MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA OF KAPOSI*

HISTOPATHOLOGIC STUDY

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Many titles and concepts of pathogenesis have been advanced since Kaposi (1) first described this disease in 1872 as "idiopathic multiple pigment sarcoma of the skin." Paun- trier and Diss (2) attributed the disease to a dysgenesis of the vessels and their neuromuscu- lar elements, and a proliferation of Schwann cells with formation of the Wagner-Meissner type of tactile corpuscle. Hudelo and Cailleau (3) believed the process was due exclusively to the proliferation of sympathetic perivascular nerve fibers. Becker and Thatcher (4), despite the use of nerve stains, were unable to confirm these findings, nor, after studying the phagocytic properties of the cells, did they agree with Dorfitt (5) that the lesions were caused by disease of the reticulo-endothelial system. They suggest that Kaposi's carcinoma has a multicentric origin from embryonal mesenchymal cells in the perithelial tissue and that degeneration of these cells may result in a true sarcoma with metastasis.

Dalla Favera (6), Lane and Greenwood (7), Dupont (8), and Dillard and Weidman (9) supported the reticulo-endothelial origin. The last stated that Kaposi's sarcoma is primarily inflammatory in nature, but may become secondarily sarcomatous. They also made the suggestion that the products of blood degeneration might act as the endothelial stim- ulus. Pollitzer (10), Balzes, Merle and Rubens Duval (11), and Lieberthal (12) stressed the sarcomatous nature of the disease. Ewing (13) agreed that the late stages might acquire neoplastic properties and give rise to a spindle cell sarcoma, but pointed out that the prominence of inflammatory signs indicated an infectious origin of granulomatous type with special involvement of the capillary endothelium. MacKee and Cipollaro (14) concurred with this opinion.

MacLeod (15) considered the process to be a proliferation of organizing connective tissue with vascular dilatation. Gilchrist and Ketron (16) thought that the disease started as an angiomia and the tumor stage resulted from proliferation of connective tissue and endothelium. DeAmicis (17) said that it is intermediate between a granuloma and a sarcoma. Rainel (18) classified it as an endothelioma and Lang and Haslhofer (19) interpreted it as a systemic angiomatosis.

We believe that Kaposi's sarcoma is never a simple inflammatory process. New blood vessels and spindle cells are present in all our sections, even those from a pinhead-sized lesion of one week's duration (figs. 1 and 2). We feel that from the beginning this disease is a potential sarcoma, that all lesions do not necessarily terminate as neoplasms, and that it may be considered a systemic angiosarcomatosis.

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HISTOPATHOLOGY

Idiopathic multiple hemorrhagic sarcoma of Kaposi is often classified as early or late, and as inflammatory, granulomatous or neoplastic. Such division is not entirely correct, for the pathologic picture does not always coincide with the duration of the process. Besides, more than one stage may exist at the same time. While such a classification is arbitrary, it is convenient and often helps to correlate the pathologic with the clinical picture.

The pathologic picture of Kaposi's sarcoma shows new blood and lymph vessels, cellular elements, connective tissue hyperplasia and hemorrhage. The cellular elements include small round cells, wandering connective tissue cells, plasma cells, angioblasts, spindle cells and fibroblasts. The process is primary in the cutis; the epidermis shows no change unless secondarily involved. The microscopic picture depends upon the phase and type of clinical lesion examined. Any of the above features may predominate and the section simulate such unrelated dermatoses as angiomas, granulomas, apparently innocent inflammatory reactions or highly malignant sarcomas.

Before any of the features show pronounced proliferation, the findings are those described by others in the early or inflammatory stage (fig. 3). The blood vessels of the upper and mid cutis are dilated, increased in number, frequently filled with blood elements, and arranged in groups or scattered diffusely throughout the cutis. The endothelial cells are swollen and have large vesicular nuclei projecting into the lumen (fig. 4). These nuclei may be round and somewhat hyperchromatic, rather than oval and vesicular. Instead of being elongated, the cells may appear rectangular (cross-section of the endothelial cell) and resemble somewhat the embryonic plasma cell of young granulation tissue. The lymph vessels and spaces are prominent. The cellular infiltration is sparse, perivascular as well as diffuse, and composed of small round and wandering connective tissue cells, angioblasts and some spindle cells. Plasma and mast cells are occasionally seen. There is no hyperplasia of connective tissue and no changes in the elastic tissue. Erythrocytes, or intracellular or extracellular granules of hemosiderin indicates hemorrhage.

As the process develops (late stage—granulomatous or neoplastic), different pictures are noted as vascular, connective tissue or cellular hyperplasia becomes prominent (fig. 5). With the proliferation of vessels, the appearance is that of an angioma (fig. 6). Vascular and cellular hyperplasia may mimic granulomas,
**Fig. 3.** Showing a Diffuse Process with Dilated Blood and Lymph Vessels, Some Lymph Spaces, and a Moderate Cellular Infiltration (98X)

**Fig. 4.** Showing Vascular Hyperplasia, Intimal Changes and a Cellular Reaction Composed of Angioblasts and Spindle Cells (700X)
glomus tumor and granuloma pyogenicum. If the vessels are associated with numerous angioblasts, Kaposi's sarcoma may simulate angiosarcoma, perithelioma or endothelioma (fig. 7). In some of our sections, there were areas that in no way differed from glomus tumor (fig. 8). Where spindle cell proliferation is the characteristic feature, the result is a spindle cell sarcoma (fig. 9). Masses of cells extend in all directions and at times show mitotic figures; other cellular elements, as well as vascular and connective tissue hyperplasia, are not prominent. If the connective tissue, rather than cellular elements, is increased, the picture suggests an angiofibroma. The growth of fibrous tissue is never

![Image of vascular and connective tissue hyperplasia and cellular reaction of angioblasts and spindle cells.](image)

**Fig. 5. Showing Vascular and Connective Tissue Hyperplasia and a Pronounced Cellular Reaction of Angioblasts and Spindle Cells**

Considerable pigment is present in the section (38X)

extensive and frequently separates the process into lobules. Frequently, areas characteristic of the various dermatoses mentioned above are seen in the same section.

The epidermis plays no primary role in the process, and changes such as thinning, acanthosis, or breaking down are secondary. The pathologic changes in Kaposi's sarcoma are in the cutis. Vascular hyperplasia, hemorrhage, angioblasts and spindle cells are found throughout the evolution of the disease except perhaps in the development of spindle cell sarcoma where the proliferation of spindle cells overshadows all other features.

Since the cytology is so important in the microscopic diagnosis of this disease, further discussion of some of the cellular elements is warranted. This, we realize,
is beset with many difficulties because of inability to actually prove contentions, and the vast differences of opinion which exist among authorities as to genesis, morphology and nomenclature.

_Spindle cells_ are found only in spindle cell sarcoma, or in a process which may eventuate in such a sarcoma. We are led to believe that the sarcomatous process is not due to a simple accumulation of spindle cells from the parent cells, but may depend on proliferation of these cells from other spindle cells. The numerous mitotic figures found in these cells would substantiate this view (fig. 10). The cytoplasm of the spindle cell is scant and the cell tapers to a point at either end; the nucleus is narrow, oval and vesicular with loosely arranged and lightly stained chromatin. The length of the cell is approximately twice that of the nucleus. We doubt that this cell plays any role in the production of collagen. Many different types of cells, even epithelial cells, may have spindle shapes; such cells should be referred to, not as spindle cells, but as spindle-shaped cells.

The relation of the _fibroblast_ to the spindle cell is unknown. Contrary to the opinion of many, we believe that the two cells are different in morphology, in function and probably in derivation. The fibroblast is much larger in all dimensions and often has fiber-like projections extending from the tapering points. It has an oval vesicular nucleus which is larger and of greater diameter than the nucleus of the spindle cell. The fibroblast is approximately two to three times the size of the spindle cell. Unlike the spindle cell, the fibroblast does form collagen.

**Fig. 10. Showing Spindle Cells with Mitotic Figures in Kaposi's Sarcoma (700X)**
The angioblast is thought to arise from endothelial cells and is referred to by some observers as an endothelioid cell. Maximow and Blum (20) believe that the term angioblast should not be used at all. While the term endothelioid cell may be acceptable, we prefer to retain the name angioblast because these cells are said to give rise to new vessels and because the mature cell usually does not resemble an endothelial cell. The angioblast has a round nucleus approximately 1½—2 times the size of the nucleus of a lymphocyte. It stains deeply, but the chromatin does not appear as a solid mass. As a rule, little or no cytoplasm is observed. However, a few of our sections show the angioblasts with considerable cytoplasm. This is not unlike the polyhedral, pavement-like appearance of endothelial cells when the flat surface is examined.

The origin of plasma cells is still unsettled. It is possible that they may be derived from the endothelial cell or from an intermediary cell which itself has arisen from an endothelial cell. The plasma cell is acorn- or pear-shaped with an eccentric nucleus. The chromatin of the nucleus is arranged at the periphery in several minute collections like the spokes of a wheel. The cytoplasm is homogeneous. The cell is easily seen and recognized with the hematoxylin stain and only rarely are special stains necessary to determine the nature of the cell. The shape of the plasma cell may differ from the usual and occasionally appear round, rectangular or even spindle-shaped. Beside the common plasma cell, multinucleated or Marschalko plasma cells may be seen (fig. 11).

The derivation of the small round cell is undecided. Some believe them to be related to lymphocytes, others do not. We are inclined to agree with the latter. The presence of small round cells in this process is a response to tissue injury and is no different from their presence in any other pathologic process. The morphology of the small round cell is different from that of the lymphocyte as seen in lymphatic leukemia. The nucleus is more solid, irregular in shape and size, and has no cytoplasm about it. Such cells are not seen in the circulating blood nor in the lumen of vessels.

We believe hemorrhage is secondary rather than primary, and is the result of erythrocytes wandering into the surrounding tissue from imperfectly formed new vessels or through ruptured or damaged vessels. The proliferation of thin-walled vessels is thus to be considered the primary process and hemorrhage is secondary.

DIFFERENTIAL DIAGNOSIS

The diseases to be considered in the differential diagnosis depend on the characteristic feature or features noted. The list of such diseases is long, and only the more important will be discussed here.

In the early phases of Kaposi's sarcoma, before extensive hyperplasia has occurred, the telangiectatic, the purpuric, the hemorrhagic and the simple inflammatory processes must be differentiated. Telangiectasia is not related to hyperplasia of blood and lymph vessels. In hyperplasia, there are new vessels, especially capillaries; in telangiectasia, the picture is that of a dilated, tortuous vessel cut at many points. Early in the process, hemorrhage is not a differential point unless combined with other features of Kaposi's sarcoma. Most
important is a consideration of cytology, including plasma cells, angioblasts and spindle cells. These cells, vascular hyperplasia and hemorrhage are not a part of a simple inflammatory process. A thorough study and proper estimation of these features should lead to a correct diagnosis.

With definite hyperplasia of the vascular, connective tissue or other cellular elements, some of the granulomas and neoplasms must be excluded. The absence of epithelioid cells, giant cells and tubercles eliminates tuberculosis. The presence of angioblasts and spindle cells plus the lack of vascular changes and plasma cell collarets rule out syphilis. Granulation tissue differs in development and evolution, terminates in complete fibrosis, shows cells not seen in Kaposi's sarcoma, fibroblasts and plasma cells are usually more abundant, angioblasts scarce and spindle cells are absent.

Among the neoplasms to be considered, the most common and important are angioma, angiosarcoma, spindle cell sarcoma, glomus tumor and granuloma pyogenicum. The typical and usual angioma gives little trouble, but if cellular elements are also present the likeness may be striking. The cellular elements are angioblasts and we believe that this type of angioma is often referred to as endothelioma or perithelioma. There are many, with whom we agree, who seriously question the existence of peritheliomas. We feel that they are angiomas associated with angioblasts. The differential diagnosis of such angiomas, which are common in our experience, is established by the absence of hemorrhage and spindle cells. Positive Perls' reaction (fig. 12) [plasma cells and increased lymphatic vessels and spaces] is not present in angiosarcoma. Without these features, the only way to differentiate Kaposi's sarcoma from angiosarcoma may be the proper diagnosis of the parent lesion.

Spindle cell sarcoma developing from a multiple idiopathic hemorrhagic sarcoma differs little from the picture of one not related to Kaposi's sarcoma. At times, the presence of angioblasts and plasma cells will help to establish the diagnosis. Differentiation is not difficult if corroborating evidence of Kaposi's sarcoma is present (fig. 13). The clinical picture and history may be of considerable importance.

Glomus tumor and granuloma pyogenicum are the most common neoplasms to be differentiated from Kaposi's sarcoma. The microscopic diagnosis of glomus tumor is comparatively simple on sections stained with hematoxylin and eosin; we find no need of special stains. Capillaries, even in the form of angiomata, are observed and about them is an intense uniform focal infiltration of angioblasts; no other cells are noted. Although muscle and nerve tissue take part in the process, we do not stress their presence. In clinically and microscopically proven cases of Kaposi's sarcoma, we frequently find areas typical of glomus tumor and establish the proper diagnosis only after careful study of the entire section.

The vascular changes in granuloma pyogenicum are similar to those of Kaposi's sarcoma, but the cytology is different. Angioblasts are numerous and diffusely arranged, but plasma cells are not conspicuous unless the lesion is secondarily infected, and spindle cells are not seen. Granuloma pyogenicum has little tendency to fibrosis.
A positive Perls' reactions is obtained in the vast majority of lesions of Kaposi's sarcoma; it is seldom missing. One would expect that hemosiderin would also be present in glomus tumor and granuloma pyogenicum, but after careful study of these lesions, we were able to demonstrate its presence in only a small percentage of cases.

The similarity of the microscopic findings, the proliferation of vessels, the complete lack or only partial development of fibrosis, and the role of the angioblast lead us to believe that glomus tumor, granuloma pyogenicum and Kaposi's sarcoma may have a common origin and be classified together under the heading of angioblastoma. Multiple idiopathic hemorrhagic sarcoma is from its inception a malignant process developing from the vascular system of the skin and internal organs. Thus, it may be considered a systemic angiosarcomatosis of the angioblastoma group.

**SUMMARY**

1. The pathology of multiple idiopathic hemorrhagic sarcoma reveals vascular hyperplasia, hemorrhage, angioblasts and spindle cells as constant features.
2. At times, Kaposi's sarcoma simulates the simple inflammatory processes, angiomas, granulomas and neoplasms; a microscopic differential diagnosis can be made.
3. The important cellular elements of Kaposi's sarcoma are discussed.
4. It is suggested that glomus tumor, granuloma pyogenicum, and Kaposi's sarcoma are angioblastomas.
5. It is further suggested that Kaposi's sarcoma may be classified under angioblastoma as a systemic angiosarcomatosis.

REFERENCES

10. POLITZER, S.: Quoted by Pautrier, L. M. and Diss, A. (see 2).