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Kaposi's Sarcoma: Pathology and Local Epidemiology in Kenya

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Kaposi's sarcoma⁹⁾ (KS) is regarded as being common among people in Africa.^{1,10)} The highest incidence of KS is found around Lake Kivu, at the edge of Tropical rain forest surrounded by Zaire, Rwanda, Burundi and Uganda, and the disease accounts for up to 12.8% of all malignant tumors. There are reports that the incidence of KS increases as one approaches to the Equator. This presentation is mainly concerned with geographical pathology and histopathology of KS in western Kenya, and additional studies in Ghana, Tanzania, the United States and Japan.

Kaposi's sarcoma in western Kenya

What we are going to present first is the results of our investigation⁷⁾ in local areas in western Kenya. Out of 23,271 surgical specimens at provincial and district hospitals in western Kenya, 107 cases were diagnosed histologically as KS during the period from 1979 to 1985. The average incidence of KS in western Kenya was 2.81% of all malignant tumors. These figures are lower than that in Zaire, Uganda, Malawi and Tanzania. The highest incidence of KS is found in the age group between 50 and 59. The youngest was a 1 year and 6 month-old boy, and the oldest was a 72-year-old male. Male : female ratio was 8 : 1. Many reports from Africa showed almost the same age distribution, and these figures are relatively younger than the classical form of KS in Europe and North America. These differences probably depend on the life style, hygienic conditions and life span in each country.

In adults, the most common site of primary lesion was the foot, followed by the leg, hand, arm, thigh, knee and ankle. In children, on the other hand, it was the lymph nodes. The western region of The Republic of Kenya stands almost exactly astride the equator. And it accounts for almost one third of the whole country in area and about one half in population. Western Kenya is composed of three provinces; Nyanza, Western and Rift Valley Province. These areas show a wide variation of climatic conditions. The highest incidence of KS (1.78 per 100,000 population) is found in Nyanza Province, where there is a tropical savannah and in the southern half, a lake basin around Lake Victoria, followed by Western Province, where there is a tropical savannah, and then Rift Valley Province, central and eastern parts of western Kenya being a tropical highlands.

The Luo tribe, the main inhabitants of Nyanza Province around Lake Victoria, showed the highest incidence of KS (2.40 per 100,000 population), followed by the Luhya tribe who are the main inhabitants of Western Province. The Kisii and Teso also showed a high incidence. The Kikuyu have the largest population of the country, but many of them are living in provinces outside western Kenya. We could not confirm the exact number of their population in western Kenya. As in KS,

the highest incidence of Burkitt's lymphoma was also seen in the Luo tribe.

In the areas showing the highest incidence of KS in western Kenya, there is also a high frequency of other tumors, such as Burkitt's lymphoma, hepatocellular carcinoma, penile cancer, and uterus cancer, which might be related to certain infectious agents. KS and Burkitt's lymphoma have relatively same geographical distribution in Africa. It is presumed that continuous foreign infectious antigenic stimulation might cause a relative immunodeficiency in African inhabitants. Reports from Europe and North America showed that the association of KS with other malignancies, especially of the lymphoreticular system, such as Hodgkin's disease, malignant lymphoma and lymphocytic leukemia is not uncommon. In our series, however, we have no case of KS with other malignancies. Many reports described that genetic factors also seem to play a role in the causation of KS. It has been reported that in Tanzania tribal concentration was observed in some small Bantu tribes, and on the other hand, in the Nilohamitic groups, KS was extremely rare. In western Kenya, however, KS is more common in the humid tropical savannah and on the tropical highlands, even among different ethnic groups. KS predominates among people in rural areas. In adults the most common site of primary lesion is the foot, followed by the leg, hand, and arm. These regions are more exposed to the environment than other sites of the body and so are more prone to be infected with transmissible agents. Nowadays, ethnic groups are gradually increasing cultural and marital exchanges each other, but they are still keeping their own identities and cultures, especially in the rural areas. Therefore, it is clear that they have had little chance to intermingle genetically.

In our series the high incidence of KS was shown among the different ethnic groups; the Luo who belong to the Nilotic, the Luhya who belong to Bantu, and Kalenjin who belong to Nilotic. But KS was extremely rare among the Maasai who are Nilohamitic and Turkana who are Nilotic, both living in dry sandy areas. It seems that these differences of incidence among the ethnic groups are dependent on the different environmental conditions and life styles. These findings suggest that environmental factors are more important in the causation of KS in Africa, although there are undoubtedly other genetic factors.

Histological process:

Histological process of skin lesions of African endemic KS was studied in African countries including Kenya, Ghana, Tanzania and the United States by observation of different nodules of the same patient and a lot of specimens from different patients at every stage of the disease. Histologically, in earlier stages of the disease, cutaneous edema and perivascular inflammatory cell infiltration, mainly lymphocytes and plasma cells, were observed. Lymphangiectasis was also a significant feature. Spindle-shaped cell proliferation appeared gradually. Hemangiosarcoma-like patterns were observed frequently in the course of the tumor. KS having an angiomatous pattern may be confused with hemangiosarcoma. In advanced stages, characteristic atypical cells with slit-like pattern (vascular cavities) were observed. The typical KS at later stages were composed of proliferating bundles of spindle-shaped cells. Collagen fibers were seen occasionally between the tumor cells. A few cases of cutaneous KS were quite anaplastic. Among spindle-shaped cells having relatively abundant cytoplasm elongated cells with basophilic cytoplasm similar to anaplastic carcinoma cells were observed.

Histology in the course of African cutaneous KS can be summarized as follows: 1) In early

stages, cutaneous edema and perivascular inflammatory cell infiltration, mainly lymphocytes and plasma cells are seen. Lymphangiectasis is also significant feature. 2) Spindle-shaped cells appears gradually. 3) Hemangiosarcoma-like pattern is observed in the course of the tumor frequently. 4) In advanced stages, characteristic tumor cells with slit-like vascular cavities are observed.

According to these findings, cutaneous KS in Africa has characteristic features of both infections and neoplasm. Majority (80%) of cutaneous KS show multicentric foci even in its early stages. In this respect, KS is a unique disease different from other similar diseases of soft tissues such as hemangioma, hemangiosarcoma, lymphangiosarcoma and malignant pericytoma.

Histological classification:

The essential histological features of KS are composed of spindle-shaped cells and vascular tissues. Various histological classifications of the disease have been used by many researchers. We classified African cutaneous KS according to the predominant components as follows: 1) granulomatous, 2) hemangiosarcomatous, 3) fibrosarcomatous or spindle-shaped cells and 4) anaplastic types.

Additional histological findings:

Another characteristic feature is the round, hyaline, eosinophilic globules of various sizes in the tumor tissue. The globules were found in some cases of African cutaneous KS, and also observed in KS of the lymph nodes. The size of the globules ranges from 1 to 10 μm . The globules occur in aggregates in the intercellular spaces and/or in the cytoplasm of tumor cells.

The eosinophilic globules had similar histochemical properties to the globular bodies found in yolk sac tumor and other tissues.¹⁵⁾ They were positive in periodic acid Schiff (PAS) reaction, PAS after diastase, trypsin and neuraminidase digestion, phosphotungstic acid hematoxylin (PTAH) staining, and autofluorescence methods. These globules were histochemically distinct from globular giant mitochondria and Mallory's alcoholic hyaline, which were PAS negative. Orcein, resorcin fuchsin, silver impregnation and iron reaction could not stain the globules. We could not demonstrate alpha-fetoprotein, alpha-1-antitrypsin and beta-subunit of human chorionic gonadotropin in the globules by immunoperoxidase methods. The globules were negative for Mayer's mucicarmine and alcian blue. These results suggest that the globules are glycoprotein.

Histogenesis:

Considering histogenesis of KS,^{3,11)} the immunoperoxidase technique was performed to the cutaneous type of KS to examine factor VIII-related antigen. Positive staining was demonstrated in only mature endothelial cells in our series.

Three forms of KS: African endemic, Classical, and AIDS

After the evolution of AIDS, *Pneumocystis carinii* pneumonia and KS have been reported as the most common "marker" diseases of AIDS.^{4,5,6,9,13,14)} KS in AIDS shows a wide variety of clinical manifestations and some cases with flat and hemorrhagic skin lesions are different in appearance from African endemic KS. KS in AIDS also show a wide variety of histological features. Although some lesions of KS in AIDS show remarkable proliferation of spindle-shaped cells similar to African

cutaneous KS, some of them have abundant vascular channels like the appearance of capillary hemangioma or hemangiosarcoma. Vascular endothelial cells of KS in AIDS show a wide variety of atypism. African endemic cutaneous KS in adults are usually long standing, growing slowly, and occasionally regressive. In our series, the longest one had a 20 year duration, and clinically it was not aggressive or fatal. KS in AIDS can show African KS-like manifestations. However, according to our experiences, the fact was not vice versa except in rare cases. Some cases of classical cutaneous KS of white adults showing multiple small nodules in the lower legs were examined histologically. The lesions were nearly the same as the African cutaneous form, although interlacing spindle-shaped cells were somewhat loose in density. As for lymph node lesions of African KS in children, proliferation of spindle-shaped cells with relatively abundant cytoplasm were observed and this type of KS seemed relatively aggressive. Lymph node lesions of adult African endemic KS showed almost the same features as African pediatric cases. Lymph node lesions in some cases of KS in AIDS were only angiogenetic rather than typical KS and were observed mainly at the capsular or pericapsular connective tissue of the lymph nodes.

These results suggest that clinical manifestations and histological features of three forms of KS are not necessarily the same, although fundamental histological pattern is proliferation of spindle-shaped cells with abundant vascular channels. African endemic cutaneous KS are occasionally fibrosarcomatous predominant, while some of KS in AIDS are hemangiomas or hemangiosarcomatous predominant.

Epidemiology:

Finally, it must be helpful to find out the etiological factors or cofactors to conduct epidemiological studies on KS in not only endemic and epidemic areas but also non-endemic and non-epidemic areas.^{2,12)} We have observed angiogenetic lesions in the retroperitoneal lymph nodes of a postmortem case 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 there may be activation of some agents in AIDS or immunosuppressive conditions¹⁶⁾ leading to the induction of angiogenetic lesions or KS even among inhabitants of historically non-endemic and non-epidemic areas of the world.

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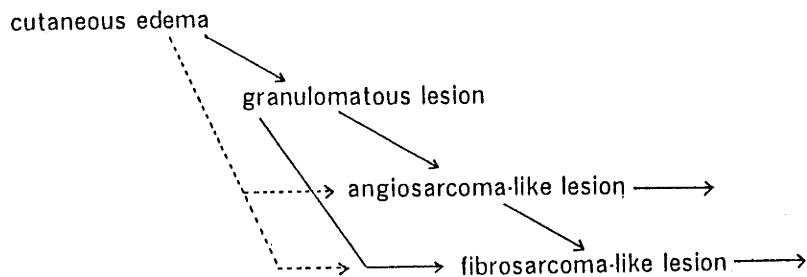


FIG. 1. CUTANEOUS KAPOSI'S SARCOMA. HISTOLOGICALLY, IN EARLY STAGES OF THE DISEASE, CUTANEOUS EDEMA AND PERIVASCULAR INFLAMMATORY CELL INFILTRATION, MAINLY LYMPHOCYTES AND PLASMA CELLS ARE SEEN. LYMPHANGIECTASIS IS ALSO SIGNIFICANT FEATURE. SPINDLE-SHAPED CELL PROLIFERATION APPEARS GRADUALLY. IN SOME CASES, HEMANGIOSARCOMA-LIKE PATTERN IS OBSERVED IN THE COURSE OF THE TUMOR. IN ADVANCED STAGES, CHARACTERISTIC SARCOMA CELLS WITH SLIT-LIKE VASCULAR CAVITIES ARE OBSERVED.

TABLE 1. Characterization of eosinophilic globules

Globules	PAS	D-PAS	Trichrom	PTAH	Auto-fluorescence	Immuno-reactivity		
						AFP	AAT	hCG
Kaposi's sarcoma	+	+	Red	+	+	-	-	-
Alpha-1-antitrypsin	+	+	Red	+	+	+	+	ND
Yolk sac tumor	+	+	Red	+	+	+	+	-
Hepatocellular carcinoma	+	+	ND	+	+	+	+	ND
Lung carcinoma	+	+	ND	+	+	ND	ND	ND
Breast carcinoma	+	+	ND	+	+	ND	ND	ND
Renal cell carcinoma	+	+	ND	+	+	-	-	ND
Giant mitochondria	-	-	Red	ND	-	ND	ND	ND

PAS: PERIODIC ACID SCHIFF, D-PAS: PERIODIC ACID SCHIFF WITH DIASTASE DIGESTION, PTAH: PHOSPHOTUNGSTIC ACID HEMATOXYLIN, AFP: ALPHA-FETOPROTEIN, AAT: ALPHA-1-ANTITRYPSIN, HCG: HUMAN CHORIONIC GONADOTROPIN, +: POSITIVE, -: NEGATIVE, ND: NOT DONE

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