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Ultrastructural development of Kaposi's sarcoma in relation to the dermal microvasculature

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Summary. Ultrastructural subtypes of endothelial cells in Kaposi's sarcoma were compared with lymphatics and the normal dermal microcirculation in different stages of lesional development. In the earliest patch stage, lymphatic channels, recognised by their dissecting growth pattern and a lack of a basal lamina and pericytes, were prominent. Venous endothelium was recognised by virtue of its multilaminated basal lamina and often showed markedly irregular luminal and abluminal cytoplasmic projections. As the histological stage progressed toward spindle cells, venous endothelium showed a tetrad of changes: dissolution of the basal lamina; fragmentation and disappearance of the pericyte sheath, decreased and often rudimentary intercellular junctions and markedly reduced numbers of Weibel-Palade bodies. These were also features of spindle cells, which were rarely seen to emerge from narrow vascular channels of indeterminate type. Spindle cells showed sparse intercellular junctions and minimal basal lamina but no Weibel-Palade bodies. These progressive venous alterations thus resulted in a mixed intermediate subtype of endothelium with the morphological traits resembling lymphatics as well as venous blood vessels. The mixed subtype included endothelial tubes surrounded by a complete basal lamina but lacking pericytes, and much more commonly, tubes with pericytes but a scanty basal lamina. Both forms had remarkably few or no Weibel-Palade bodies. In the spindle cell stage, normal vessels were largely replaced by the mixed subtype and an indeterminate type of frequently disrupted endothelial tube which lacked a basal lamina as well as a pericytic investment. Dissecting lymphatic channels could not be confidently distinguished from the latter vessels. Direct anatomical connections between morphologically recognizable lymphatics and venules, blood capillaries or endothelial tubes of mixed subtype were difficult to demonstrate. Lymphaticovenous shunts were represented by gaps in all endothelial subtypes, the gaps sometimes due to cell degeneration.

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Introduction

Kaposi's sarcoma (KS) is a multicentric endothelial proliferation which may develop spindle cell morphology. Histological (Dictor 1986), histochemical (Dorfman 1962; Beckstead et al. 1985) and immunohistochemical (Dictor and Andersson 1988; Holden 1989) studies have suggested involvement of both lymphatics and blood vessels. Lymphatic blockage and shunting between the two vascular systems have been detected by angiography (Palmer 1972) and are also consistent with the recent results of lymphangioscintigraphy using intradermal radioactively labelled albumin (Witte et al. 1990). To explain the morphological basis of these observations, we studied the vascular components of KS lesions in successive stages and traced the development of spindle cells in electron microscopic sections. In particular, attention was directed to those morphological attributes of different types of blood vessels which allow their distinction from each other and from lymphatics (Ghadially 1988).

The microcirculation of normal skin may be divided into segments, each with characteristic histological features: superficial and deep arteriolar and venular plexuses, ascending arterioles, terminal arterioles, arterial and venous capillary loops, post-capillary venules and descending collecting venules (Yen and Braverman 1976; Braverman and Yen 1977; Higgins and Eady 1981). Intermeshed with the microcirculation are lymphatic capillaries which begin as blind tubes in the papillary portion of the dermis, form a superficial lymphatic plexus and contain valves (Daróczy 1988). Blood capillary endothelium has numerous tight junctions and is surrounded by a complete basal lamina but a discontinuous layer of pericytes. Venular endothelium shows irregular luminal and abluminal surfaces on ultrastructural study and round or indented nuclei unlike the elongated nuclei of

Table 1. Ultrastructural features of normal dermal microcirculation and lymphatics

	Smooth muscle	Pericyte sheath	Elastic lamina	Basal lamina	Endothelial margins	Weibel-Palade bodies	Cell junctions
Ascending arteriole	Single or multiple layers	None	Present	Continuous	Smooth	Occasional	Numerous, well-formed
Superficial arteriolar plexus	Single or multiple layers	None	Present	Continuous	Smooth, elongated nuclei	Occasional	Numerous
Terminal arteriole	One layer (or pericytes)	Complete (or smooth muscle)	None in smallest vessels (10–15 μm outer diameter)	Continuous	Smooth, elongated nuclei	Occasional	Numerous, including between endothelium and pericytes
Arterial capillary	None	Discontinuous	None	Homogeneous, delimited by veil cells	Smooth	Occasional	As above
Venous capillary	None	Discontinuous	None	Multilaminated	Microvilli	Frequent	As above
Postcapillary venule	None	Complete	None	Multilaminated	Irregular projections	Frequent	As above
Superficial venular plexus	None	Complete	None	Multilaminated	Irregular projections	Frequent	As above
Descending venule	Single or multiple	None	None	Multilaminated	Irregular projections	As above	Present
Lymphatic capillary	None	None	None	Usually lacking	Smooth	None in post-embryonic cells	Sparse, frequent gaps

relatively uniform arteriolar endothelium. Post-capillary venules and venules of the superficial plexus are furthermore invested with a complete layer of pericytes which in arterioles and descending venules are replaced by smooth muscle. An incomplete elastic lamina lies beneath endothelium in larger arterioles, but the elastic lamina is not found in small terminal arterioles (10–15 μm outer diameter) or venules. Venous capillaries and venules are further characterised by multilamination of the basal lamina, which according to Higgins and Eady (1981) is the most consistent criterion for distinguishing venous from arterial endothelium.

Normal adult dermal lymphatic capillaries show a discontinuous or absent basal lamina and lack pericytes. Lateral cell borders generally have few junctions and frequent small gaps (<1 μm). Adult lymphatic capillaries also lack the rod-shaped microtubulated body of Weibel and Palade, an organelle restricted to normal post-embryonic blood vessel endothelium (Ghadially 1988) and shown by immunoelectron microscopy to concentrate factor VIII-related antigen (Warhol and Sweet 1984). The above vascular features are summarised in Table 1.

Materials and methods

Punch biopsies of the skin were obtained from the limbs of 14 patients with clinically and pathologically confirmed KS. All but 1 were male and they ranged in age from 36 to 86 years. One elderly patient had diabetes mellitus and 3 patients had the acquired immunodeficiency syndrome (AIDS). No patient had received systemic anti-tumour treatment or radiation therapy for the lesions prior to biopsy. Patient age, sex, biopsy site and histological staging (vide infra) are given in Table 2.

Biopsy specimens were immediately divided into 1 mm^3 cubes using razor blades and fixed in either 2% glutaraldehyde for 4 h or in 2% paraformaldehyde-lysine-periodate for an equivalent time. Material was then post-fixed in 2% osmium tetroxide, dehydrated in graded ethanol, cleared in ethylene propoxide and embedded in Epon. Semi-thin sections were cut at 1.5 μm and stained with

Table 2. Clinical data and histological stages

Case	Sex/age (years)	Site	Stage
1	M/72	Lower leg	1
2	M/39	Leg (AIDS)	1
3	M/71	Foot	1
4	M/64	Elbow	1
5	M/55	Thigh	1
6	M/39	Lower leg (AIDS)	1
7	M/77	Lower leg	1 (sclerosis)
8	M/75	Lower leg	1, 1t2
9	F/74	Lower leg	1, 1t2, 2
10	M/83	Lower leg	1t2
11	M/75	Lower leg	1t2, 2
12	M/69	Trunk	1t2, 2
13	M/86	Foot	2
14	M/36	Thigh (AIDS)	2

toluidine blue. Only areas with minimal lymphoid infiltrates were sectioned and overall these included superficial, mid-dermal and deep regions. Selected blocks were chamfered to a mesa, sections from which were cut and floated onto a single-hole copper grid covered by a Formvar membrane. These allowed montages of electron micrographs to be made for more precise anatomical orientation. Larger sections from the preserved face of the block were placed on copper net grids. All sections were contrasted in uranyl acetate and lead citrate. A total of 30 blocks were examined, generally 1–3 per patient, in a Zeiss EM 10 at a magnification between ×2,000 and ×10,000.

Each semi-thin tissue section was grouped according to histological stage using previously published criteria, with modifications (Dictor 1986). Briefly, stage 1 is characterised by variable proliferation of small blood vessels and dissecting lymphatic-like vascular channels without nuclear atypia. Stage 2 is the coalescent spindle cell nodule with vascular slits. The transition between these two stages (1t2) is recognised by the emergence of short spindle cell aggregates 3–4 cells thick, often accompanied by collapse of lymphatic channels. Our material included 16 blocks of stage 1, 5 of stage 1t2 and 6 of stage 2 KS.

Results

In semi-thin sections of stage 1, the two most conspicuous types of vessel were small round endothelial tubes enclosed in either a loose or continuous pericyte sheath, and wide irregular channels, with or without blood, which lacked pericytes and dissected between collagen bundles (Fig. 1a). Only in rare instances was an elastic lamina demonstrated and then only in large arterioles.

In the electron microscope, the dissecting channels were lined by a single thin endothelial layer resting often directly upon collagen or elastic fibres and only occasionally separated from them by a short stretch of basal lamina (Fig. 1b). In places, thin cytoplasmic endothelial bands (as opposed to valves) traversed the lumen. Nuclei were often elongated parallel to the axis of the channel or projected peg-like into the lumen. Elastin was frequently present along the walls of the lymphatic-like channels. The endothelial cells of these channels occasionally showed erythrophagocytosis and contained ferritin granules which were also present in subjacent fibroblasts. The endothelial cells contained some rough endoplasmic reticulum, a few mitochondria and, periodically, lateral interdigitations, in addition to end-to-end and overlapping cell borders. Anchoring filaments did not generally appear about these channels. The ultrastructure of irregular channels thus corresponded most closely to lymphatics, although with variation in nuclear size, shape and orientation.

Endothelial tubes juxtaposed to the dissecting channels were lined by a single cell layer enclosed by either a continuous or multilaminated basal lamina in which pericytes were embedded (Fig. 2a). A prominent feature was highly irregular cytoplasmic projections frequently covering the luminal, and more strikingly, the abluminal surface (Fig. 2b). Endothelial cells often appeared to occlude the lumen, but this effect may be noted in sections of the normal microcirculation. The majority of intact endothelial tubes resembled arterial or venous capillaries, post-capillary venules and collecting venules, venous structures being predominant. The dendritic pericyte processes appeared often splayed and atrophic. In places, they disappeared, which ultimately produced rare tubes lined by a thin endothelium and enclosed by a

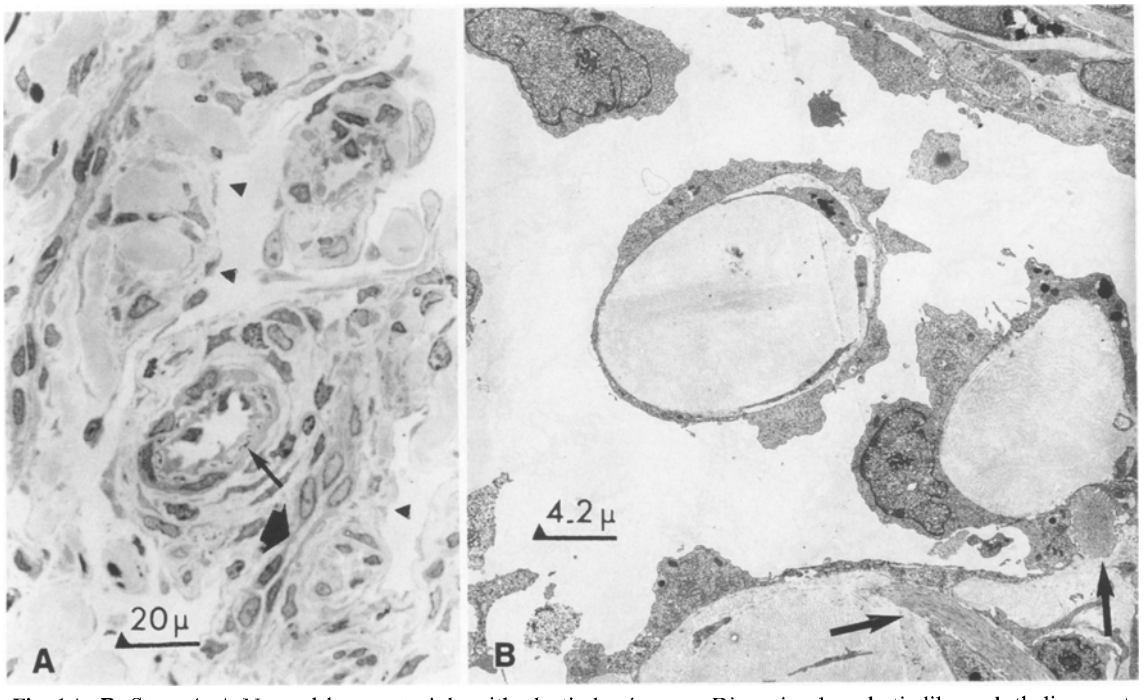


Fig. 1A, B. Stage 1. **A** Normal large arteriole with elastic lamina (*long arrow*) is juxtaposed to irregular dissecting endothelial clefts (*arrowheads*) and longitudinally sectioned capillary-like structure (*short arrow*); case 5, semi-thin section, toluidine blue, ×480. **B** Dissecting lymphatic-like endothelium rests on collagen or elastin (*arrows*) and has a thin cytoplasm, overlapping and end-to-end cell borders and no distinct basal lamina; case 3, ×2,400

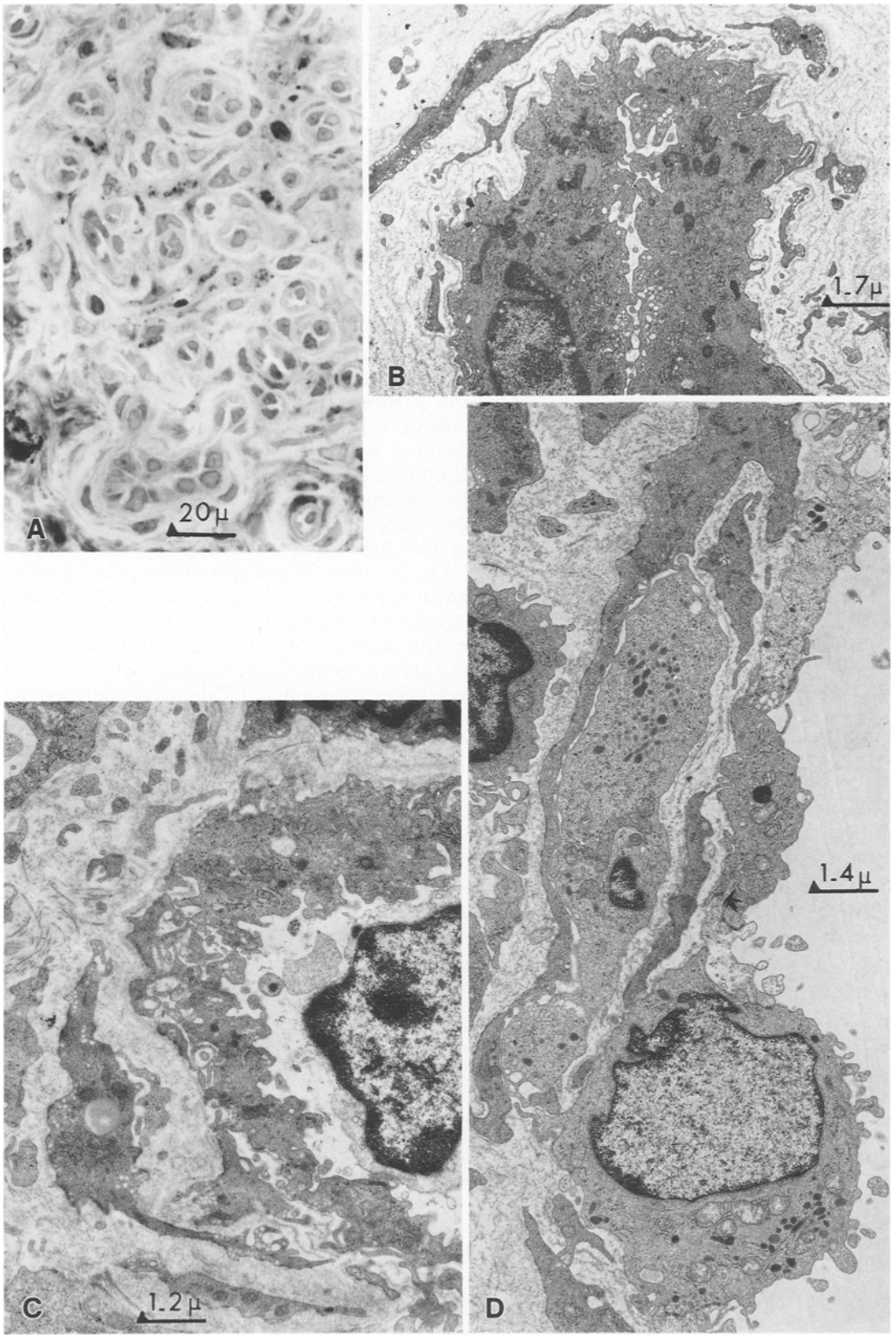


Fig. 2A–C. Stage 1. **A** Numerous closely spaced vessels resemble blood capillaries and venules; case 3, semi-thin section, toluidine blue, ×480. **B** Venous endothelium shows distinct multilaminated basal lamina, decreased pericyte processes and irregular endothelial borders suggesting a venule; case 4, ×6,000. **C** Indistinct laminations surround a venule with exaggerated cytoplasmic projections; case 5, ×8,670. **D** Stage 1t2. Venous endothelium appears to dissect between pericyte processes, which show subplasmalemmal dense plaques and a rich complement of microfilaments; case 12, ×6,900

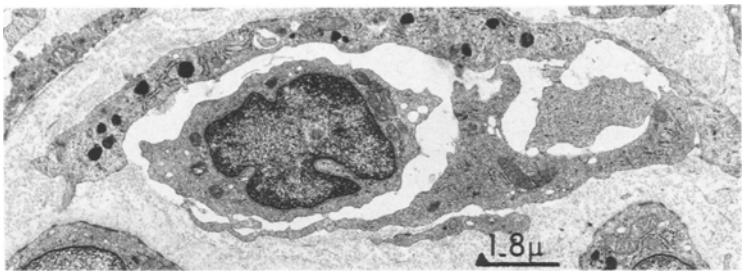


Fig. 3. Endothelial cell of indeterminate subtype with a large gap in the wall is devoid of a basal lamina, pericyte sheath and Weibel-Palade bodies; case 8, ×5,500

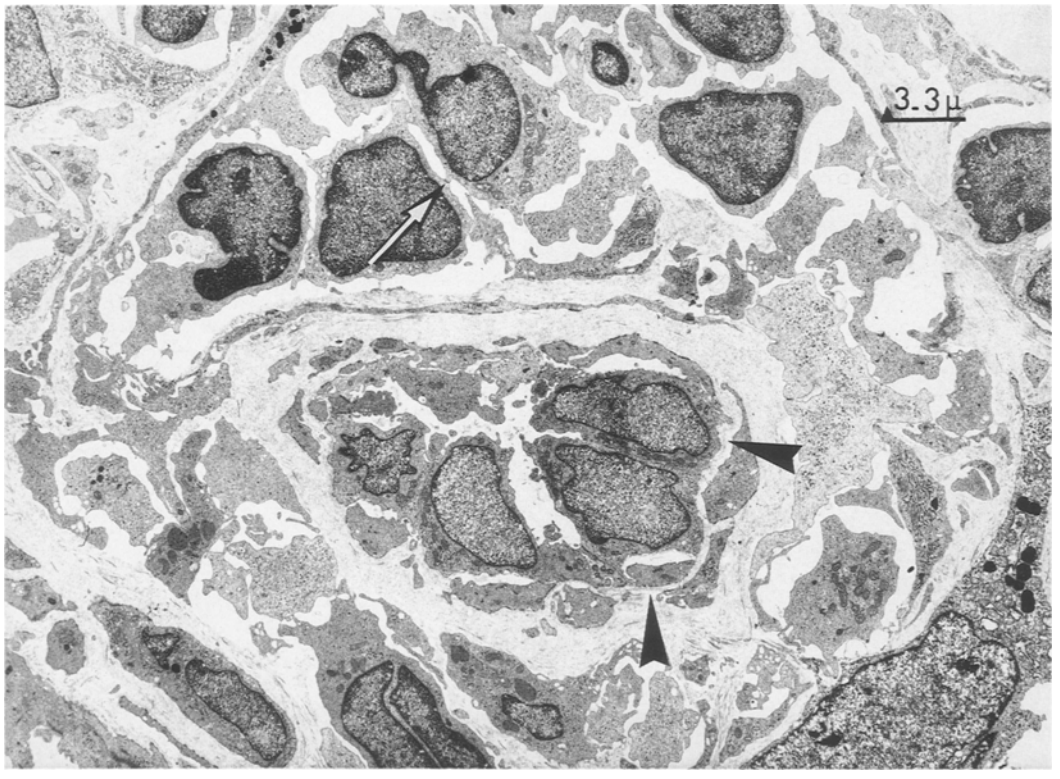


Fig. 4. Stage 1t2. Glomeruloid structure with a central vessel of mixed subtype, probably derived from venous endothelium. Pericytes surround the vessel which contains only short stretches of basal lamina (*arrowheads*). The collapsing circumferential lymphatic space contains lymphocyte-like degenerating endothelial cells connected by occasional poorly formed junctions (*arrow*); case 8, ×3,000

complete basal lamina only. Much more commonly, a discontinuous pericyte sheath was accompanied by a basal lamina which had an indistinct flocculent appearance or was disrupted or missing (Fig. 2c). Rarely, tongues of apparent endothelium extended between pericyte processes, suggesting dissection of some cells beyond the vessel proper (Fig. 2d).

In terms of the degree of change in these two major morphological traits, basal lamina and pericytes, such variants comprised a mixed subtype. This displayed only a few rudimentary cell junctions. In spite of the fact that the mixed subtype arose mainly from blood capillaries and venules, Weibel-Palade bodies were difficult to find. In the lymphatic channels, large intercellular gaps were particularly common, but gaps were also observed in rare endothelial tubes which lacked pericytes as well as basal laminae (Fig. 3). The specific origin of this indeterminate subtype could not be resolved, since it might represent either the irregular dissecting channels after marked narrowing or further evolution of the mixed subtype.

Transition to early spindle cells in stage 1t2 was marked by a general increase in cellularity and collapse of the irregular channels, including glomeruloid structures (Fig. 4). Rarely, the endothelium lining vessels in stage 1 was replaced by foci of spindle cells (Fig. 5a). Polyribosomes became numerous in some cells, and in two cases of non-AIDS KS, the cytoplasm was alternately rarefied or condensed as more degenerated endothelial cells were shed into the lumens both of lymphatic channels and venules. Early spindle cells showed few or no junctions, and basal lamina was minimal or absent and sometimes replaced with an indistinct interstitial matrix such as noted about venous endothelium. In the absence of cell junctions, basal lamina or Weibel-Palade bodies, single spindled endothelial cells were difficult to identify as such. Fibroblasts were embedded in a sclerotic matrix with bipolar processes extending often in parallel more than 40 μm and contained dilated rough endoplasmic reticulum and mitochondria.

Within the nodule of stage 2, irregular dissecting channels were no longer identified is semi-thin sections.

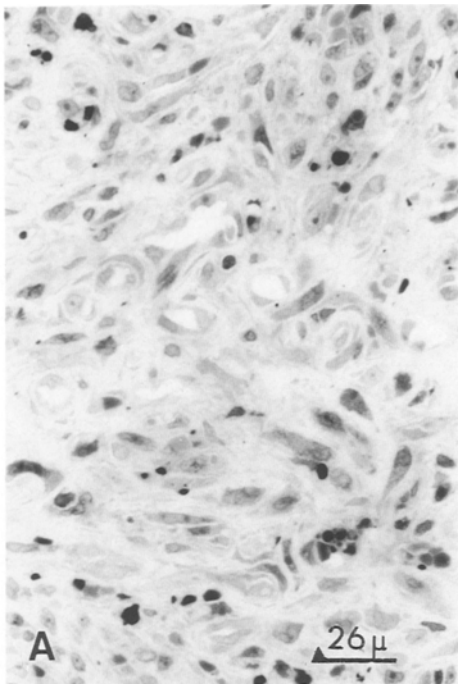
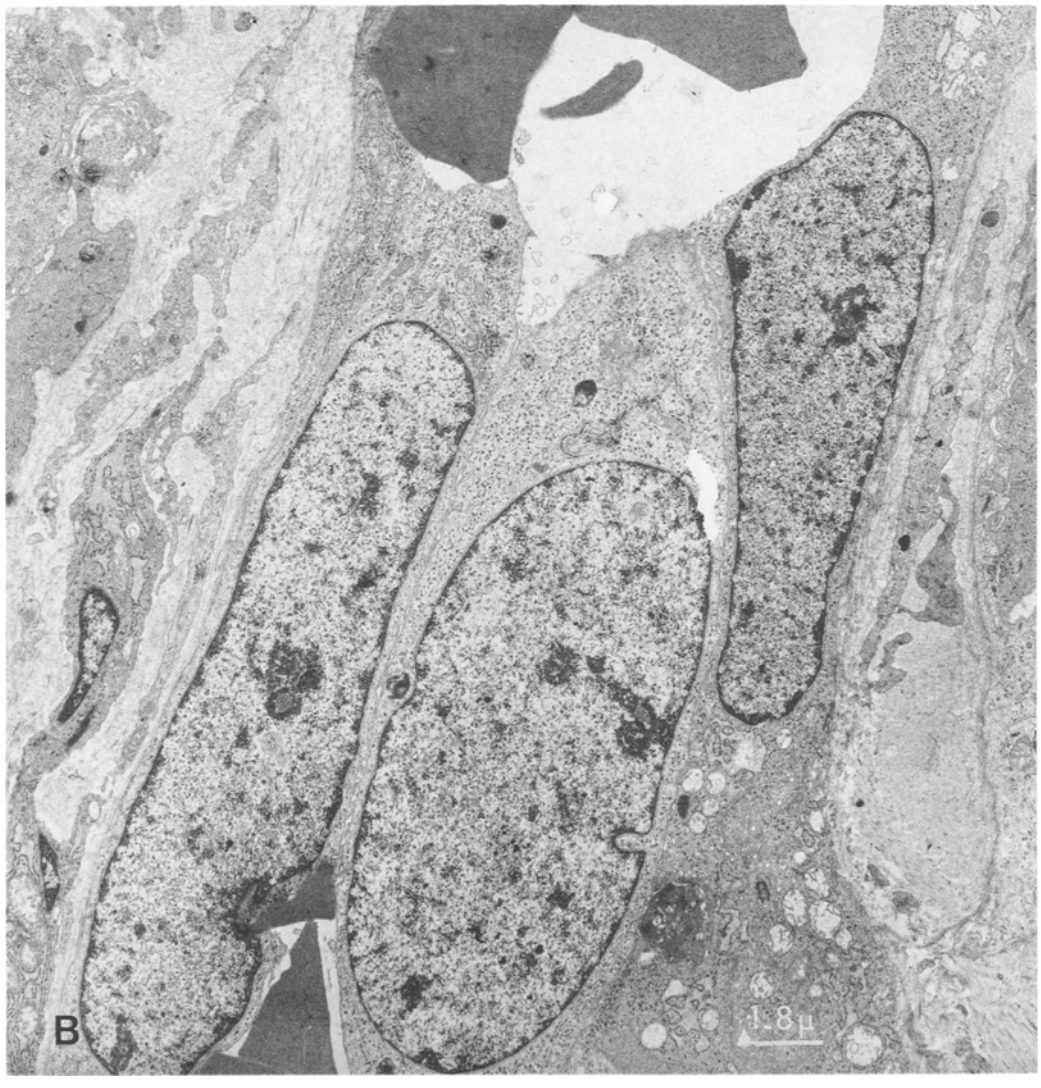


Fig. 5. A Stage 1t2. Spindle cells among capillary-like vessels which often lack pericyte sheaths; case 11, semi-thin section, toluidine blue ×380. **B** Stage 2. Spindle cells lack cell junctions, Weibel-Palade bodies and a basal lamina. They line part of a vascular space which also lacks a basal lamina and pericytes; case 12, ×5,680



Normal blood vessels were relatively sparse, having been replaced by the mixed and indeterminate subtypes of endothelial tubes. Morphologically spindle cells were of various types largely differing in nuclear shape and chromatin density. Some were undoubtedly fibroblasts and others pericytes or degenerative endothelial cells, but in the absence of cell contacts and basal lamina, KS spindle cells were most readily recognised in groups and with dispersed or slightly clumped and thinly marginated nuclear chromatin. They showed features more or less as in stage 1t2 (Fig. 5b). Spindle cells not obviously forming a vascular slit usually lacked cell junctions. In stages 1–2, mast cells and macrophages were present, the latter especially numerous in stage 1t2 in conjunction with the decreasing integrity of the endothelium.

We could thus identify four broad categories of vascular structures varying in frequency between stages 1 and 2: (1) normal vessels of the microcirculation, which diminished in progressive stages and in which capillary and venular characteristics predominated; (2) irregular channels of a lymphatic subtype, which also diminished in time due at least partly to endothelial degeneration and collapse; (3) a type of vessel, most numerous in stage 2, showing mixed features, particularly with respect to the presence or absence of a complete basal lamina and a pericyte sheath, while generally lacking Weibel-Palade bodies; and (4) an indeterminate subtype of narrow sprout-like endothelial tubes, most prominent in stage 2 and lacking both a basal lamina and a pericyte sheath.

Organelles other than Weibel-Palade bodies were similar in type and amount in all endothelial cells. Golgi apparatus, mitochondria, ribosomes, rough endoplasmic reticulum and erythrophagocytosis have been well described (McNutt et al. 1983; Waldo and Sidhu 1988) and were present in varying amounts, but did not allow discrimination of specific endothelial types. Micropinocytosis occurred to a minor extent. Endothelial cells sometimes contained relatively abundant microfilaments but rarely as many as in pericytes or smooth muscle. Subplasmalemmal dense plaques were also found in areas, but were more abundant in pericytes. In lymphendothelium, there were scattered lysosomes and dense bodies containing infrequent barely discernible thick longitudinal striations. Ferritin particles (and in one section even phagocytosed red cells) could be found in lymphendothelium and fibroblasts in the earliest stage as an indication of shunting and destruction of red cells.

No viral particles were found at the magnification used, but endothelial cells in one AIDS case only (case 6) contained tubuloreticular inclusions, as has been described in a variety of autoimmune and viral diseases, including AIDS and virus-induced tumours (Sidhu and Friedman-Kien 1988, Luu et al. 1989).

Discussion

The major fraction of vessels in the superficial plexus of the normal dermal microcirculation is composed of venous endothelium (Yen and Braverman 1976). KS probably does not alter this relative venous predominance and may actually increase it initially, as judged by the lack of elastic-containing arteriolar vessels in stages 1–2 and the marked increase in capillaries and venules in stage 1. Morphological evidence does not thus support a significant role for the proliferation of arterioles. The hallmark of dermal venous endothelium, a multilaminated basal lamina, occurred more often in all stages than the continuous basal lamina of arterial capillary endothelium. In support of an active role for venous endothelium in KS, the normally irregular venous endothelial surfaces (Higgins and Eady 1981) were both frequently covered by exaggerated cytoplasmic projections.

Successive morphological changes involved traits which distinguish blood vessels from lymphatics, an impression also gained from a recent immunohistochemical study of KS by histological stage (Dictor and Andersson 1988). Such changes occurred simultaneously with lymphatic proliferation and indicate a situation more complex than would a suggestion that the initial lesion in KS is sufficiently explained by lymphatic hyperplasia (Brooks 1986). McNutt et al. (1983) described a general diminution in the number and prominence of pericytes, gaps in capillary walls and breaks in the basal lamina, features that we have confirmed and attempted to place in broader chronological perspective. Thus we observed increasing dissolution of the venous basal lamina, diminished pericyte processes and markedly reduced numbers of Weibel-Palade bodies and cell junctions from the earliest stage of lymphatic dissection (stage 1) to the spindle cell nodule (stage 2). In terms of the lymphatic-blood vessel dichotomy, this process resulted in vessels with mixed morphological features.

Other proliferating vessels in the early lesion conformed to lymphatic capillaries morphologically, as previously described (McNutt et al. 1983). The endothelial cells lining these channels were not surrounded by pericytes, showed scarcely any basal lamina, rarely had prominent abluminal densities along the cell membrane and sometimes interdigitated with adjacent cell membranes. We and others have found that some vessels in early KS were normal blood capillaries and contained Weibel-Palade bodies. In the present study, the lymphatic versus blood vessel character of some endothelial tubes could not be determined (indeterminate subtype). Capillary sprouts from normal blood vessels lack pericytes and a basal lamina, for example (Schoefl 1963), and conceivably the indeterminate endothelial tubes in KS may represent sprouts from blood capillaries or simply narrow cross-sections of lymphatics. It is more compelling to view them as a further step in the ongoing changes in venous endothelium. Such indeterminate vessels were most numerous in stage 2, when normal vessels were most infrequent.

Taken together, these vascular changes may have several explanations. The progressive transformation of venous endothelium to a lymphatic-like morphology may indicate lymphatic neogenesis from blood vessels, with lymphatics eventually being overgrown by spindled endothelial cells. Such an interpretation is easier to reconcile with the occurrence of orthograde lymphaticovenous unions in KS, which have been described histologically

as radial venolymphatics (Dictor 1986). It also gains some support from a fine structural study of the embryogenesis and regeneration of rabbit lymphatics and blood vessels by Magari (1987), who noted a continuous "fuzzy" coat in place of a defined basal lamina around blood vessels on the 18th fetal day. This is similar to the basal lamina changes noted in the present study in stage 1. In addition, abluminal fungiform projections were described as being more frequent in small blood vessels, and in the regenerative state the two types of vessels were difficult to distinguish. These observations correspond to our findings in KS. However, Magari found Weibel-Palade bodies in both types of newly formed capillary, the structure disappearing eventually in lymphatics. While this observation serves to emphasise the possible common histogenesis of lymphatics and blood vessels, our KS sections showed reduced numbers of Weibel-Palade bodies in altered blood vessels and none in lymphatic-like channels.

Alternatively, lymphatic and venous endothelium may be histogenetically separate, but the growth and integrity of each would be influenced by growth factors produced intrinsically or derived from another cell type (although growth factors could play a similar role regulating growth and differentiation even in the case of a common histogenesis). Recently, angiogenesis factors produced by lymphocytes infected with the human T-cell leukaemia virus-II retrovirus have been found to promote the growth of KS cells in vitro. Paracrine and autocrine mechanisms were postulated to account for the continued growth of the lesion (Nakamura et al. 1988). Not previously considered is the possibility that KS is secondary to a destruction of pericytes, causing potential loss of the growth inhibition exerted on endothelial cells by transforming growth factor type beta (Antonelli-Orlidge et al. 1989).

Yet a third consideration is that KS is simply a neoplasm of lymphatics and that the blood vessel changes represent only non-specific degeneration in tumour vessels. Such a view is belied by the fact that blood vessels in the earliest stages of carcinomatous growth do not regularly lose their integrity to the point of producing microhaemorrhages and do not become spindled. Also, studies of certain neoplasms of the nervous system, for example (Hirano et al. 1972; Ward et al. 1974) have emphasised fenestrae rather than wide gaps in vessels, although breaks in the basal lamina do occur. Tumour vessels have not been shown to display sequential loss of their major wall components.

Indirect connections between lymphatics and blood vessels are due to breakdown of vessel walls and migration of fluid and blood cells across a short stretch of interstitium. Waldo and Sidhu (1988) described necrosis even in non-AIDS cases, and we found that cell degeneration may be prominent in such cases, particularly in the transition to the spindle cell stage. Despite our construction of montages from electron photomicrographs of several promising vascular confluences, connections between identifiable lymphatic channels and venous derivatives were not demonstrated convincingly. Given the presence of mixed subtypes, however, direct anastomoses caused by the failure of endothelial differentiation to maintain anatomical separation of both vascular systems remain a possibility that might be more amenable to study by computerised three-dimensional reconstruction of serial sections (Braverman and Braverman 1986).

In stage 1t2, spindle cells appeared rarely in indeterminate vessels, which, by definition, makes their origin in one or the other vascular system impossible to state with certainty. As in the present study, the spindle cells of KS have been reported to show very few cell junctions and only meagre segments of basal lamina. Weibel-Palade structures have been difficult to demonstrate (Holden 1989), with notable exceptions (Schulze et al. 1987). In an ultrastructural survey of more than 3,000 KS cells, Rappersberger et al. (1990) recorded single Weibel-Palade bodies only in two spindle cells.

Variably positive cytoplasmic staining for factor VIII-related antigen has been shown in occasional normal and pathologically altered lymphatics and in the spindle cells of KS, as summarised by Holden (1989). Immunoelectron microscopic studies have previously implicated Weibel-Palade bodies in the storage or processing of this antigen with variable reactivity in other endothelial structures, including endoplasmic reticulum (Wagner et al. 1982). If this is the case, then this immunohistochemical reactivity is at odds with the marked paucity of Weibel-Palade bodies in spindle cells, unless the staining emanates more often from factor VIII-related antigen located within other cytoplasmic structures.

Another apparent anomaly concerns immunoreactive laminin, which along with type IV collagen, has been repeatedly shown to surround individual spindle cells (Autio-Harmainen et al. 1988; Holden 1989; Rappersberger et al. 1990). Since we and others (McNutt et al. 1983; Bendelac et al. 1985; Rappersberger et al. 1990) detected only minimal stretches of basal lamina about spindle cells in the electron microscope, the development of other protein components in the basal lamina may be inadequate, a question open to further immunohistochemical study.

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