

## Review Article

# A Conception of Kaposi's Sarcoma in Pathology

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More than 120 years have passed since Kaposi (1872) described an unusual tumor, "Idiopathisches multiples Pigmentsarkom der Haut", now called Kaposi's sarcoma (KS) that principally affected the skin of the lower extremities in a multifocal and often symmetrical fashion. Since Acquired Immunodeficiency Syndrome (AIDS) has evoked, KS became a well-known disease as one of the main complications of AIDS, especially among homosexual patients. Etiology and entity of KS are still controversial.

*Epidemiology:* Epidemiology and geographical pathology of KS are quite characteristic as shown in the classification of the disease.

*Classification:* Conventional classification of KS has been based on historical and epidemiological background as follows: 1) Classic form of KS among Jewish and Italian background in Europe described by Kaposi (1872). Sporadic cases of KS in other parts of the world before AIDS evolution should be this form. 2) Endemic form of KS peculiar to African people, especially in the equatorial Africa. 3) HIV-related form of KS of AIDS patients. 4) Immunosuppressive form of KS among patients of post-organ transplantation treated with immunosuppressive therapy. KS complicated with other malignant neoplasms should be included in this group.

*Clinical course and disease manifestations:* Clinical course of classic form of KS is relatively long-standing. Repeated appearances and spontaneous regression are not uncommon. Macroscopically, classic KS lesions are maculopapular. Patients are usually middle and old aged. The age distribution of African endemic KS shows two age peaks; in the early age and in middle to advanced age (Oettle, 1962; Lulat, 1989; Komuro and Toriyama, 1991). Most African endemic KS in children initially occur in the lymph nodes, while those of middle to advanced age show primary lesion in the skin. The high incidence of endemic type KS in children is observed ethnically in the Luo group, and geographically in Nyanza province around Lake Victoria of western Kenya (Toriyama *et al.*, 1987a; Toriyama, 1988). In African older patients endemic KS follow a slow benign course for years. It appears mostly on the skin, as discrete nodules or plaques. After years of chronicity, it may appear on the skin as a fleshy-looking tumor described as "florid" (Kyalwazi, 1972; Kungu and Gatei, 1981). In

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Africa, infantile KS invades the lymph nodes and is usually more aggressive. Patients of HIV-related KS are usually young or middle-aged homosexuals, and clinical course is usually rapid. The lesions are multiple, dark red, maculo-papular (Hymes *et al.*, 1981; Gottlieb and Ackerman, 1982; Krigel and Friedman-Kien, 1985; Ross *et al.*, 1985; Safai, 1985).

*Histopathology:* Histology of KS nest is fundamentally composed of two main components of tissues; 1) proliferation of endothelial lining cells of capillary type of vascular tissue, and 2) spindle-shaped cells in interspaces of vascular tissue. Collagenous fibrosis surrounding KS nests indicating scar formation may be observed, especially in older nests of African endemic KS. Hemangiomatous features may also be seen in somewhat new lesions. Eosinophilic globules may be seen in some cases. Hemorrhagic changes followed by localized hemosiderosis are observed in some cases.

*Histological process:* The spectrum of histological changes varies with the time course of the disease. According to the chronological study of histology of cutaneous African endemic KS, the lesions are characterized by a subcutaneous edema with prominent inflammatory component in early stages, angiomatous proliferation in middle stages, and fibrosarcomatous lesion in later stages (Itakura *et al.*, 1986). The two components of KS, spindle-shaped cells and angiomatous tissue show hyperplasia in early stages and neoplastic proliferation in later stages. Some cases of African endemic cutaneous KS may become quite anaplastic in later stages. We proposed histological classification of African endemic cutaneous KS on the basis of chronological studies as follows: 1) granulation tissue type, 2) angiosarcoma type, 3) fibrosarcoma type, and 4) anaplastic type (Itakura *et al.*, 1986).

*Immunohistochemistry:* Various kinds of immunohistochemistry by our group (Komuro and Toriyama, 1991) indicated that proliferated endothelial cells and spindle-shaped cells are primitive mesenchymal cells.

*Ultrastructural findings:* An ultrastructural comparison of early lesions of KS in homosexual men with other vascular proliferations in skin revealed more marked irregularity of vascular structure in KS (McNutt *et al.*, 1983). Electron microscopic observation by our group (to be published somewhere) showed incomplete blood capillary structure covered with endothelial like cells, and between them there were irregular shaped but monotonous cells, suggesting primitive mesenchymal cells. Fibroblasts, fibrocytes, and collagen fibers were obvious. Diaporesis of erythrocytes in tissue clefts without erythrolysis was also characteristic.

*Flow cytometry:* Diploidy of proliferated cells of African endemic KS by our flow cytometry studies indicated that the lesion should be benign (Eto *et al.*, 1992a, b).

*Histogenesis:* Histogenesis of KS is still controversial. Several hypotheses put forward by some scholars have proposed that KS cells may have been derived from vascular endothelial cells (Rutgers *et al.*, 1986; Hashimoto *et al.*, 1987), lymphatic endothelium (Russell-Jones *et al.*, 1986; Beckstead *et al.*, 1985; Dictor, 1986), Schwann cells (Pepler, 1959), mesenchymal cells (Harrison and Kahn, 1978), or fibroblasts (Mottaz and Zelickson, 1966; Nickoloff and Griffiths, 1989). Beckstead *et al.* (1985) found that the abnormal cells of KS resembled most closely to the phenotype seen in lymphatic endothelium. Moreover, we have observed lymphostasis occasionally at adjacent regions to KS nests (Itakura *et al.*, 1986). Postmastectomy

lymphangiosarcoma followed by lymphostasis is one of the important diseases in respect to histogenesis of KS. However, KS cells are far less atypical than postmastectomy lymphangiosarcoma cells.

According to our observation, original cells of KS seem to be pluripotent mesenchymal cells (Komuro and Toriyama, 1991).

*Diagnostic pathology:* Histological diagnostic criteria of KS is difficult to describe. Conventional histological criteria for diagnosis of KS are not necessarily perfect. Differential diagnosis of KS from other similar soft tissue diseases is as follows: 1) All hemangiomas composed of various types of vascular proliferation, whether localized or diffuse, are fundamentally hamartoma or true benign neoplasm. Usually they have proliferated small vessels covered by a single layered endothelium, except benign hemangioendothelioma which shows multilayered endothelial cells. Capillary hemangioma composed of capillary-sized small vessels is covered by a single layered endothelium. Cavemous hemangioma shows sponge-like vascular structures covered by a single layered endothelium.

Arterio-venous hemangioma (racemose hemangioma, cirroid hemangioma) composed of malformation-like tortuous and thickened vessels, with arterial, venous, or arteriovenous components, is far from KS. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia, histiocytoid hemangioma, inflammatory angiomatous nodules, pseudo- [atypical] pyogenic granuloma, papular angioplasia, intravenous atypical vascular proliferation) with unknown pathogenesis is either a true vascular neoplasm or a reactive healing. However, there is a strong evidence that this lesion is a phenomenon following trauma, infections or humoral imbalance (Enzinger and Weiss, 1988a). Some cases of pyogenic granuloma (hemangioma of granulation tissue type) composed of abundant lobular capillary vessels with inflammatory reaction may resemble KS in manifestation in endemic areas. Diffuse type of hemangioma (hemangiomatosis, systemic hemangioma) resembles occasionally KS when it shows multicentric or diffuse vascular lesions in large areas of trunk, extremities, and in single or more than two organs. Histological appearances of the above mentioned diseases are different from KS.

2) Benign hemangiopericytomas of the hand, neck, upper and lower extremities, and retroperitoneal regions, of mainly adults of both sexes, forming perivascular tumor cell proliferation, vascular structures covered with a single layered endothelium, and characteristic anastomosing of small and large sized vessels are quite different from KS features. 3) Among vascular tumors of intermediate (or borderline) malignancy, epithelioid hemangioendothelioma with myxoid matrix, and spindle cell hemangioendothelioma with coexistence of cavernous hemangioma and spindle cells (Weiss and Enzinger, 1986) have different patterns from KS. 4) Malignant endovascular papillary angioendothelioma in which the redundant endothelium creates endovascular papillations with central hyaline cores is far from KS. 5) Malignant vascular tumors, such as angiosarcoma composed of Factor-VIIIIRa positive endothelial cells with atypia (Enzinger and Weiss, 1988b), proliferating (systemic) angioendothelomatosis, malignant glomus tumors, or malignant hemangiopericytoma are far from KS on the points of arising site, histological and clinical aspects. 6) Fibrosarcoma surrounded by enormous col-

lagen fibers with a herringbone pattern of spindle cells and no slit like lumens (Enzinger and Weiss, 1988c) shows different histological features from those of KS. 7) Benign tumors of lymph vessels, such as cavernous lymphangioma or diffuse lymphangiomatosis do not display a clear evidence of close relationship with KS. 8) Lymphangiosarcoma has no definite evidence of KS. Furthermore, no similar histological appearance to KS in postmastectomy lymphangiosarcoma as described above.

*Entity and definition:* Although many pathologists accept KS as a neoplasm, some, however, have proposed that it ought to be considered a diffuse hyperplasia of vascular tissue, probably occurring in response to viral infection (Mirra, 1986). Proponents of the view of hyperplasia cite as primary evidence the fact that KS does not clearly produce metastatic disease in the manner of conventional sarcomas but rather develops in a multifocal fashion. Nevertheless many hypotheses concerning the nature of KS have also been proposed as; a malignant tumor (Master *et al.*, 1970), tumor with low grade malignancy, tumor-like lesion or reversible hyperplasia (Brooks, 1986), and yet there has been no conclusion reached. KS is currently classified as a vascular tumor of intermediate (or borderline) malignancy by some pathologists (Enzinger and Weiss, 1988d).

Classic KS of aged patients shows occasionally spontaneous regression. Granulation tissue with inflammatory reaction is predominant in African endemic KS, if secondary infection occur. In the late stage of endemic KS, the long-standing lesion may transform into neoplastic lesion. In endemic KS of older patients, transformation of hyperplasia of spindle-shaped cells and angiomatous tissues into neoplastic proliferation could occur in the long course of the disease. Fungating growth of KS nests in the vascular canal may occur as tumor-embolism. Spontaneous regression of KS lesions is another characteristic feature of the disease. It is difficult to obtain a clear evidence of metastasis. Partial incomplete vascular cavities with incomplete basement membrane are quite characteristic ultrastructural patterns of KS. These pathological findings of KS are quite different from the other types of vascular tumors. Multifocal lesions are another important points to consider the entity of KS.

The pattern of KS may be influenced by genetic, immunological, and human ecological factors. Each form of KS has its own disease background; characteristic ethnical prevalence of classic KS, ethnical and geographical concentration of African endemic KS (Toriyama *et al.*, 1987a; Toriyama, 1988), and characteristic human ecology of HIV-related KS of homosexuals. Geographical and ethnological coincidence of African endemic KS and Burkitt's lymphoma found out by our group (Toriyama, 1988) suggests that environmental factors as well as constitutional or genetic predisposition are important in the causation of KS. Both pediatric and adult type KS show similar ethnic and geographic distributions (Schmid, 1973; Taylor *et al.*, 1971). Geographically prevalent areas of KS are definite in Africa. KS is more common in the humid tropical savannah and on the tropical highlands (Toriyama *et al.*, 1987a, b). Inflammatory reaction of cutaneous tissue in African endemic KS nests suggests that there are some causative agents. It is presumed that continuous endemic infectious antigenic stimulations cause a relative immunodeficiency in African inhabitants. Immunological suppression or deficiency may play a role in the occurrence of KS. The association of KS

with other malignancies, especially of the lymphoreticular system, such as Hodgkin's disease, malignant lymphoma, or lymphocytic leukemia is not uncommon. Malignant disease-associated KS also suggests the role of immunological suppression or deficiency in arising of KS lesion. Different clinical manifestations of three forms of KS; classic, endemic, and HIV-related suggest that there is a relationship between human ecology and disease manifestations.

*Etiology and pathogenesis:* It must be helpful to find out the etiological factors or cofactors of KS to conduct epidemiological studies not only in endemic and epidemic areas but also in non-endemic and non-epidemic areas (Bayley *et al.*, 1985; Oettle, 1962). Although some kinds of mycotoxin are known as angiogenic agents, the pathological lesions are far from KS. Extensive geopathological studies suggest that some environmental factors, such as high temperature and humidity, play indirect but important roles in causation of KS (Davies and Lothe, 1962; Toriyama *et al.*, 1987a). We have observed angiogenetic lesions in the retroperitoneal lymph nodes of a postmortem of Japanese hemophiliac AIDS patient. We think these KS or KS-like lesions arising in Japanese AIDS patients are very significant, because KS has been quite rare in the Orient. These findings suggest that some agents in AIDS or immunosuppressive conditions lead to the induction of angiogenetic lesions of KS even among inhabitants of historically non-endemic and non-epidemic areas of the world (Ulbricht and Santa Cruz, 1981). It has been reported that the incidence of AIDS-related KS is rapidly decreasing because of changing sexual behaviors among homosexuals (Haverkos *et al.*, 1990). If this is true, human ecology is one of the important backgrounds in the occurrence of KS. Direct causative agents of KS are still controversial.

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