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The Histogenesis of Kaposi's Sarcoma

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The histogenesis of Kaposi's sarcoma has been controversial since its first description by Moritz Kaposi in 1872 (1). Although previously rare, the recent increase in its incidence associated with the acquired immune deficiency syndrome (AIDS) (2) has stimulated new interest in its origin. Early studies of the histogenesis have been the subject of several reviews (3,4). A remarkable list of cells of origin was proposed in these early studies. However, more recent studies have focused on an endothelial or pluripotent mesenchymal cell origin. These studies, utilizing electron microscopy, enzyme histochemistry and immunohistochemistry have also failed to unequivocally establish the cell of origin in Kaposi's sarcoma (5-27).

We have rigorously tested the prevailing hypothesis that the lesion is derived from vascular endothelial cells. We utilized a combination of enzyme histochemistry and immunohistochemistry in plastic and frozen sections. We used seven markers to characterize human endothelial cells: three antigens (Factor VIII-related antigen, HLA-DR/Ia, macrophage/endothelial antigens), three enzymes (5'-nucleotidase, ATPase, alkaline phosphatase), and lectin binding (*Ulex europaeus* I). We found distinctive phenotypes for normal vascular and lymphatic endothelial cells and that the abnormal cells of Kaposi's sarcoma most closely resembled the phenotype seen in lymphatic endothelium.

Materials & Methods

Biopsy specimens from 40 patients were studied with plastic embedding techniques. All of these specimens were examined histochemically for 5'-nucleotidase, ATPase, and alkaline phosphatase, immunohistochemically for Factor VIII-related antigen (FVIII RA), and HLA-DR/Ia antigen, using immunoperoxidase, and also with the *Ulex europaeus* I (UEA) lectin directly conjugated to peroxidase. The details of these procedures have been previously published (28-31). Biopsies from an additional 9 patients were snap-frozen, cryostat-sectioned, and stained immunohistochemically for FVIII RA, HLA-DR/Ia, and 3 macrophage/endothelial (M ϕ /E) antigens (clones 63D3 and 61D3 from D. Capra, University of Texas at Dallas, and Leu M3), using previously described procedures (30,32).

Results

These studies revealed considerable phenotypic variation in the endothelial cells of different vessel types. This is summarized in Table 1.

Table 1—Characterization of Normal Human Endothelium

Endothelium	Staining With Endothelial Markers						
	FVIII RA	HLA-DR/Ia	UEA	Alk ϕ	ATPase	5'-N	M ϕ /E
Lymphatic	0*	0*	+++	0	0	+++	0*
Arteriole	++	++	++	++	++	+	+
Capillary	+++	++	++	+++	++	++	+
Venule	+++	++	++	+	++	+	+

FVIII RA, Factor VIII-related antigen; HLA-DR/Ia, HLA-DR/Ia-like antigen; UEA, *Ulex europaeus* I lectin; M ϕ /E, macrophage/endothelial antigens; Alk ϕ , alkaline phosphatase; 5'-N, 5'-nucleotidase; ATPase, adenosine triphosphatase; 0, negative; 0*, a rare weakly positive cell; +, weakly positive; ++, positive; +++, strongly positive.

Only minor differences were apparent in the phenotypes of the different blood vessel endothelial cells, but there were significant deviations from this phenotype in the lymphatic endothelial cells. Lymphatic endothelium lacked the enzymes ATPase and Alk ϕ but had the strongest 5'-N reaction of all vessels. There was very little staining with HLA/DR, FVIII RA, or M ϕ /E antigens, but a strong reaction with UEA was seen.

The lesions of Kaposi's sarcoma are frequently a complex mixture of normal vessels and a spectrum of abnormal elements ranging from irregular vascular channels to spindle cells. The abnormal endothelial cells showed consistent staining with UEA and 5'-N, although the staining was weaker and more patchy in the spindle cells. The other endothelial markers (FVIII RA, HLA-DR/Ia, and M ϕ /E, Alk ϕ , ATP) generally failed to stain the abnormal endothelial cells or spindle cells. All the normal vessels in the lesion showed a staining pattern consistent with normal blood vessel endothelium and served as internal controls. These results are summarized in Table 2.

Table 2—Characterization of Kaposi's Sarcoma

Cell type	Staining with endothelial markers*						
	FVIII RA	HLA-DR/Ia	UEA	Alk ϕ	ATPase	5'-N	M ϕ /E
Plastic sections							
Abnormal endothelial cells of Kaposi's sarcoma	0/34	0/35	30/36	0/40	0/38	27/31	ND
Spindle cells of Kaposi's sarcoma	1/22	0/20	15/22	0/25	0/23	5/16	ND
Frozen sections							
Spindle cells of Kaposi's sarcoma	2/9	0/9	ND	ND	ND	ND	0/9

FVIII RA, Factor VIII-related antigen; HLA-DR/Ia, HLA-DR/Ia-like antigen; UEA, *Ulex europaeus* I lectin; Alk ϕ , alkaline phosphatase; ATPase, Adenosine triphosphatase; 5'-N, 5'-nucleotidase; ND, not done.

* Data are given as number of cases positive per number of cases tested with adequate survival of marker. Only solid clusters of abnormal spindle cells are tabulated so that confusion with reactive stromal elements is avoided.

Discussion

We have demonstrated that the phenotype of the abnormal proliferating cell in Kaposi's sarcoma differs significantly from that of non-neoplastic blood vessel endothelium. The phenotype [FVIII RA(-), HLA-DR/Ia(-), M ϕ /E(-), UEA(+), ATP(-), Alk ϕ (-), 5'-N(+)] more closely resembles that of normal lymphatic endothelium. This data is supported by the electron-microscopic studies of McNutt et al. (18), who found a striking similarity between early Kaposi's lesions and dermal lymphatics. A lymphatic endothelial origin has also been suggested by several early studies based on clinicopathologic data (3,4,7).

We conclude that the irregular vascular spaces in the earliest recognizable lesions of Kaposi's sarcoma are formed by cells closely resembling lymphatic endothelial cells. These lesions are complex with an intermixture of inflammatory cells and neovascularization by phenotypically normal blood vessels. With continued proliferation some of the abnormal endothelial cells lose the ability to form channels which is accompanied by a considerable loss of UEA binding and 5'-N. Morphologic evidence of clear transitions between these two states suggests that the spindle cell element is derived from the abnormal endothelial cells. These studies strongly suggest that the lymphatic endothelial cell is the cell of origin in Kaposi's sarcoma.

References

1. Kaposi, M.: Idiopathisches multiplex Pigment Sarcoma der Haut (English transl., *Ca--A Cancer J. for Clinicians* 32: 342-347, 1982). *Arch. Dermatol. Syphilis* 4: 265-273, 1872.
2. Friedman-Kien, A. E., Laubenstein, L. J., Rubenstein, P., et al.: Disseminated Kaposi's sarcoma in homosexual men. *Ann. Int. Med.* 96: 693-700, 1982.
3. Tedeshi, C. G.: Some considerations concerning the nature of the so-called sarcoma of Kaposi. *Arch. Pathol.* 66: 656-684, 1958.
4. Bluefarb, S. M.: Kaposi's Sarcoma: Multiple Idiopathic Hemorrhagic Sarcoma. Charles C. Thomas, Springfield, IL, 1957.
5. Kopf, A. W.: The distribution of alkaline phosphatase in normal and pathologic human skin. *Arch. Dermatol.* 75: 1-37, 1957.
6. Pepler, W. J.: The origin of Kaposi's haemangiosarcoma: A histochemical study. *J. Pathol. Bacteriol.* 78: 553-557, 1959.
7. Dorfman, R. F.: Kaposi's sarcoma: The contribution of enzyme histochemistry to the identification of cell types. *Acta Un. Int. Cancer* 18: 464-476, 1962.
8. Becker, J. P.: The histogenesis of Kaposi's sarcoma. *Acta Un. Int. Cancer* 18: 477-486, 1962.
9. Mustakallio, K. K., Levonen, E., and Raekallio, J.: Histochemistry of Kaposi's sarcoma: I. Hydrolases and phosphorylase. *Exp. Mol. Pathol.* 2: 303-316, 1963.
10. Hashimoto, K., and Lever, W. F.: Kaposi's sarcoma: Histochemical and electron microscope studies. *J. Invest. Dermatol.* 43: 539-549, 1964.
11. Niemi, M., Raekallio, J., Levonen, E., and Mustakallio, K. K.: Histochemistry of Kaposi's sarcoma: II. Cholinesterases, monoamine oxidase, and adenosine triphosphatase. *Exp. Mol. Pathol.* 3: 648-657, 1964.
12. Braun-Falco, O., and Schmoeckel C. Hubner, G.: Zur Histogenese des Sarcoma idiopathicum multiplex haemorrhagicum (Morbus Kaposi): Eine histochemische und elektronenmikroskopische Studie. *Virchows Arch. [Pathol. Anat.]* 369: 215-227, 1976.
13. Sterry, W., Steigleder, G., and Bodeux, E.: Kaposi's sarcoma: Venous

- capillary hemangioblastoma. A histochemical and ultrastructural study. *Arch. Dermatol. Res.* 266: 253-267, 1979.
14. Niemi, M., and Mustakallio, K. K.: The fine structure of the spindle cell in Kaposi's sarcoma. *Arch. Pathol. Microbiol. Scand.* 63: 567-575, 1965.
 15. Mottaz, J. H., and Zelickson, A. S.: Electron microscope observations of Kaposi's sarcoma. *Acta Derma-Venereol.* 46: 195-200, 1966.
 16. Gokel, J. M., Kurzl, R., and Hubner, G.: Fine structure and origin of Kaposi's sarcoma. *Pathol. Europ.* 11: 45-47, 1978.
 17. Harrison, A. C., and Kahn, L. B.: Myogenic cells in Kaposi's sarcoma: An ultrastructural study. *J. Pathol.* 124:157-160, 1978.
 18. McNutt, N. S., Fletcher, V., and Conant, M. A.: Early lesions of Kaposi's sarcoma in homosexual men: An ultrastructural comparison with other vascular proliferations in skin. *Am. J. Pathol.* 111: 62-77, 1983.
 19. Akhtar, M., Bunuan, H., Ashraf, M., and Godwin, J. T.: Kaposi's sarcoma in renal transplant recipients: Ultrastructural and immunoperoxidase study of four cases. *Cancer* 53: 258-266, 1984.
 20. Burgdorf, W. H. C., Mukai, K., and Rosai, J.: Immunohistochemical identification of factor VIII-related antigen in endothelial cells of cutaneous lesions of alleged vascular nature. *Am. J. Clin. Pathol.* 75: 167-171, 1981.
 21. Sehested, M., and Hou-Jensen, K.: Factor VIII-related antigen as an endothelial cell marker in benign and malignant diseases. *Virchow's Arch. [Pathol. Anat.]* 391: 217-225, 1981.
 22. Miettinen, M., Holthofer, H., Lehto, V., Miettinen, A., and Virtanen, I.: *Ulex europaeus* I lectin as a marker for tumors derived from endothelial cells. *Am. J. Clin. Pathol.* 79: 32-36, 1983.
 23. Nadji, M., Morales, A. R., Ziegler-Weisman, J., and Penneys, N. S.: Kaposi's sarcoma. Immunohistochemical evidence for an endothelial origin. *Arch. Pathol. Lab. Med.* 105: 274-275, 1981.
 24. Guarda, L. G., Silva, E. G., Ordonez, N. G., and Smith, J. L., Jr.: Factor VIII in Kaposi's sarcoma. *Am. J. Clin. Pathol.* 76: 197-200, 1981.
 25. Modlin, R. L., Hofman, F. M., Kempf, R. A., Taylor, C. R., Conant, M. A., and Rea, T. H.: Kaposi's sarcoma in homosexual men: An immunohistochemical study. *J. Am. Acad. Dermatol.* 8: 620-627, 1983.
 26. Flotte, T. J., Hatcher, V. A., and Friedman-Kien, A. E.: Factor VIII-related antigen in Kaposi's sarcoma of young homosexual men. *Arch. Dermatol.* 120: 180-182, 1984.
 27. Ordonez, N. G., and Batskis, J. G.: Comparison of *Ulex europaeus* I lectin and factor VIII-related antigen in vascular lesions. *Arch. Pathol. Lab. Med.* 108: 129-132, 1984.
 28. Beckstead, J. H., Halverson, P. S., Ries, C. A., and Bainton, D. F.: Enzyme histochemistry and immunohistochemistry on biopsy specimens of pathologic human bone marrow. *Blood* 57: 1088-1098, 1981.
 29. Beckstead, J. H.: The evaluation of human lymph nodes, using plastic sections and enzyme histochemistry. *Am. J. Clin. Pathol.* 80: 131-139, 1983.
 30. Beckstead, J. H., Wood, G. S., and Fletcher, V.: Evidence for the origin of Kaposi's sarcoma from lymphatic endothelium. *Am. J. Pathol.* 119: 294-300, 1985.
 31. Beckstead, J. H.: Optimal antigen localization in human tissues using aldehyde-fixed plastic-embedded sections. *J. Histochem. Cytochem.* 33: 954-958, 1985.
 32. Wood, G. S., and Warnke, R.: Suppression of endogenous avidin-binding activity in tissues and its relevance to biotin-avidin detection systems. *J. Histochem. Cytochem.* 29: 1096-1204, 1981.