

KAPOSI'S SARCOMA: EVIDENCE SUPPORTING ITS ORIGIN FROM THE LYMPHATIC SYSTEM

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ABSTRACT

The histogenesis of Kaposi's sarcoma (KS) remains a subject of dispute. The weight of evidence, however, favors derivation of the spindle cell of KS from the lymphatic system and very likely from lymphatic endothelium. This conclusion is based on light microscopic and morbid anatomical observations and is further supported by the unique distribution of lesions in the skin, and in the submucosa of the gastrointestinal tract, following the lines of lymphatics; by the remarkable predilection of KS for lymph nodes (often without skin lesions); by the absence of lesions in organs which are devoid of lymphatics, i.e. the brain and eyeball; and by observations made by the author and others, utilizing electron microscopy, enzyme histochemistry and immunohistochemistry. It is recognized nonetheless that reactive elements such as fibroblasts, myofibroblasts and histiocytes may also be involved in the proliferative process.

Theories of the nature and origin of the spindle cells of Kaposi's sarcoma (KS) have stimulated lively discussions and speculation in the literature and, at times, heated debate at symposia organized by various agencies in an effort to resolve this controversy. This author had the privilege of attending the symposium on Kaposi's sarcoma held at Makerere Medical College, Kampala, Uganda in

1961, under the auspices of the Union Internationale Contre Cancrum (1). Various arguments were put forward by different observers in support of their hypotheses. In his summation, Becker (2) noted that indirect evidence had been advanced for an origin from the following cellular sources: reticuloendothelial system; primitive mesenchymal cells; neuromyoarterial apparatus; blood vascular endothelium; lymph vascular endothelium; fibroblast; smooth muscle; perithelial cells; combined endothelial and perithelial cells; and the perivascular Schwann cell.

In the early years hypotheses were based largely on morphological observations correlated with clinical behavior and course of the disease. Subsequently, methods such as enzyme histochemistry and electron microscopy were applied to the study of KS. Attempts were made to establish cell lines in tissue culture and to reproduce the disease experimentally in animals. During the past decade more sophisticated methods, such as the application of monoclonal antibodies and techniques to identify viral genomes have been utilized in the investigation of this enigmatic disorder. A review of the literature indicates that the endothelial cell represents the most likely source of origin of the spindle cell of KS (3-14); however, there is still much discussion as to whether this cell is of lymphatic or blood vascular derivation. Since 1961, based initially on the results of enzyme

histochemical studies of KS (3), I have steadfastly supported the origin of KS from the lymphatic system. The weight of evidence, provided by recent reports, clearly favors this hypothesis, an analysis of which comprises the subject of this paper.

Light microscopic, anatomical, and clinical observations

The histogenesis of the spindle cells in KS has interested investigators as far back as 1899, when Schwimmer (15) suggested an origin from lymphatic endothelial cells. Lothe and Murray (16), participants at the Kampala symposium in 1961, emphasized the predominant localization of lesions in the lymphatic system of African children and the striking distribution of lesions around blood vessels, often in the form of thick strands of tumor tissue extending around the outer walls of these vessels for a considerable distance. This distribution could be seen by the naked eye to follow the portal tracts in the liver and histologically to be closely associated with branching blood vessels in the spleen and in the lung. The location of these lesions was considered to be in keeping with their origin from lymphatics, present in the outer coat of blood vessels. Tumor tissue could also be seen around nerve fibers and along the lines of lymphatics in the limbs (*Fig. 1*). The striking absence of lesions in the brain and in the eyeball was emphasized and it was noted that these organs are devoid of lymphatics, apart from small capillaries following the course of blood vessels and cranial nerves.

It was suggested that the various hemodynamic disturbances exhibited by some patients with KS could be explained on the basis of lymphaticovenous anastomoses. Such lesions were in fact demonstrated by Palmer (17) during the Kampala conference. Some twenty-five years later, Dictor (6), after a review of histopathologic material from nine autopsies and 35 skin biopsy specimens of KS in male homosexuals, indicated that aber-

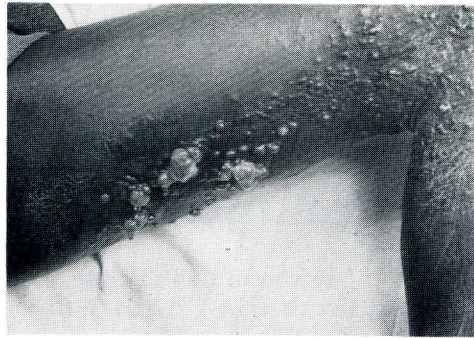


Fig. 1. Ulcerating and "lymphangiomatous" lesions of Kaposi's sarcoma distributed along the lines of lymphatics in the lower limb of an African male (reprinted with permission from Karger, S, AG Basel, P Keen. The clinical features of Kaposi's sarcoma in the South African Bantu. (Acta Union Int. Contre. Cancrum 18 (1962), 380-388).

rant venous connections occur in the earliest stage of Kaposi's sarcoma. He suggested that the initiation of the lesion may be an abnormal recapitulation of the coupling of venous and lymphatic sinuses which occurs during embryonic growth.

More recently, Beckstead et al. (7) and Dorfman et al. (13) have noted a pattern of morphologic development suggestive of lymphatic origin. The earliest lesions in skin and lymph nodes appear to consist of irregular, thin-walled vascular spaces lined by endothelial cells morphologically consistent with lymphatics. In the dermis these vascular structures surround and separate preexisting collagen bundles, vessels and nerves to form a distinct spongy network. In more advanced lesions, the picture is complicated by neovascularization, producing distinctive structures with a core composed of morphologically and phenotypically normal capillary, venule or arteriole, a modest amount of collagen and moderate numbers of inflammatory cells, covered by layers of proliferating abnormal endothelial cells. With further proliferation the abnormal endothelial cells accumulate and occasionally form solid cords. The vascular cores also proliferate, apparently in response to the tumor. This proliferation produces vascular lesions in which the abnormal endothelium may be difficult to distinguish from

the reactive normal vessels. Continued proliferation of the abnormal endothelial cells ultimately overwhelms other elements resulting in solid sheets of spindled cells. Inflammatory cells, particularly plasma cells and macrophages containing hemosiderin pigment, are frequently intermixed.

Angiosarcomas of blood vascular origin arise primarily in the skin and/or viscera (such as spleen or liver) and metastasize via the blood stream to distant organs including the brain and lung. This contrasts with the manifestations of KS which, in some instances shows a predilection for lymph nodes, often without skin lesions, particularly in African children (5) (Figs. 2 and 3), and



Fig. 2. Lymphadenopathic Kaposi's sarcoma in a 2-1/2 year old South African boy. Note massive enlargement of preauricular, postauricular and cervical lymph nodes (reprinted with permission from Raven Press. Dorfman, RF. Kaposi's sarcoma, with special reference to its manifestations in infants and children and to the concepts of Arthur Purdy Stout. *Am. J. Surg. Pathol.* 10(suppl.1) (1986), 68-77).

occasionally in elderly heterosexual men. Lymphadenopathic KS has more recently been described in homosexual men and in children with AIDS (5,18,19). The spread of KS supports multicentric origin rather than metastasis, as evidenced by the remarkable symmetry of skin lesions that may be encountered in patients with KS (5) (Fig. 4) and by the character of the edema which occurs in patients with advanced disease (Fig. 5).

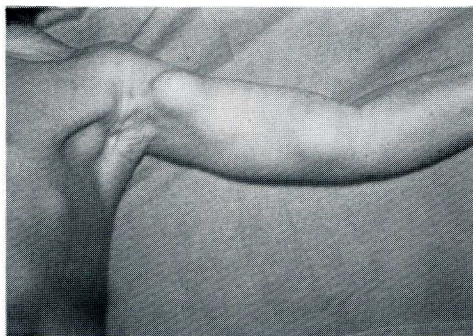


Fig. 3. Lymphadenopathic KS in a 2-1/2 year old South African boy with involvement of axillary and epitrochlear lymph nodes (reprinted with permission from Raven Press. Dorfman, RF. Kaposi's sarcoma with special reference to its manifestations in infants and children and to the concepts of Arthur Purdy Stout. *Am. J. Surg. Pathol.* 10(suppl.1) (1986), 68-77).



Fig. 4. Cutaneous KS in an adult African, demonstrating the remarkable symmetry of plaque lesions on the dorsum of both hands (reprinted with permission from Raven Press. Dorfman, RF. Kaposi's sarcoma with special reference to its manifestation in infants and to the concepts of Arthur Purdy Stout. *Am. J. Surg. Pathol.* 10(suppl.1) (1986), 68-77).

Observations at the electron microscopic level

In 1964, I recorded an ultrastructural study of biopsies from three black African and three white American patients



Fig. 5. Advanced KS in the lower limbs of an African male associated with prominent lymphedema.

with KS (20). In retrospect the ultrastructural findings were identical to those recently described by McNutt et al. (21) in early lesions of Kaposi's sarcoma in homosexual men. These authors reported that 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. They also noted the presence of necrotic endothelial cells, fragmentation of basal lamina, and breaks in the continuity of the capillary endothelium, providing a mechanism for the extravasation of erythrocytes, presumed to enter the lymphatic system via abnormal lymphatic-venous anastomoses. Similar observations were made by this author (4) (Fig. 6).

Enzyme histochemical and immunohistochemical studies

My observation of strong alkaline phosphatase activity in the endothelial cells of vessels surrounding fascicles of spindle cells of KS in contrast to the complete absence of such enzyme activity in the spindle cells (Fig. 7), provided strong evidence against their origin from blood vessel endothelium or from fibroblasts (3). I postulated that multicentric neof ormation of lymphatics was a primary process in the histogenesis of Kaposi's sarcoma and that the predominant localization of lesions corresponded to the normal distribution of lymphatics.

More recently Beckstead et al. (7), utilizing a combination of enzyme histochemical and immunohistochemical techniques concluded that the phenotype of the spindle cells in Kaposi's sarcoma closely resembled that of lymphatic endothelium but not of blood vessel endothelium. The phenotype demonstrated (FVIIIIRAg⁻ negative, HLA-DR/la⁻ negative, MO/E⁻ negative, UEA⁺ positive, ATP⁻ negative, Alkaline phosphatase⁻ negative, 5' nucleotidase⁺ positive) is similar to that of normal lymphatic endothelium.

There is much controversy over the presence or absence of factor VIII-related antigen in the spindle cells of KS (8-11,13). Moreover there is a difference of opinion as to whether FVIIIIRAg is present in normal lymphatics (8,11,23-26). These conflicting opinions have raised the issue of variation in antibody specificity and sensitivity and of differences in methodology (22,27,28).

It may also be pertinent to point out that recent immunohistochemical studies by Turner et al. (29) have identified phenotypic subsets of endothelial cells that correlate with specific morphological subtypes. These include (a) arterioles, capillaries, and venules; (b) high endothelial venules and hepatic sinusoidal lining cells; (c) lymphatics and glomerular capillaries; (d) splenic sinusoidal lining cells; and (e) umbilical cord endothelial

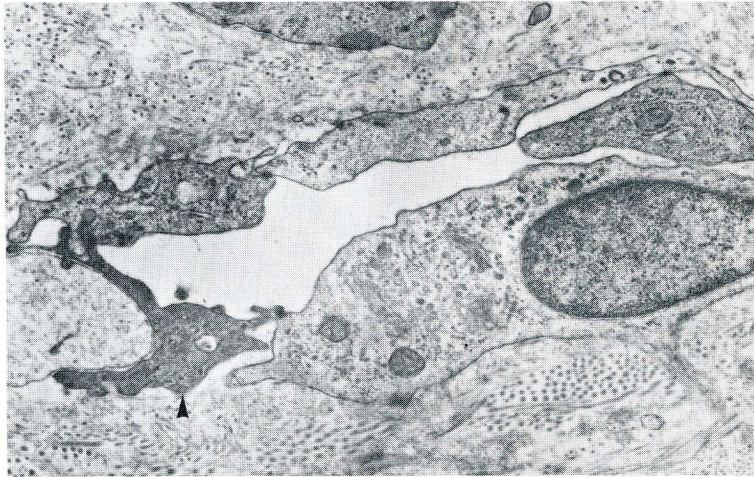


Fig. 6. Cutaneous KS in an elderly heterosexual man. A small capillary shows discontinuity of the endothelium, with fragmentation of the basal lamina and degenerative changes in the cytoplasm of one shrunken endothelial cell (arrowhead) (uranyl acetate and lead citrate stain $\times 15,000$) (reprinted with permission from W.B. Saunders Company. Dorfman, RF. Kaposi's sarcoma revisited. *Hum. Pathol.* 15 (1984), 1013-1017).

cells. Moreover, some of these endothelial cells share functional and phenotypic properties with cells of the monocyte-macrophage lineage.

Nonetheless, the majority of reports have emphasized that the spindle cells of KS fail to elaborate FVIIIIRAg (5,7,8,11,13,14). Because immunohistochemical staining for FVIIIIRAg in KS has led to such confusion, it is clear that this antigen is not a reliable and reproducible immunohistochemical marker for the spindle cell component of KS.

Kaposi's sarcoma and the lymphatic system

In preparation for this symposium participants were requested to provide a brief description of their hypotheses of the pathogenesis of Kaposi's sarcoma and its relationship to one or more of the components of the lymphatic system. My hypothesis is based on the above-described observations, previously reported (3-5,12,13,19) and summarized briefly in a contribution to "Lymphspiration" (12). Reference was made in the latter article to Graham et al.'s concentration on the controversy over the

staining characteristics of vascular endothelium and of the spindle cells of KS for FVIIIIRAg (24). It was emphasized that my hypothesis was initially proposed in 1962 (3), some 13 years before the identification of FVIIIIRAg and more than 15 years before the development of monoclonal antibodies to this antigen. Graham et al. (24) had suggested the use of a second endothelial marker such as *Ulex europaeus* lectin (UEA) in the study of KS. Beckstead et al. (7) recently utilized UEA in their investigations and concluded that the phenotype of the neoplastic cells in KS closely resembled that of lymphatic endothelium but not of blood vessel endothelium. Jones et al. (11) carried out similar studies and strongly favored a lymphatic derivation for this tumor. They indicated that this has important implications as it suggests that lymphatic endothelium may have special characteristics that lead to neoplastic transformation in patients with retrovirus infections.

Is Kaposi's sarcoma a malignant tumor?

Surprisingly, this is a matter of dispute (3). Lo and Liotta (31) have pro-

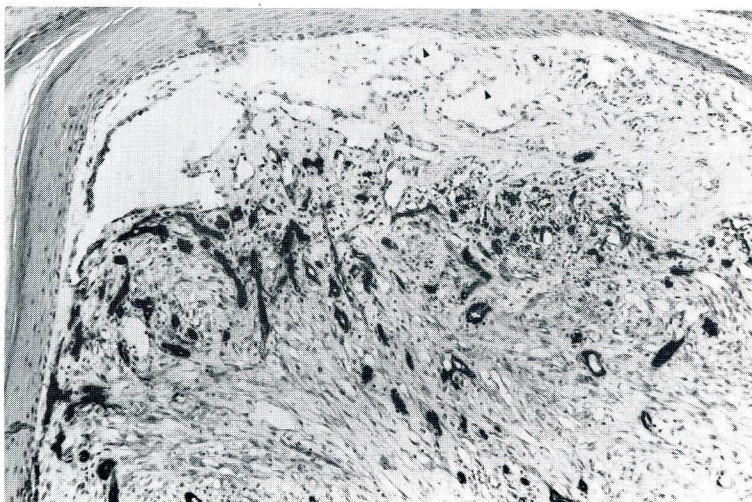


Fig. 7. Cutaneous Kaposi's sarcoma in a heterosexual adult African. Alkaline phosphatase activity is evident in the endothelial cells lining capillaries in the mid-dermis and endothelium lining dilated lymphatics in the upper dermis (small arrowheads) show no activity of this enzyme (calcium-cobalt method. Nuclear fast red counterstain $\times 120$) (reprinted with permission from Karger, S, AG Basel. Kaposi's sarcoma; the contribution of enzyme histochemistry to the identification of cell types. *Acta. Union Int. Contre. Cancrum* 18 (1962), 464-476).

vided powerful support for the neoplastic nature of KS. They reported that DNA obtained from Kaposi's sarcoma tissue successfully transformed phenotypically normal NIH/3T3 cells: when injected into nude mice, the transfected lines produced vascular tumors, which they considered histopathologically similar to KS. Thus Lo and Liotta suggest that DNA from KS may contain one or more distinct transforming genes.

The question of malignancy can be approached in other ways, i.e.:

1. Establish cell lines in culture in order to determine whether these are immortal.
2. The detection of activated oncogenes in these cell lines (and perhaps in cells derived from tissues).
3. Karyotype analysis--do these cell lines possess abnormal karyotypes?
4. Can tumors be induced in appropriate hosts by passive transfer of cell lines?
5. Do these cell lines contain viral genomes, i.e. CMV, EBV, or HIV?
6. Is it possible to establish clonality

using cell lines from an established cell culture derived from a female patient by determining which X-chromosome might be inactivated? This should be based on studies of isoenzymes (e.g., glucose-6-phosphate dehydrogenase, which is an X-chromosome-linked gene; if both isoenzymes of G6PD are present, this would indicate polyclonality).

If KS is a malignant tumor, what is the origin of the spindle cell?

The controversy over the specificity of FVIIIIRAg for normal vascular endothelial cells versus lymphatic endothelial cells, let alone the discrepancy as to whether the spindle cells of KS react with monoclonal or polyclonal antibodies directed against this antigen, suggest that the use of this marker is not the appropriate manner in which to investigate this problem. A better approach would be to establish cell lines in tissue culture, and attempt to prepare more specific monoclonal antibodies. Confirmation of clon-

ality along the lines suggested above would also be helpful in identifying the spindle cell as representative of the malignant clone. Confirmation of Lo and Liotta's findings (3) by other workers would also be most important.

Why is KS declining in the AIDS population in contrast to the increasing frequency of malignant lymphomas?

Experiments to study this phenomenon should include epidemiological studies and the identification of antibody titers directed against Epstein-Barr virus, cytomegalovirus and the human immunodeficiency virus. One assumes that the malignant lymphomas occurring in immunocompromised patients are EBV induced, whereas it is more likely that Kaposi's sarcoma is CMV induced. Thus, epidemiological studies of antibody titers directed against these two viruses would provide important information. Identification of viral genomes (EBV in patients with malignant lymphomas and CMV in Kaposi's sarcoma) would be the minimum requirement to identify such an association.

Reconstituting immunity invokes the immune surveillance system (particularly in patients with malignant lymphoma) and may be used as a method of treating these patients. It would be interesting to determine whether the same strategy could be employed in the treatment or perhaps prevention of Kaposi's sarcoma, utilizing drugs that are immunostimulants.

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