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ANGIOGENESIS AND KAPOSI'S SARCOMA

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Proliferation of vasculature is a prominent feature of Kaposi's sarcoma. Unlike most sarcomatous or cancerous states, Kaposi's tumor has often been described as undergoing spontaneous resolution or responding to diverse therapies, some not usually supposed to be effective in malignancy. When it behaves thus, it could be described as sharing features with other phasic vascular tumors, examples being the strawberry capillary naevus or pyogenic granuloma, in which endothelium proliferates for a variable length of time, and this is followed by a steady state, and then ultimate resolution (1).

Migration, mitosis, and pattern formation

Angiogenesis can be divided into several phases. Most often it is characterized by migration of endothelial cells, while proximally, or at a later time, mitosis becomes a feature and only later angiogenesis is completed when the vessels form distinctive patterns. Kaposi's sarcoma does not develop a distinctive pattern characteristic of a normal vascular tree with capillaries, venules, arterioles, arteries, and veins. Nor does it develop the pattern seen commonly in cancer or around wounds in which there is clear orientation of vessels towards the center of the pathways. Like angiogenesis in general, the endothelial cells in Kaposi's appear to be advancing and elongating, as if migrating, and mitotic figures are a more variable feature. However, some tumors have been described in which mitosis is a very prominent feature, and it could be that this represents a different entity masquerading with the same morphology as other tumors less inclined to have vigorous mitosis. In considering angiogenic factors one has to distinguish between those which stimulate migration and those factors which stimulate mitosis. Chemotaxis towards an angiogenic chemical factor, or haptotaxis, which is migration along an adhesion gradient, would in general seem to be more relevant to the pathogenesis of Kaposi's sarcoma than chemical factors known to directly stimulate mitosis. But it also has to be noted that the lack of any obvious direction of growth suggests that chemokinesis rather than chemo-attraction must be examined. In other words, the cells are just busily moving without an obvious destination.

Lymphedema

Throughout the history of the descriptions of Kaposi's sarcoma, it has been noted that edema may be extensive and precede the onset of tumors. Its distribution may bear little relation to the rather localized deposits of the sarcoma. If this association has significance and lymphedema is a principal feature of the condition, then it is worth noting that wherever lymphedema occurs, and whatsoever the cause, then both blood capillaries and lymphatic capillaries tend to proliferate. This being so, the "sarcomatous" element of Kaposi's sarcoma would seem to be merely a localized exaggera-

Table 1
Effects of Chronic Lymphedema on Blood Vascular and Lymphatic Endothelium in Dog Leg

	Blood Vessels		Lymphatics	
	Normal	Lymphedema	Normal	Lymphedema
Small Vesicles				
Diameters (nm)	52	52	52	53
Nos. free ($x10^{-8}/cm^2$)	55	110***	67	130***
Total Numbers	160	300***	200	370***
Free Vacuoles				
Diameters (nm)	190	190	180	220
Numbers ($x10^{-8}/cm^2$)	0.089	2.1***	0.072	1.8***
Proportions of Junctions				
Open or Partly Open	0.00	0.35***	0.054	0.32***

From Casley-Smith et al. (2). Asterisks indicate statistically significant differences from normal.

tion of a phenomenon which is occurring more widely, perhaps in response to lymphedema. This proliferation of capillaries of both kinds in lymphedema is unfortunately difficult to measure and is not well documented, but *Table 1* is taken from Casley-Smith (2) and suggests a doubling in the number of blood capillaries in the tissues of lymphedema.

Lymphatic and blood vessel origins

The author will not discuss markers which may or may not distinguish blood endothelium from lymphatic endothelium, but it must be pointed out that such a distinction may be a somewhat artificial concept. Endothelium in Kaposi's sarcoma may simply be responding to factors which instruct it to behave like either blood vessels or lymphatics, and the bemused endothelial cell may have no intrinsic determination to be either. A significant feature of Kaposi's sarcoma is the presence of red cells in the interstitium as well as within the growing capillaries. By contrast, in lymphedema, while red cells may pass from blood vessels into lymphatics, lying around in the interstitium is not usually a prominent characteristic. It does seem to be an important feature of Kaposi's sarcoma that the normal containing function of blood capillaries and/or the capacity of the interstitium and lymphatics to remove red cells, is impaired. By contrast, lymphatic vessels do not normally effectively contain their contents. Two factors which suggest that in Kaposi's sarcoma the vessels are more like lymphatics than blood vessels, are therefore the lack of containment of content and the tendency for the endothelium to line all available tissue spaces. Perhaps also worth noting is that Kaposi's sarcoma tends to have an anatomical distribution in the tissues more nearly correlating with the anatomical distribution of lymphatics than that of blood capillaries. In the skin, it seems to arise just deep to the subpapillary venous plexus at exactly the site where one finds most lymphatics *(Fig. 1)* and it is not usually seen in the adipose tissue, where initial lymphatics are sparse. Similarly, other organs which are well endowed with lymphatics, such as the gut, are frequently involved, whereas an organ such as the brain or eye, which

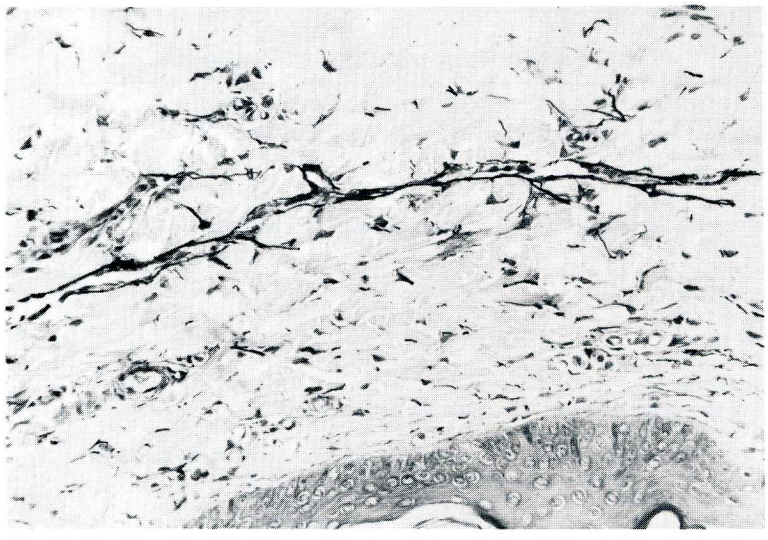

Fig. 1. Elastin stains identify a mid-dermal lymphatic. It is at this site in the dermis that Kaposi's sarcoma most often arises.

has no lymphatics, is involved in only fulminant systemic disease.

Relationship to immunological suppression

While the occurrence of Kaposi's sarcoma in renal transplant patients suggests that it is secondary to immune suppression, consideration should also be given to the possibility that a failure of the lymphatic system to distinguish itself from the blood vascular system may also contribute to immunosuppression. The early observations of investigators in Africa, such as Templeton and Bhana (3), on the failure of DNCB sensitization in patients with Kaposi's sarcoma could be explained if the pathways from the skin to the lymph nodes were obstructed or diverted. When antigen cannot find its way to a lymph node but can find its way directly into the blood stream through the wall of a peripheral blood capillary or via a lymphatico-venous shunt, then this may be an explanation of T-cell suppression.

Physical factors in angiogenesis

Table 2 lists chemical and physical factors contributing to angiogenesis (4). As indicated above, in lymphedema there does seem to be an enhancement of blood capillary and lymphatic capillary growth. This might be due to the presence of new angiogenic factors, but it could equally well be due to a failure of clearance of normal metabolites or inflammatory agents. The possibility that lymphatic endothelial cells are predisposed to line spaces and that the physical presence of such spaces is in itself a stimulus to lymphatic growth should also be considered. It is especially relevant to the migratory aspect of angiogenesis. Angiogenesis is enhanced by guide wires, preferential pathways and low-resistance pathways. It is possible that endothelial cells will migrate anywhere given a low-resistance pathway.

The anchoring fibers described as attachments to lymphatics are especially sensitive to volume changes in interstitial fluid. It is possible that attachment is enhanced by the physical properties of such changes and this attachment provides a certain stability tending to suppress mitosis (5). Exactly what happens to such attachments in the lymphatic-like spaces of Kaposi's would be worthy of study. The presence of an elastin network requires that elastases be inhibited

Table 2
Factors Contributing to Angiogenesis

Chemical influences on growth of new blood vessels:

- Metabolic products--increased metabolic demands from increased cellularity, hypoxia, or ischemia
  - Hyperplasia
  - Inflammation
  - Cancer: Angiogenin
  - Tissues capable of high rates of glycolysis (aerobic or anaerobic)
    - Retina
    - Epidermis
    - Leucocytes
    - Cancer
    - Fetal tissue
  - Inflammatory products
    - Cellular products
      - Neutrophil--proteases, free radicals, prostaglandins
      - Lymphocyte--lymphokines
      - Macrophage--proteases, prostaglandins, mitogens, numerous monokines
      - Mast cell--histamine, heparin, prostaglandins enzymes
      - Platelets--histamine, serotonin, prostaglandins, ADP
    - Products from tissue injury, or leaked from circulation
      - Proteases, free radicals, prostaglandins, complement factors, coagulation factors
  - Factors affecting cellular adhesion, migration
    - Fibronectin
    - Laminin
    - Proteases
  - Cellular and tissue 'angiogenic' factors
    - Tumor
    - Retina
    - Epidermis
    - Corpus luteum
    - Synovial fluid
    - Submaxillary gland
    - Vitreous humor
    - Leucocytes
  - Other growth factors
    - Fibroblast growth factor
    - Epidermal growth factor
  - Inhibitors isolated from
    - Hyaline cartilage
    - Aorta
    - Vitreous humor
    - Cornea

Physical influences on growth of new blood vessels:

- Mechanical tension
  - Effects on cell shape and propensity to growth
    - Hemodynamic influences--vasodilatation, axial stretching
    - Axial stretching from outside forces
  - Orientation of fiber and vascular networks, providing oriented pathways for migration
- Substrata for endothelial migration
  - Structural elements
    - Fibrin, collagen, basement membrane
  - Effects on cellular adhesion and propensity towards cellular migration and proliferation
    - Fibronectin
- Nature of perivascular environment and its effect on facilitation or inhibition of vessel growth
  - Cellular contact-pericytes
  - Nature of basement membrane
  - Nature of interstitial tissue--compliance or stiffness
- Temperature
  - Effect on level of metabolic demands
  - Effect on compliance of tissue
  - Effect on blood viscosity

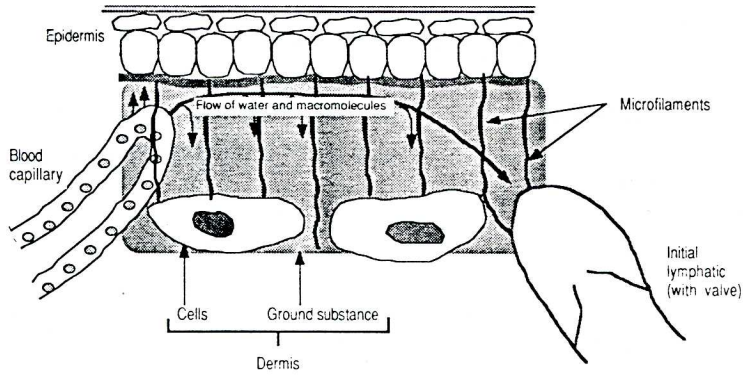

Fig. 2. The elastin lymphatic low-resistance pathway is the primary exit for macromolecules and excess water from the skin. Failure of such exit causes dermal edema with swelling of the ground substance and disturbance of induction of tractional forces on cell membranes, the intensity of which is controlled by cell contractility and fiber flexibility.

and the presence of such inhibitors and of binding factors coating elastin, such as vitronectin (6), are all worthy of further study. It is conceivable that the physical forces of oncotic and hydrostatic pressure which the lymphatics undoubtedly help to control are significant determinants of all factors contributing to adhesion complexes. Disruption by edema is a cause of cell blindness to the transmission of physical forces and the transduction into chemical mediators. The balance between the swelling of ground substance, the flexibility of fibers and the contractility of cells in creating forces *(Fig. 2)* which are tensile and induce traction, may well be upset by the failure of the lymphatic system, and this may predispose to reactive vascular changes such as Kaposi's sarcoma.

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