Virchows Arch [Pathol Anat] (1986) 409:23–35

Virchows Archiv A

Kaposi's sarcoma

Origin and significance of lymphaticovenous connections

Michael Dictor
Department of Pathology, Kaiser Medical Center, San Francisco, California, USA

Summary. Review of histopathological material in nine autopsies and 35 skin biopsy specimens of Kaposi's sarcoma in male homosexuals suggested that aberrant lymphaticovenous connections occur in the earliest stage of the Kaposi lesion. Venular glomeruloid structures in the dermis and their analogous radial venolymphatic channels in medium-sized and larger veins signified coupling of the lymphatic and venous systems, a characteristic previously noted in angiographic studies and considered to be unique in Kaposi's sarcoma. Lymphatic channels penetrated veins selectively rather than arteries, particularly in deep fat, liver, gastrointestinal submucosa and the hilum of lymph nodes. The initiation of the Kaposi lesion thus may be an abnormal recapitulation of the coupling of venous and lymphatic systems which occurs during embryonic growth. A chronological staging scheme is used which proposes lymphaticovenous union as the initial morphological differentiating event. The precise origin of the characteristic spindle cells in the developing lesion remains unclear, although convergent differentiation of lymphatic and blood vascular endothelium may be considered.

Alteration of the microcirculation, particularly that distal to the capillary bed, may explain several of the histopathological and haemodynamic features of Kaposi's sarcoma, including lesional thrombosis and infarction, tissue haemorrhage, vascular dilatation, cavernous pseudoangiomas and acute right-sided heart failure.

Key words: Kaposi's sarcoma – Lymphatics – Veins

Current opinion favors endothelium or lymphendothelium in the histogenesis of Kaposi's sarcoma (KS), although the precise origin of the characteristic spindle cells is debated. General agreement exists as to the predominantly multicentric, as opposed to metastatic, nature of the Kaposi lesion (Cox and Helwig 1959). In the dermis, it begins as a hyperplasia and dilatation

Offprint requests to: M. Dictor's present address: Department of Pathology, University Hospital, S-221 85 Lund, Sweden

of lymphatic capillaries (Gange and Wilson-Jones 1979; Gottlieb and Ackerman 1982). Vasoproliferation with spindle cells forming narrow vascular slits are the dominant histological features of Kaposi's sarcoma before the slits are obliterated by increased spindle cell growth. Spindle cell proliferation may resemble a true sarcoma if nuclear atypia develops (Templeton 1972; Cox and Helwig 1959). All tissues with a lymphatic supply have been found susceptible to the development of Kaposi's sarcoma (Templeton 1972), and the brain has rarely been reported as a metastatic site (Rwomushana et al. 1975).

Palmer (1972) published a large roentgenographic study of African and American patients with Kaposi's sarcoma in which the following angiographic characteristics of Kaposi nodules were observed:

1. individual arerial supply with dual venous and lymphatic drainage
2. rapid venous drainage, but pooling and impaired limb drainage if nodules were multiple
3. lymphaticovenous shunts with simultaneous filling of veins and lymphatics; visualization of nodules following lymphangiography, and conversely, demonstration of lymph nodes following angiography
4. dilatation and obstruction of skin and perivascular lymphatics

Lymphaticovenous anastomoses develop in man in response to lymphatic obstruction and are demonstrated by lymphangiography (Wallace et al. 1964). However, the bidirectional flow noted above may be specific for Kaposi's sarcoma. In order to evaluate the morphological nature of Kaposi's sarcoma in relation to Palmer's important observations, histopathological material selected from multiple patients with Kaposi's sarcoma was investigated to determine the distribution of the developmental stages of KS in relation to the blood vascular and lymphatic systems.

Materials and methods

The material was obtained during the recent epidemic of Kaposi's sarcoma among homosexual males, none of whom displayed significant lymphoedema or congestive heart failure. In nine autopsies, all sections of subcutaneous and deep fat, lymph nodes, lung, liver and gut which were stained with haematoxylin and eosin (H&E) were reviewed. Selected sections were stained by the Verhoeff-van Gieson technique for elastic and collagen. Skin biopsy specimens of Kaposi's sarcoma from 36 homosexual males were also reviewed. The biopsies were taken mostly from the distal extremities, often by the shave technique, cut at 3–4 microns and stained with H&E. Autopsy and skin biopsy specimens represented almost all KS cases on file in the Department of Pathology for 1981 through March, 1985.

Four developmental stages, listed below, were used in analysis of the material; the results are shown together with brief historical data for the autopsy patients in the Table 1. the histological features of each stage, except radial venolymphatic channels (1b), have been described in the literature (Cox and Helwig 1959; Templeton 1972). The exception will be described under Results.

1. Lymphaticovascular connection
   a) lymphatic dilatation and hyperplasia; endothelial hyperplasia; formation of glomeruloid structures
   b) radial venolymphatic proliferation
2. Spindle cell proliferation with formation of narrow vascular slits
3. Sarcomatoid atypia in spindle cells with loss of slits
4. Anaplasia

Table 1. Clinical data and histological stages of Kaposi's sarcoma in selected organ sites (for stage explanation see text)

	Age	Duration[a] (mos.)	Associated diseases	Initial skin biopsy	Nodes	Lung	Liver	GI	Subcutis/ deep fat
1.	34	5	Immunoblastic B-cell lymphoma, necrotizing pneumonia	NA	1b, 2	–	1b, 2	2	–
2.	38	12	Toxoplasmosis, PCP, CMV	2 (pharynx)	2	1b, 2	–	1a	1b (mesenteric)
3.	45	–	Multiple myeloma, CMV, PCP	–	–	–	1b, 2	NA	1b, 2
4.	35	–	Staphylococcal pneumonia	–	1a, 2	–	NA	NA	–
5.	35	6	PCP, CMV	1a	–	1b, 2, 3	–	1b, 2	1b, 2
6.	51	–	Hodgkin's disease, PCP	NA	–	2	1b, 2	2	–
7.	51	12	Cryptococcosis, CMV	2	1b, 2	2	–	2	2 (perinodal)
8.	30	4	Toxoplasmosis, CMV	NA	2	1b, 2	–	–	1b, 2 (perinodal, mesenteric)
9.	47	5	Cryptococcal meningitis, CMV	2	–	1b, 2	–	1a	–

PCP denotes Pneumocystis carinii pneumonia, CMV cytomegalovirus, NA not available

[a] survival after histological confirmation of KS

– denotes not involved (autopsy limited to thorax in cases 4&5)

Results

The earliest histological stage (1a) of mesenchymal proliferation in the skin consisted of prominent widening of jagged, empty lymphatic spaces lined by hyperplastic attenuated cells with dark, oval nuclei. In the absence of known histochemical and immunohistochemical markers specific for lymph-endothelium, its identification as such in this study rested upon architectural features. Small lymphocytes and sparse plasma cells frequently lay near the lymphendothelial cells, although several specimens were practically devoid of inflammatory cells. The spaces appeared to arise from clefts between collagen bundles and to surround eccrine structures and nerves. In some spaces the lining cells were degenerated or absent. Glomeruloid structures, lymphatic spaces with at least one small central blood vessel, were identified in 11 of 13 pure stage 1a specimens. Some of these vessels were arterioles and capillaries, but others were venules often located in the superficial and deep plexuses. In venular glomeruloid structures the vascular lumen was surrounded by two layers of cytologically identical hypertrophic endothelial cells with pale, occasionally sparsely granular and degenerated cytoplasm (Fig. 1a). Larger, lighter staining nuclei similar to those of the endothelial

cells could be found among the cleft lining cells in glomeruloid structures (Fig. 1b). The lymphatic clefts in five stage 1a skin specimens contained erythrocytes, consistent with the development of aberrant lymphaticovascular connections (Fig. 2). In all but one, haemosiderin granules were present in the cytoplasm of lymphatic lining cells. Minute submucosal foci of stage 1a were present in the stomach and intestines of cases 2 and 9, but glomeruloid structures were not identified (Fig. 3), probably due to lack of postmortem preservation.

Occasional areas of tissue haemorrhage, as opposed to lymphatic suffusion, appeared to result from rupture of these blood-filled clefts. In three of six skin specimens which showed mixed stage 1a and early stage 2 changes with few spindle cells, glomeruloid structures were diminished markedly in number and prominence. Endothelial cell proliferation resulted in microangiomatoid capillary clusters in many skin specimens, even among the 14 which contained predominantly stage 2 lesions. The stage 1a lymphendothelial and endothelial cells rarely showed mitotic figures; lymphendothelium was not cytologically atypical beyond the presence of slight nuclear enlargement and hyperchromasia, with the exception of rare isolated cells noted in one skin biopsy. Horizontal bands of sclerotic collagen occurred only in one early stage 2 skin biopsy. Three skin specimens showed stage 3 KS, one of which harbored rare cytomegalovirus inclusions in spindle cells.

In the autopsy material, blood-filled, jagged lymphatic channels, similar to the hyperplastic lymphatic capillaries in the skin sections, penetrated the media and endothelium of vein segments in a radial and often circumferential manner (Fig. 4a, b). These radial lymphatic vessels (stage 1b) were readily distinguished in eight of the nine autopsy cases and were represented at least once in all reviewed organ sites as noted in the table. In microscopic fields, veins were distinguished from accompanying arteries by a greater maximal luminal dimension, lack of internal elastic membrane, thinner media and frequently more abundant adventitia, but venolymphatic penetration could be accurately identified only in medium-sized and larger veins. Involvement of occasional vessels was so extensive as to preclude accurate identification of their venous nature by histological criteria (Fig. 4c). In 14 different sections of radial venolymphatic channels listed by organ site in the table, one or more accompanying arteries were identified in eight. They consistently lacked penetrating lymphatic channels, although channels were often present in the arterial adventitia. Areas useful for comparison of arteries and veins were found most often in the lymph node hilum, hepatic septa and deep fat near viscera (Fig. 5). As in the skin, lymphatic channels were often supplanted by stage 2 spindle cells (Fig. 6). Alternatively, the channels degenerated to be replaced by spokes of hyalinized stroma.

Of tubular structures other than vessels in liver and lung, only occasional bronchi showed radial, blood-filled channels, which appeared in places to enter the submucosa. The liver in case 1 contained a focus of multiple large vascular spaces embedded within a fibroelastic stroma (Fig. 7).

A further association between the KS lesion and the lymphatic system

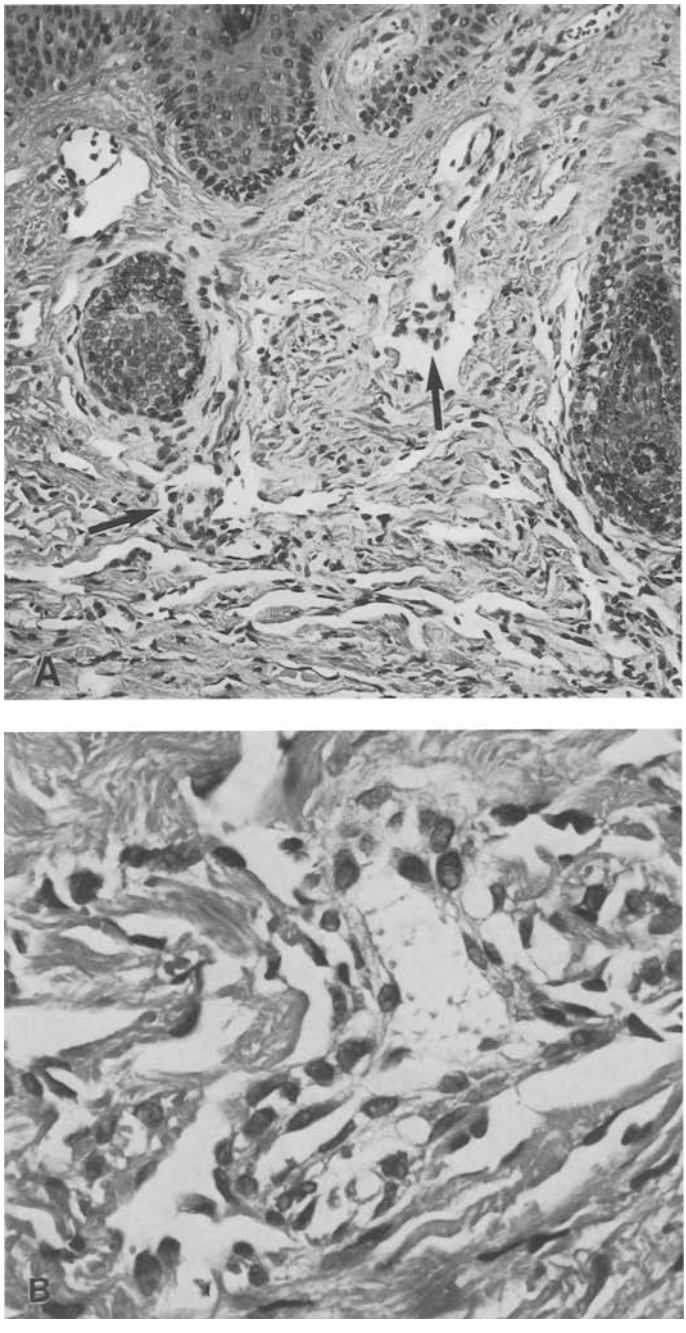

Fig. 1 a, b. Establishment of lymphaticovascular connections in the dermis. H&E stain. **a** Venular glomeruloid structures consisting of central endothelial bilayer (arrows) surrounded by jagged, hyperplastic lymphatic capillaries (×150). **b** Axial section shows comingling of the two main cell types (×400)

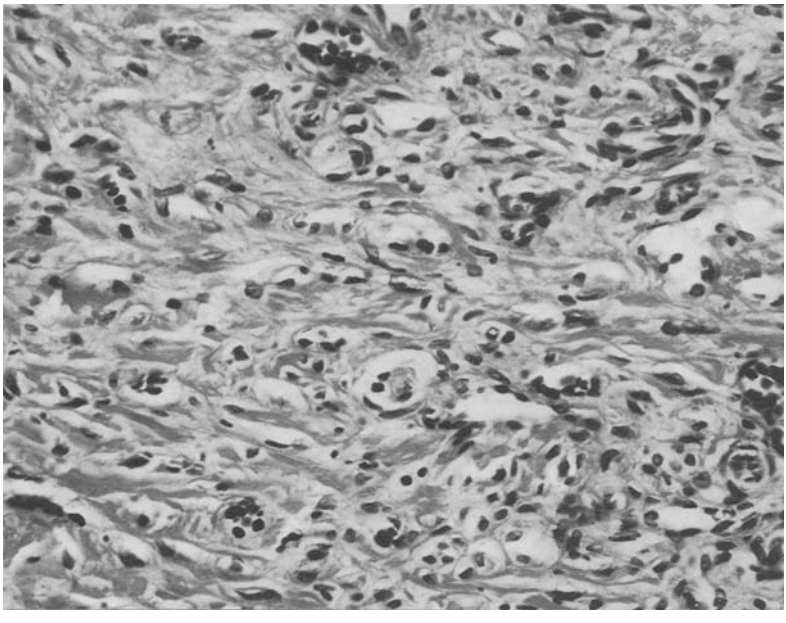

Fig. 2. Erythrocytes in aberrant lymphatic capillaries. (H&E, ×300)

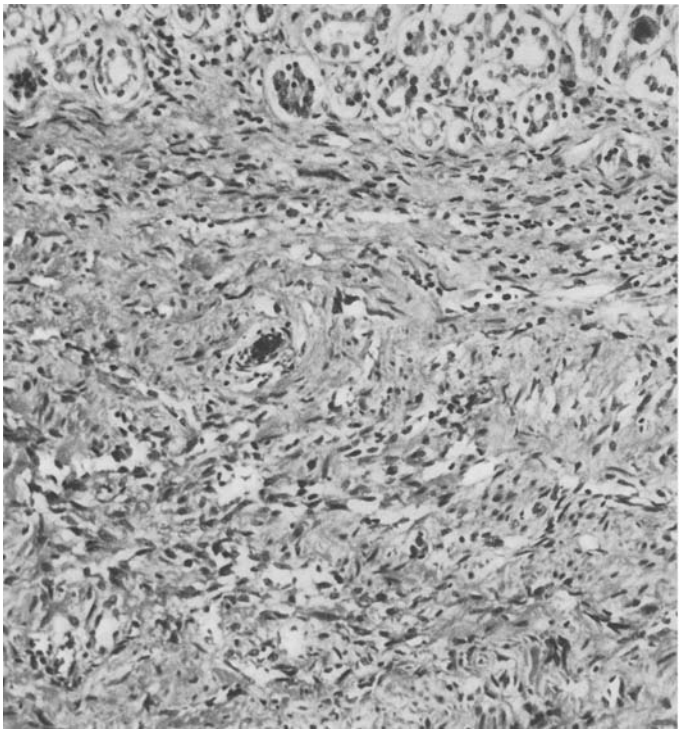

Fig. 3. Stage 1a in gastric submucosa of case 2 lacks preserved glomeruloid structures. (H&E, ×170)

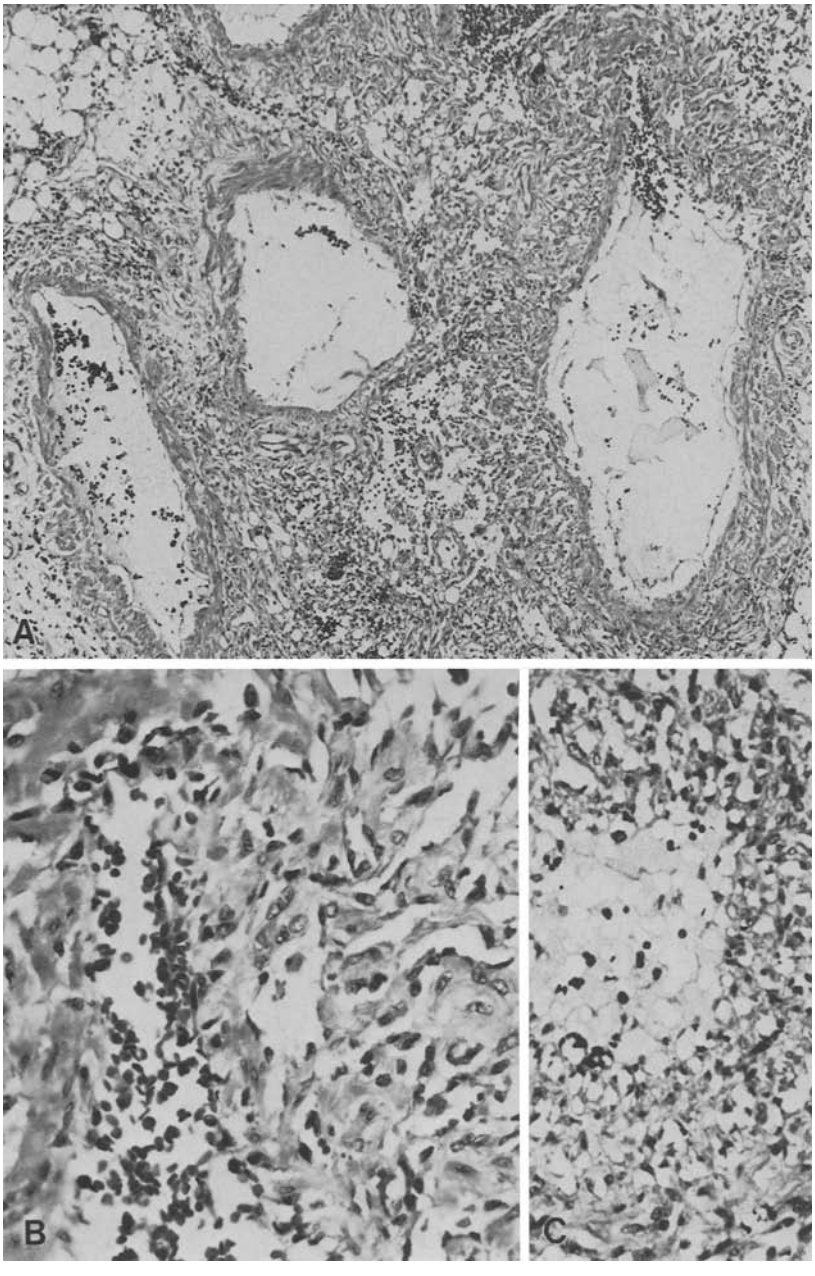

Fig. 4a–c. Radial venolymphatic channels (H&E). **a** Linking of vein segments in anterior mediastinal fat (× 45). **b** Cells lining channels are cytologically similar to those in Fig. 1a (× 240). **c** Vessel wall unrecognizable due to marked lymphatic increase (× 175)

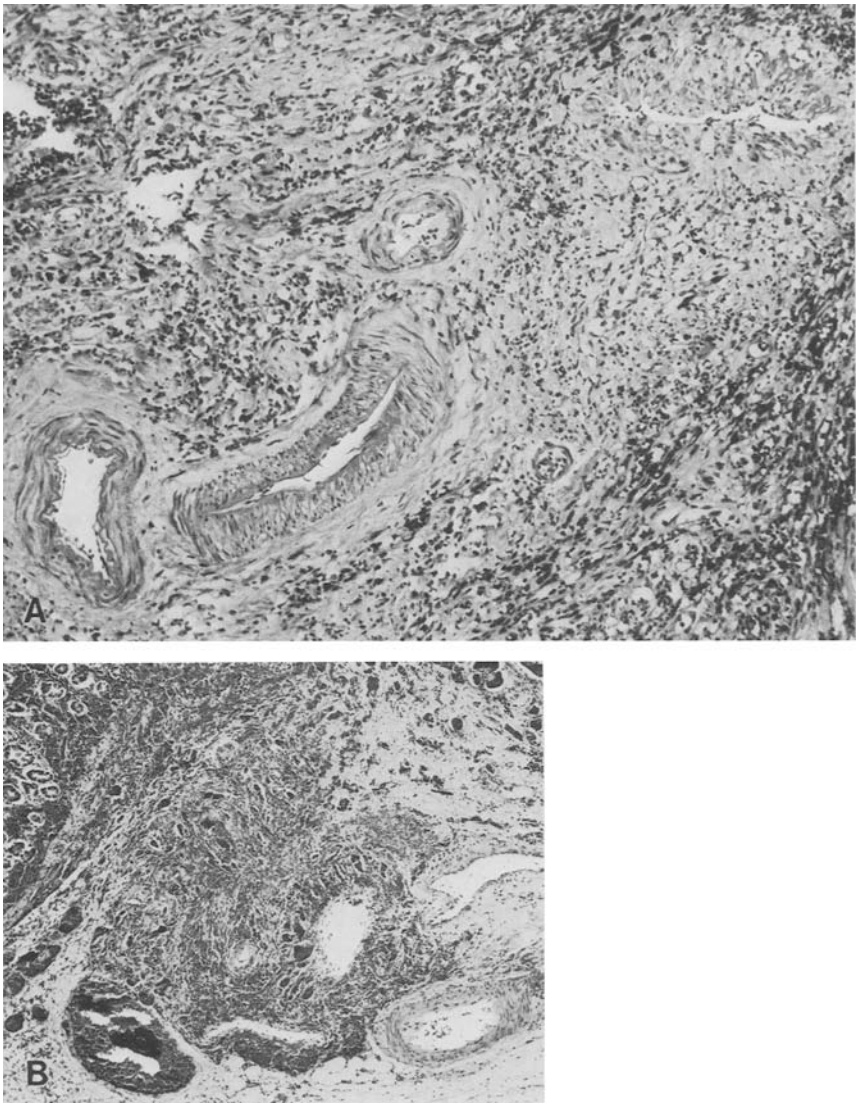

Fig. 5a, b (H&E). **a** Uninvolved artery (*left*) and sclerotic vein wall (*upper right*) with narrow lymphatic channels (×80). **b** Engorged venolymphatics with free artery in gastric submucosa (×40)

was suggested by characteristic "tracking" of stage 2 lesions in lymphatic-rich septa of the subcutis, liver and lung and the presence of stage 1a and 2 lesions in marginal sinuses of lymph nodes. In addition, areas of confluent lymphatic drainage such as the pleura-septal interface and submucosa of the gastrointestinal tract were sites of predilection. Although hepatic lesions tended to center about septa and portal zones, the infiltrating margin

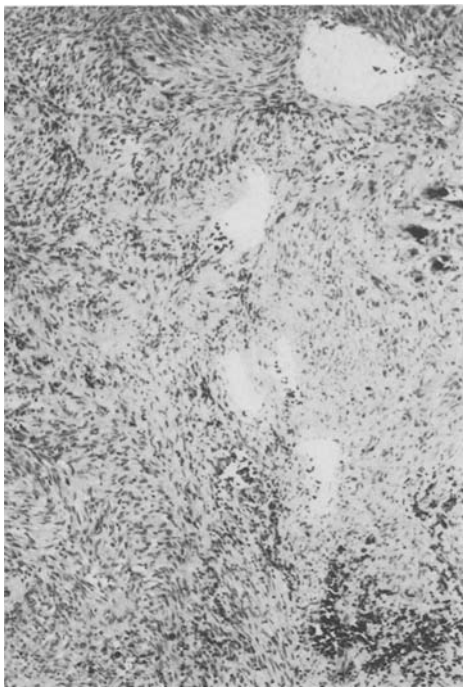

Fig. 6. Loss of venous radial channels due to spindle cell proliferation (H&E, × 60)

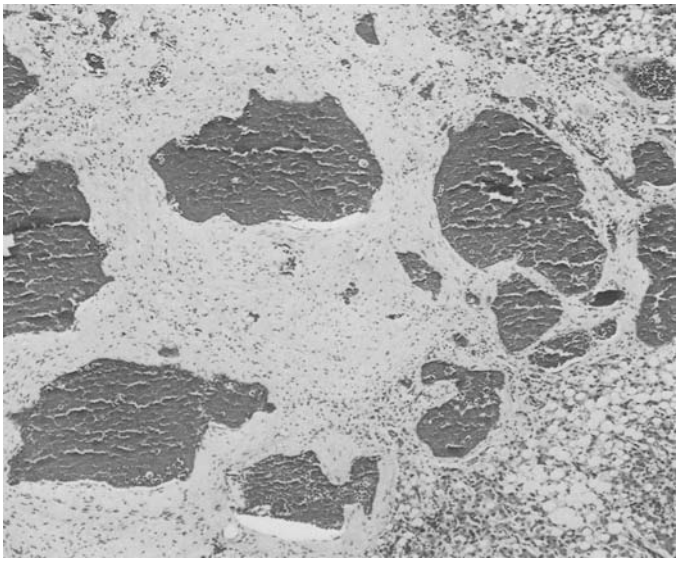

Fig. 7. Hepatic pseudoangioma (H&E, × 40)

interdigitated with disrupted sinusoids of the lobules. Similarly, extensive replacement of lung parenchyma often occurred about involved septa.

Stage 3 lesions were noted in three skin biopsy specimens and in a solitary small pulmonary focus in case 5. No stage 4 foci were present in any sections.

Discussion

A commonly used histological classification of KS (Templeton 1981) divides the lesion into three stages: mixed cellularity, which is roughly equivalent to stage 2 in this study; monocellular, corresponding to stage 2 but mainly 3; and anaplastic, equivalent to stage 4. The early stage 1 lesion, previously described as rare (Gange and Wilson-Jones 1979), is usually neglected in classification schemes, although lymphatic proliferation has been stressed by many investigators (Gange and Wilson-Jones 1979; Gottlieb and Ackerman 1982; Lothe and Murray 1962). However, in the present study stage 1 with and without foci of early stage 2 is the most common presenting stage in the skin of homosexual males with AIDS, which is probably due to increased awareness of the clinical macular lesion and early biopsy. Similarly, larger veins situated in the center or periphery of stage 1 or 2 areas within deep tissues and organs may readily demonstrate tortuous proliferation of adventitial lymphatic channels through the smooth muscle of the media and into the endothelium. These radial venolymphatic vessels have hitherto been inadequately described, and the central vessel has sometimes been misidentified as an arteriole, as in the report by Lee (1968). However, characteristic extension of Kaposi's sarcoma along veins of the extremities and "vascular invasion" with intraluminal growth has often been emphasized (Templeton 1972; Lothe and Murray 1962; Lothe 1963). In the author's opinion, this invasive feature represents an initial aberrant neoproliferation of the lymphatic vessels normally present in the adventitia of veins. Dorfman (1962) has expressed a similar view and has cited additional clinical evidence for lymphaticovenous anastomoses. McNutt et al. (1983) presented evidence that the cleft lining cells most closely resembled lymphendothelium by virtue of an incomplete basal lamina in the electron microscope, the presence of a few dense intercellular junctions and a rudimentary or absent pericyte layer. Histochemical, immunohistochemical and lectin staining have also indicated these cells to be lymphendothelium (Beckstead et al. 1985).

In conjunction with Palmer's (1972) angiographic results as detailed above, the findings herein indicate that lymphaticovenous connections extend anatomically within separate nodules of Kaposi tissue, as both connections and nodules develop from the capillovenular bed distally to large veins. Since the violaceous stage 1a plaques in young patients are not initially associated with clinically recognizable lymphoedema, this is probably the result rather than the cause of lymphatic hyperplasia. Analysis of the developing skin lesion shows increasing amounts of blood in the new lymphatic capillaries, which may be only partly patent to the larger lymphatics. Rup-

ture results in frank tissue haemorrhage, and as expected this was more pronounced around the larger veins of deep tissues than in the dermis.

The morphology and development of venolymphatic channels correspond to the lymphatic proliferation within glomeruloid structures noted in the dermis and both structures appear to represent the most compelling morphological evidence of lymphaticovenous connections. Firm confirmation may require simultaneous histological correlation with radiological studies using microangiographic and newer lymphographic techniques.

The subsequent spindle cell growth phase erases the histological features, though by Palmer's (1972) studies presumably not the anatomical pathways, of the unification process both in the skin and around larger vein segments (fig. 2d), the lumens of which may become progressively narrowed. Sterry et al. (1979) report involvement of venous but not arterial capillaries in the genesis of spindle cells on the basis of histochemical and electron microscopical studies, although both arterial and venous capillaries are present within the spindle cell nodule. In the present study, nuclear characteristics of early spindle cells were similar to those of venular endothelium, which is consistent with their observations. Perithelial cells have also been suggested as the origin of spindle cells (Braun-Falco et al. 1976). An alternative to the conclusion of McNutt et al. (1983), that spindle cells are derived from lymphendothelium would be that they are the product of convergent differentiation of lymphatic and vascular endothelium. Thus the morphological fate of lymphendothelium in stage 2 lesions is still unclear.

The spindle cells proliferate parallel to the enlarged lymphatic vessels, concentrically around small blood vessels, and develop characteristic slit-like spaces containing red blood cells. The series of events suggests the consolidation of the stage 1 lymphaticovenous lesion from which the slits are derived. However, generally the spindle cell component contains variable numbers of cross-sectioned single cell capillary vessels, and the lymphaticovenous origin of the structure is not obvious histologically. The presence of a few atypical nuclei is variable.

The third histological stage is marked by an increasingly dense proliferation of atypical mitotically active spindle cells with concomitant loss of vascular slits. It was found in a single small pulmonary focus in case 5 and in three skin biopsies. Whether lymphaticovenous connections are maintained is doubtful, but this point requires further study. The tumour was difficult to distinguish from spindle cell sarcomas of various types, which is a frequently reported observation (Templeton 1972; Cox and Helwig 1959). Others report extremely rare brain metastases with stage 3 or 4 histological characteristics (Rwomushana et al. 1975), although metastases were not apparent in the present study. The stage 4 lesion was not represented in our material, but has been reported to behave as a metastasizing angiosarcoma, which it resembles morphologically (Rwomushana et al. 1975; Tedeschi 1958).

The development of Kaposi's sarcoma thus appears to represent a mesenchymal sequence of hyperplasia – atypical hyperplasia – neoplasia superimposed on an initial aberrant reunification of lymphatic vessels with veins,

venules and possibly blood capillaries. The biological events affecting this reunification process presumably occur in endothelium, lymphendothelium, or in a third cell type.

Aberrant channels linking veins to veins and lymphatic vessels might be expected to cause the blood pooling noted above by Palmer (1972) and conceivably an effective increase in postcapillary volume in patients with extensive disease. If these events resulted in increased blood volume, sudden loss of significant amounts of early stage tissue by widespread progression to a higher stage, by immunologically mediated regression or by ischaemia and hyalinization might result in a rapidly elevated blood volume. This event could explain the acute right-sided cardiac failure noted in occasional KS patients (Lothe and Murray 1962). Appropriate physiological studies are needed to support such a possibility. On the basis of the above observations, microinfarcts occasionally seen in stage 1 and 2 tissue in various organs may be due to low oxygen tension with or without the vascular thrombosis noted in KS by others (Templeton 1981; Lothe 1963).

The potential for causing a high output cardiac state has been imputed to Kaposi's sarcoma on the basis of haemodynamic studies performed on a single patient (Hecht et al. 1967). The authors ascribed the haemodynamic changes to the formation of arteriovenous shunts, but such shunts have not been convincingly demonstrated histologically at the prearteriolar level. The present study revealed instead venovenous shunts by way of lymphatics, with apparent sparing of arteries in all fields in which they were paired with involved veins. This does not eliminate the possibility of physiological shunting in lung tissue, however. Due to architectural distortion, heavy involvement of bronchi with stage 2 tissue, and the normal anatomical separation of larger pulmonary artery branches and veins, it was often difficult to exclude the possibility of newly formed penetrating lymphatic vessels in pulmonary artery branches.

In accordance with other reports (Lothe and Murray 1962; Mitsuyasu and Groopman 1984), a low incidence of serious bleeding complications was noted, despite gastrointestinal and bronchial mucosal involvement with the Kaposi lesion. Only one of the five patients with demonstrated gastrointestinal involvement (case 6) in the present series had terminal haemorrhage, although ulcerated lesions were present in several cases. None of the five with bronchial KS developed significant haemoptysis prior to death. It is unlikely that prearteriolar arteriovenous shunts could develop in submucosal areas with little connective tissue support without prompt and serious haemorrhage ensuing.

Altered microcirculation in and about the Kaposi lesion may result in the dilated venous and lymphatic structures sometimes present on the lesion's edge. Structures resembling various benign vascular tumours have in the past been assumed to represent a primary growth property of the vascular neoproliferation (Tedeschi 1958). The area of cavernous pseudoangioma present in the liver of case 1 suggests instead to the author fibrous replacement of stage 2 KS which previously linked segments of a portal vein branch, causing them to become tortuous and dilated.

References

Beckstead JH, Wood GS, Fletcher V (1985) Evidence for origin of Kaposi's sarcoma from lymphatic endothelium. Am J Pathol 119:294–300

Braun-Falco O, Schmoeckel C, Hübner G (1976) Zur Histogenese des Sarcoma idiopathicum multiplex haemorrhagicum (Morbus Kaposi) – eine histochemische und elektronenmikroskopische Studie. Virchows Arch [Pathol Anat] 369:215–227

Cox FH, Helwig EB (1959) Kaposi's sarcoma. Cancer 12:289–298

Dorfman RF (1962) Kaposi's sarcoma, the contribution of enzyme histochemistry to the identification of cell types. Acta-Unio Int Contra Cancrum 18:464–476

Gange RW, Wilson-Jones E (1979) Lymphangioma-like Kaposi's sarcoma. Br J Dermatol 100:327–334

Gottlieb GJ, Ackerman AB (1982) Kaposi's sarcoma: an extensively disseminated form in young homosexual men. Human Pathol 13:882–891

Hecht HH, Candiolo BM, Malkinson FD et al. (1967) On cardio-cutaneous syndromes. Trans Assoc Am Phys 80:91–96

Lee FD (1968) A comparative study of Kaposi's sarcoma and granuloma pyogenicum in Uganda. J Clin Pathol 21:119–128

Lothe F (1963) Kaposi's sarcoma in Uganda Africans. Acta Pathol Microbiol Scand 161 (Suppl):5–71

Lothe F, Murray JF (1962) Kaposi's sarcoma: autopsy findings in the African. Acta-Unio Int Contra Cancrum 18:429–452

McNutt NS, Fletcher V, Conant MA (1983) Early lesions of Kaposi's sarcoma in homosexual men – an ultrastructural comparison with other vascular proliferations in skin. Am J Pathol 111:62–77

Mitsuyasu RT, Groopman JE (1984) Biology and therapy of Kaposi's sarcoma. Semin Oncol 11:53–57

Palmer PES (1972) Haemangiosarcoma of Kaposi. Acta Radiol (Suppl) 316:1–52

Rwomushana RJW, Bailey IC, Kyalwazi SK (1975) Kaposi's sarcoma of the brain – case report with necropsy findings. Cancer 36:1127–1131

Sterry W, Steigleder G-K, Bodeux E (1979) Kaposi's sarcome: Venous capillary haemangioblastoma – a histochemical and ultrastructural study. Arch Dermatol Res 266:253–267

Tedeschi CG (1958) Some considerations concerning the nature of the so-called sarcoma of Kaposi. Arch Pathol 66:656–684

Templeton AC (1972) Studies in Kaposi's sarcoma-postmortem findings and disease patterns in women. Cancer 30:854–867

Templeton AC (1981) Kaposi's sarcoma. In: Sommers SC, Rosen PP (eds) Pathology Annual, part 2. Appleton-Century-Crofts, New York, pp 315–336

Wallace S, Jackson L, Dodd GD, Greening RR (1964) Lymphatic dynamics in certain abnormal states. Am J Roentgenol 91:1187–1206

Accepted January 27, 1986