Similarly, endothelial lining discontinuities at the tips of vascular sprouts have been demonstrated by Schoefl,[34] using vascular labeling techniques as well as ultrastructure, in studies of growing blood vessels, in response to corneal injury.[35] The differences between KS and granulation tissue are readily apparent at the ultrastructural level.

The great reduction in prominence of dendritic pericytes is also a readily apparent difference between KS and most of the benign lesions, when the structures of the smallest blood vessels are compared. The dendritic pericytes are inapparent in many sections of many of the small vessels, so that a reasonable assumption is that they are absent from at least some regions of many of these vessels. In normal capillaries the dendritic nature of the pericytes and their relationship to the capillary walls have been clearly defined anatomically.[36] Pericytes are closely apposed to the basal lamina of the endothelium and also have a similar coating on their surface, so that the basal lamina of the capillary appears to split to enclose the pericyte and its processes.[37] Lymphatic capillaries lack a prominent basal lamina and lack dendritic pericytes.[36] Their lumens also have irregular shapes. These features occasionally make it difficult to distinguish the small blood vessels in KS from lymphatic channels. Leak[38] has reviewed the distinctive ultrastructural features of lymphatic capillaries and has noted that their endothelium forms dense attachment structures that contact fine reticulin fiber bundles. These serve to hold lymphatic channels open during edema. Normal lymphatics also have small discontinuities in their lining and have endothelial cells that form overlapping cell borders with few dense intercellular junctions. KS vessels usually lack overlapping cell borders and specialized dense attachments to reticulin bundles in electron micrographs. The morphologic similarity between patch stage KS vessels and lymphatics is also occasionally striking at the light-microscopic level when the KS vessels contain few erythrocytes and have an associated collection of small lymphocytes and plasma cells.[13,33] The striking similarities in structure between KS vessels and lymphatics have additional implications, in that some cases of KS appear to involve the lymphatic system. The high frequency of lymph node involvement by

cutaneous KS and the occasional primary lymph node KS case can be interpreted to imply an origin of KS in lymphatic vessels.[39,40] Cox and Helwig[2] observed that 13 of their 50 cases of KS had pronounced lymphedema, which preceded the KS in 7 of the 13 patients. Other authors have also pointed to the close resemblance between KS and the lymphangiosarcoma which arises in long-standing lymphedema.[1] The distinction between the vessels in KS and lymphatic endothelium has been clarified by the demonstration that the cells lining vessels in KS stain for Factor VIII-related antigen and for alkaline phosphatase in a manner similar to that of blood vessel endothelium.[30-32]

It is clear that there are blood capillaries in KS that have a continuous basal lamina and an investment of dendritic pericytes; however, these are infrequent and may represent normal tissue components entrapped by the neoplastic tissue or else carrying blood into and away from the vascular neoplasm. Observations similar to ours on the loss of dendritic pericytes were reported in a case report by Schmoeckel and Braun-Falco.[41] In contrast, others have emphasized the presence of pericytes in cases of cutaneous angiosarcoma of the scalp.[20] Some confusion is introduced when authors use the term pericytic cells to refer to any cells adjacent to the blood vessels that have a fibroblastic appearance even when they lack basal lamina and are not dendritic. Also, speculation that the spindle-cell component of KS tumor nodules is derived from pericytes has obscured the fact that most of the small vessels of KS lack an investment of dendritic pericytes.

An early stage in the development of embryonic capillaries involves another type of blood vessel that resembles the small vessels of KS at the ultrastructural level, particularly with regard to the lack of basal lamina and the absence of pericytes. This has been shown most clearly in a few tissues that offer a precise sequence of capillary development.[42]

With the exception of the toxin-induced telangiectasia in Case 35, the lack of dendritic pericytes is a very helpful feature in the diagnosis of KS. In Case 35, the pericytes were destroyed presumably by the locally high dose of chemotherapeutic agent. It is interesting that a similar dilation of capillaries occurs in retinal vessels in diabetes, so that microaneurysms are formed at sites of destruction of pericytes.[43,44] It is tempting to speculate that the loss of pericytes in the proliferating blood vessels in KS leads to the formation of a network of numerous ectatic anastomosing blood vessels, which have a wall structure resembling lymphatics.

There is little doubt that the KS arising in young homosexual men is an aggressive variant of the disease. Interestingly, McCarthy and Pack[1] state that there was no relation in their cases between the age of the patient and the activity of the disease. However as mentioned in the Introduction, Cox and Helwig[2] noted that their series showed a higher mortality under age 45. Hansson[45] also had the opinion that KS progressed more rapidly in the young age group in his series of 23 patients.

Hemosiderin deposition was relatively slight in patients in this series, perhaps since the lesions from which biopsy specimens were taken tended to be on the trunk, upper arm, or upper thigh, rather than on the lower leg. Cox and Helwig[2] compared the amount of hemosiderosis in biopsy speciments of KS according to site and concluded that the more dependent parts of the body had the greatest hemosiderosis.

Other ultrastructural studies have emphasized the presence of abundant erythrophagocytosis by endothelial cells as a distinguishing feature of Kaposi's sarcoma when compared with angiosarcoma of the scalp[20] as well as benign lesions.[47] In our study, hemosiderosis and erythrophagocytosis were not striking features of KS in the homosexual population, perhaps due to biopsies being of early patch lesions and from locations other than the lower legs.

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Acknowledgment

We thank the many attending physicians and residents who obtained biopsy material in this study and particularly Helen Scheitinger, RN, for coordination of clinical data from the Kaposi's Sarcoma Study Group, University of California, San Francisco. The valuable technical assistance of Mr. Noel Taylor, Ms. Ann Francisco, and Ms. Elizabeth Juhasz made this study possible.