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GEOPATHOLOGY OF ENDEMIC PEDIATRIC LYMPH NODE KAPOSI'S SARCOMA IN WESTERN KENYA

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Abstract: We conducted an epidemiological and histological analysis of the endemic lymph node-type Kaposi's sarcoma (KS) in African children (under 16 years old) in Western Kenya in order to determine the ethno-geographical distribution of the disease and to clarify its histological features and histogenesis during the 12-year period between 1979 to 1990. The age distribution of all endemic type KS in Western Kenya showed two age peaks; one in early childhood and the other in middle to advanced age. Most endemic KS in children initially occurred in the lymph nodes, while that of people of middle to advanced age showed a primary lesion in the skin. The male to female ratio of the endemic KS was 3.1 to 1 (in all pediatric types), 3.4 to 1 (in the pediatric lymph node-type) and 10.8 to 1 (in all adult types). A high incidence of the lymph node-type KS in children was observed in the Luo group ethnically and in Nyanza Province around Lake Victoria geographically. The lymph node-type KS originated at the paracortical areas and gradually grew along the reticulin network originating from the trabeculae. The lesion of KS histologically consisted of several types of cells, especially spindle-shaped cells, macrophage-like cells and immature endothelial cell-like cells and was accompanied by almost normal small blood vessels, lymphatic vessels and postcapillary venules. No abnormal mitoses were observed in any of the cells. There were no primary necroses due to tumor proliferation and also no extracapsular invasions. Immunohistochemically, spindle-shaped cells, immature endothelial cell-like cells and mature endothelial cells were positive for Vimentin, but only mature endothelial cells were positive for Factor-VIIIRa and UEA-1. Macrophage-like cells were positive for Factor-XIIIRa. These findings suggested that: 1) there are certain differences in the etiological co-factors of KS between the endemic lymph node-type KS in children and the endemic cutaneous type KS in adults, 2) KS cells originate from pluripotent mesenchymal cells and 3) KS might not be a malignant tumor, but rather a benign neoplasm, tumor-like lesion or reactive hyperplasia.

INTRODUCTION

Kaposi's sarcoma (KS) was first described by Kaposi in 1872 as an "Idiopathic multiple pigmented sarcoma of the skin". Since then, it has been considered a specific neoplasm which occurs in the skin of elderly men, mainly among people of Jewish origins in Eastern Europe and the inhabitants of the Mediterranean basin. The first patient with KS in African continent was reported by Jojot and Laigret (1922) from Cameroon. It is now a well

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recognized fact that KS is more prevalent in Equatorial Africa than in any other part of the world (Oettle, 1962).

KS can be divided broadly into four types; the classical (European) type, the endemic (African) type, the epidemic (Acquired immunodeficieny syndrome-related) type and the type associated with immunosuppressive therapy. However, there are certain differences among the four types of KS with regard to sex ratio, age distribution, macroscopic findings, histologic findings and biological behavior (Safai, 1985; Gottlieb and Ackerman, 1988).

Pediatric cases of KS are uncommon, except in the African endemic type. According to the published literatures, the majority of pediatric cases of KS in Equatorial Africa initially occurred in the lymph node and often showed a generalized lymphadenopathy (Dutz and Stout, 1960; Davies and Lothe, 1962; Slavin *et al.*, 1970; Olweny *et al.*, 1976; Owor, 1977; Molyneux, 1979; Toriyama *et al.*, 1987a, b). However, no epidemiological and histological analysis of the lymph node-type KS in African children has ever been published.

Previous reports stated that KS is derived from vascular endothelial cell (Rutgers *et al.*, 1986; Hashimoto *et al.*, 1987), lymphatic endothelial cell (Russelljones *et al.*, 1986; Beckstead *et al.*, 1985; Dictor, 1986), Schwann cell (Pepler, 1959), mesenchymal cell (Harrison and Kahn, 1978) or fibroblast (Mottaz and Zelickson, 1966; Nickoloff and Griffiths, 1989). However, the cell origin of KS remains unknown.

Many hypotheses have been raised about the nature of KS, for example that it is a malignant tumor (Master *et al.*, 1970; Taylor *et al.*, 1971), tumor with low-grade malignancy, tumor-like lesion or reversible hyperplasia (Brooks, 1986; Mirra, 1986), but no conclusion has been reached.

We studied the lymph node-type KS in children in Western Kenya to elucidate its ethno-geographical distribution and to determine its histological features and histogenesis.

Table 1 Dilution ratio of primary antibodies

Primary antibodies	Animal	Dilution	Pre-digestion†	Sources
Factor-VIIIRa	rabbit/poly	1:200	+	DAKO
Factor-XIIIRa	rabbit/poly	1:150		BEHRING
Vimentin	mouse/mono	1:25		DAKO
Actin	mouse/mono	1:100	+	S.K.
Desmin	mouse/mono	1:100		DAKO
ACT	rabbit/poly	1:300	+	DAKO
CD35	mouse/mono	1:20	+	DAKO
S-100	rabbit/poly	1:400		DAKO
UEA-1*	rabbit/poly	1:200		E-Y

DAKO: DAKOPATTS, Copenhagen, Denmark. Behring: Behringwerke AG, Marburg, Germany. S.K: Seikagaku Kogyo Co. Ltd., Tokyo, Japan. E-Y: E-Y Laboratories, Inc., San Mateo, CA, USA. Avidin-biotin peroxidase complex were obtained from Vector Laboratories: Vectastain ABC Kit, Burlingame, CA, USA.

* Peroxidase-conjugated rabbit immunoglobulins to UEA-1.

† Incubated with trypsin in phosphate-buffered saline at 37°C for 5 min.

MATERIALS AND METHODS

Twenty-two cases of the lymph node-type KS in children under 16 years old were selected from 185 cases histologically diagnosed as KS. This study was carried out in three provinces, that is, Western, Nyanza and Rift Valley Province, in the Western part of the Republic of Kenya, East Africa during the 12-year period between 1979 and 1990. Clinical data and epidemiological information were recorded as accurately as possible with reference to age, sex, ethnic group and habitant place. The specimens were examined histologically and immunohistochemically. Specimens of the cutaneous type KS and the lymph node-type KS in adults were used as controls.

After fixation in formalin and embedding in paraffin, the specimens were cut in 4 μm-thick slices. In addition to routine staining with hematoxylin and eosin (HE), they were subjected to periodic acid-Schiff (PAS), Azan-Mallory, reticulin, elastica van Gieson (EVG), and mucicarmine stains. For immunohistochemical staining, twelve selected cases of pediatric lymph node-type KS were used and Factor-VIIIRa, Factor-XIIIRa, Vimentin, Actin, Desmin, Alpha-1-antichymotrypsin (ACT), CD-35 and S-100 were used as primary antibodies at the dilution ratio shown in Table 1 and by the avidin biotin peroxidase complex (ABC) technique (Hsu *et al.*, 1981). Lectin binding with Ulex europaeus agglutinin 1 (UEA-1) was also performed.

RESULTS

Epidemiological results:

Figure 1 and Table 2 describe the age distribution of the lymph node-type KS and the cutaneous type KS in Western Kenya. There were two peaks in the age distribution of KS;

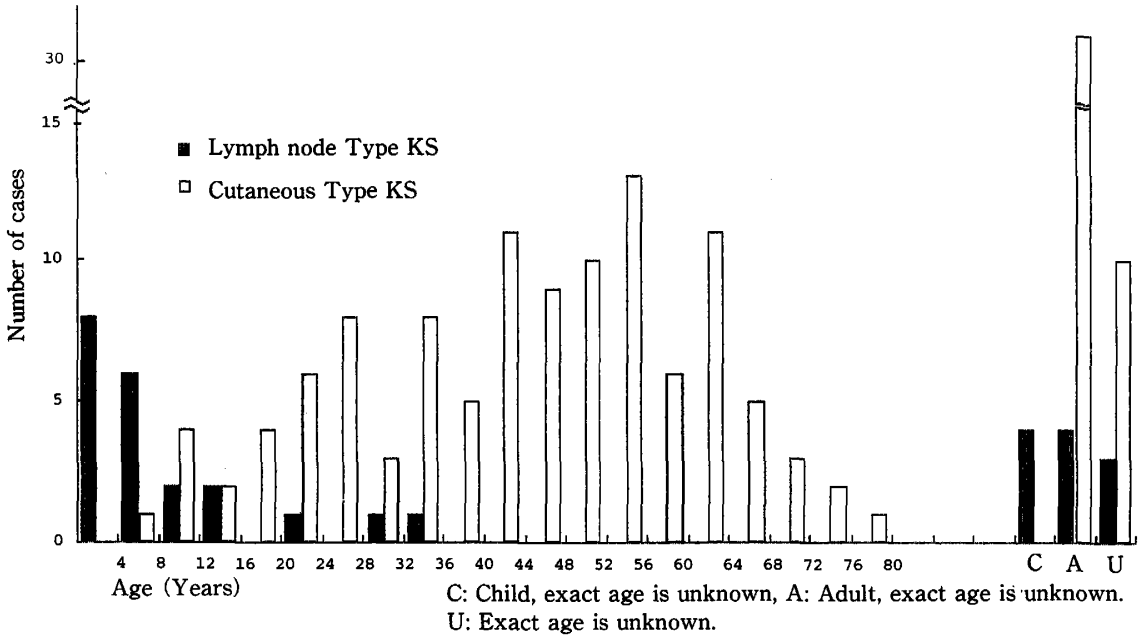

Figure 1 Age distribution of endemic lymph node-type and cutaneous type Kaposi's sarcoma.

Table 2 Lymph node-type Kaposi's sarcoma in children

Case	Age	Sex	Site of lesion	Ethnic group	District	Province
1	1	M	Inguinal lymph node	Luhya	Busia	Western
2	1y6m	M	Generalized lymph nodes	Luo	South Nyanza	Nyanza
3	1y6m	M	Unknown lymph node	Luo	Kisumu	Nyanza
4	1y8m	M	Generalized lymph nodes	Luo	Kisumu	Nyanza
5	1y9m	M	Generalized lymph nodes	Luhya	Kakamega	Western
6	1y9m	M	Generalized lymph nodes	Luo	Siaya	Nyanza
7	2y6m	M	Generalized lymph nodes	Luhya	Kisumu	Nyanza
8	3	M	Generalized lymph nodes	Luhya	Kakamega	Western
9	4	F	Unknown lymph node	Luo	South Nyanza	Nyanza
10	4	M	Generalized lymph nodes	Luo	Nakuru	Rift Valley
11	4	M	Generalized lymph nodes	Luo	?	?
12	5	F	Generalized lymph nodes	Luo	South Nyanza	Nyanza
13	6	M	Generalized lymph nodes	Luo	Kisumu	Nyanza
14	7	M	Generalized lymph nodes	Luo	Kakamega	Western
15	8	M	Elbow lymph node	Kisii	Kisii	Nyanza
16	10	F	Unknown lymph node	Luhya	Kakamega	Western
17	12	M	Generalized lymph nodes	Luo	Kisumu	Nyanza
18	12	M	Cervical lymph node	Luo	Kisumu	Nyanza
19	Child*	M	Generalized lymph nodes	Luo	Kisumu	Nyanza
20	Child*	M	Unknown lymph node	Luo	Kisumu	Nyanza
21	Child*	F	Unknown lymph node	Luo	Kisumu	Nyanza
22	Child*	F	Unknown lymph node	Luo	Kisumu	Nyanza

*Exact age is unknown (under 16 years old).

Table 3 Age and sex distribution of 185 cases of Kaposi's sarcoma

Age group	In lymph node			Other lesions			Total
	Male	Female	Unknown	Male	Female	Unknown	
0-15	15	3	0	5	2	0	25
Child*	2	2	0	0	0	0	4
subtotal	17	5	0	5	2	0	29
Over 16	3	0	0	98	7	0	108
Adult†	4	0	0	24	5	2	35
subtotal	7	0	0	122	12	2	143
Unknown‡	2	1	0	9	1	0	13
Total	26	6	0	136	15	2	185

*Exact age is unknown (under 16 years old).
†Exact age is unknown (over 16 years old).
‡Age is unknown.

childhood and middle to advanced age. Although 17% (32/185) of all KS patients had lymph node lesions, 76% (22/29) of the pediatric type KS showed primary lesions in the lymph nodes and 59% (13/22) of the lymph node-type KS in children showed generalized lymph node involvement without any skin lesions.

Table 3 describes the sex distribution of the endemic KS in Western Kenya. The male to female ratio of KS was 3.1 to 1 (in all pediatric types), 10.8 to 1 (in all adult types) and 3.4 to 1 (in the pediatric lymph node-type).

A high incidence of the lymph node-type KS in children was observed in the Luo group ethnically and Nyanza province around Lake Victoria geographically.

Histological results:

The early stage of KS, that is, initial focus localized in an infinitesimally small part of the lymph node, revealed that KS originated at a site near the paracortical area, gradually growing toward the subcapsular sinus along the reticulin network from the trabeculae (Photo. 1). The center of the lesion consisted mainly of spindle-shaped cells, while the marginal sites consisted of immature blood or lymphatic vessel-like structures. Until the late stage when KS occupied most of the lymph node, lymph follicles remained at the marginal sites and were slightly compressed and atrophic (Photo. 2). Finally, the lymph node was completely replaced by KS cells, but there were no extracapsular invasions. In the medullary area of lymph node, there was only a small number of spindle-shaped cells with marked dilatation of blood and lymphatic vessels. Infiltration of plasma cell was slight (Photo. 3).

Histologically the KS lesions consisted of several types of cells, especially spindle-shaped cells, macrophage-like cells and immature endothelial cell-like cells and were accompanied by almost normal small blood vessels, lymphatic vessels and postcapillary venules.

The spindle-shaped cells in the lymph node-type KS had more round nuclei than those in the cutaneous type KS, and had long, thin, eosinophilic and slightly wavy cytoplasm. They showed an interlacing bundle pattern. There were slit-like structures containing erythrocytes among some spindle-shaped cells, which were indicative of an immature vascular structure. However, the distinct formation of vascular basement membrane and communication with other vascular spaces were obscure. These spindle-shaped cells showed various sized compact nodules, and argyrophil fibers developed extensively around them (Photo. 4). These spindle-shaped cells might have the ability to produce collagen fiber thereafter.

The macrophage-like cells with relatively clear and abundant cytoplasm and round nuclei showed phagocytic activity because of cell debris in the cytoplasm. There were numerous macrophage-like cells interposed among the spindle-shaped cells, creating a starry sky appearance (Photo. 5).

Immature endothelial cell-like cells with hyperchromatic and slightly small plump nuclei showed a hob-nail structure in the slit-like lumens. In several fields, some of the immature endothelial cell-like cells showed a transformation to spindle-shaped cells.

In marginal sites of the lesion, there was a proliferation of blood vessels, lymphatic vessels and postcapillary venules with relatively tall endothelial cells (Photo. 6).

Mitotic figures were observed only in spindle-shaped cells and macrophage-like cells; the number of mitotic figures was 2-5 per each high power field (×200). No abnormal mitoses were observed in any of the KS cells.

Although there were secondary necroses due to hemorrhage from the thin-walled dilated blood vessels in several cases, there were no primary necroses due to tumor proliferation.

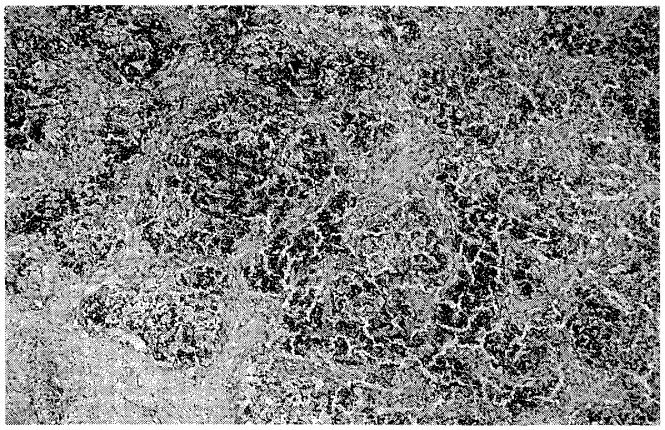

Photo. 1 KS cells proliferate along the reticulin network which originated from the trabeculae of lymph node (H.E. original magnification, ×40).

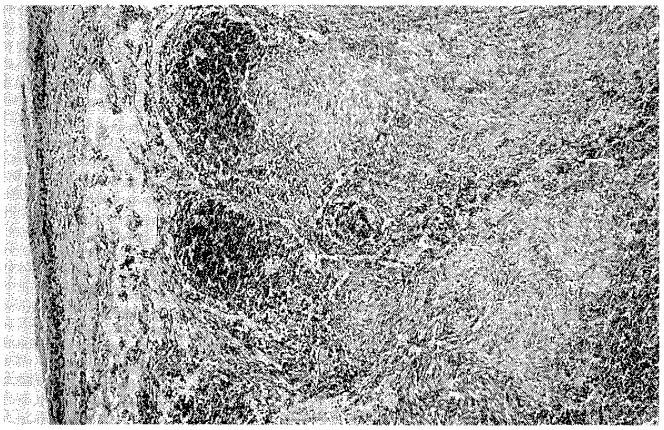

Photo. 2 KS cells proliferate in the paracortical area (in center) and lymph follicles are compressed by KS cells (in left side). (H.E. Original magnification, ×40).

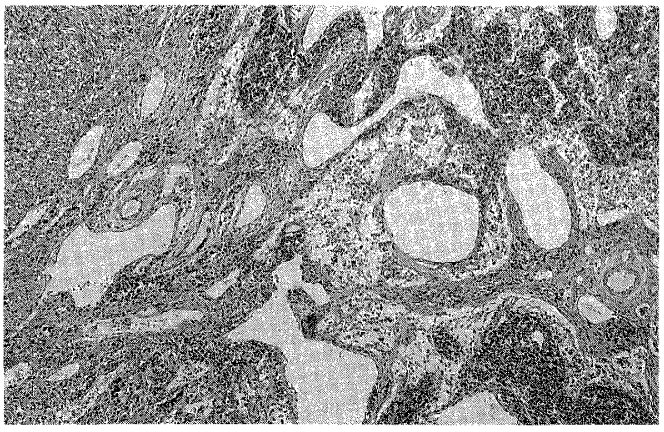

Photo. 3 A small number of spindle-shaped cells in the medullary area with marked dilatation of blood and lymphatic vessels (H.E. original magnification, ×40).

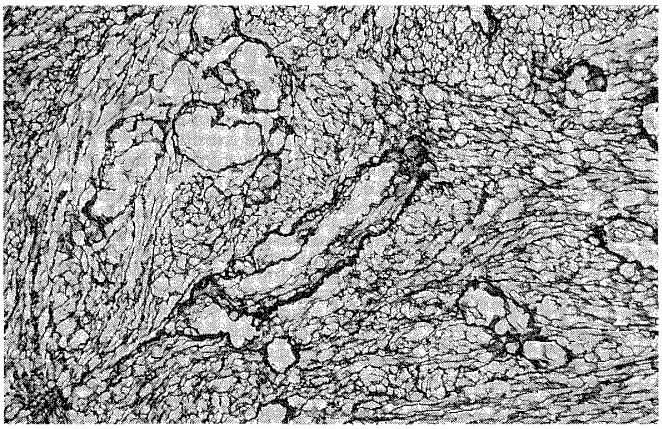

Photo. 4 Argyrophil fibers prolong around spindle-shaped cells, without distinct formation of vascular basement membrane and communication with other vascular spaces (Reticulin stain, original magnification, ×100).

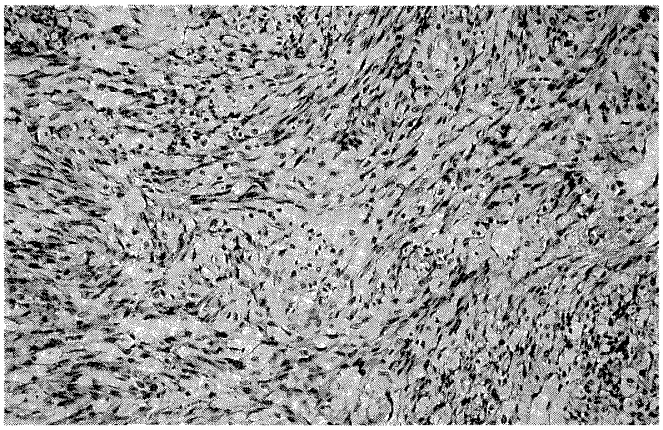

Photo. 5 Macrophage-like cells which having clear and abundant cytoplasms with phagocytic activity interpose among spindle-shaped cells (H.E. original magnification, ×100).

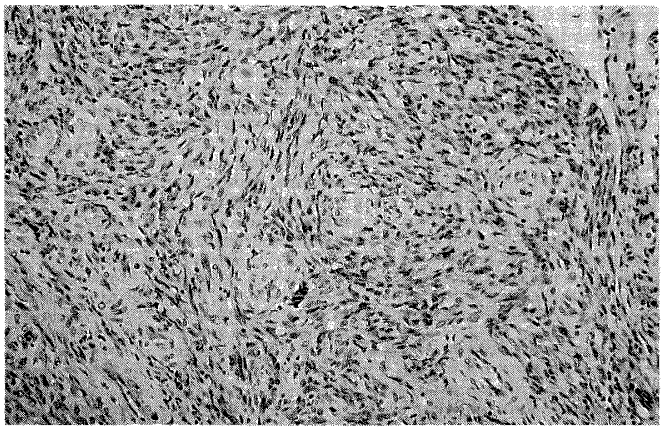

Photo. 6 Postcapillary venules which having relatively tall endothelial cells interpose among spindle-shaped cells (H.E. original magnification, ×100).

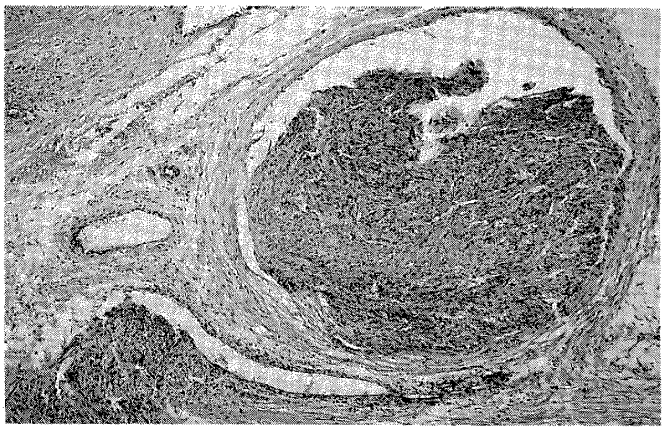

Photo. 7 Marked proliferation of endothelial cells in blood and/or lymphatic vessels adjacent to a lymph node, resembles intravascular papillary endothelial hyperplasia (H.E. original magnification, ×40).

Photo. 8 Vimentin is strongly positive in spindle-shaped cells and endothelial cells but is negative in macrophage-like cells (ABC technique. original magnification, ×100).

The characteristic findings were papillary proliferation of KS cells in the blood vessels and/or lymphatic vessels adjacent to the lymph node (Photo. 7). In the proliferative cells of this lesion, there were no cellular atypia or mitotic figures.

In the immunohistochemical examination, spindle-shaped cells, immature endothelial cell-like cells and mature endothelial cells were positive for Vimentin (Photo. 8), but only mature endothelial cells were positive for Factor-VIIIRa and UEA-1. Macrophage-like cells were positive for Factor-VIIIRa. All types of KS cells were negative for Desmin, Actin, S-100, CD-35 and ACT (Table 4).

Discussion

Our epidemiological results and several reports showed that the African endemic-type KS is characterized by its occurrence in two age peaks; one in early childhood and the other

Table 4 Immunohistochemical results

Primary antibodies	Cell types					
	SC	MLC	IEC	PCV	LV	BV
F-VIIIRa	−	−	−	+	+	+
F-XIIIRa	−	+	−	−	−	−
Vimentin	+	−	+	+	+	+
Actin	−	−	−	−	−	−
Desmin	−	−	−	−	−	−
ACT	−	−	−	−	−	−
CD35	−	−	−	−	−	−
S-100	−	−	−	−	−	−
UEA-1	−	−	−	+	+	+

SC: Spindle-shaped cell. MLC: Macrophage-like cell. IEC: Immature endothelial cell-like cell. PCV: Post-capillary venule. LV: Mature lymphatic vessel. BV: Mature blood vessel.

in middle to advanced age (Oettle, 1962; Lulat, 1989). Most endemic KS cases in children initially occurred in the lymph node, while those of people of middle to advanced age showed primary lesions in the skin. In addition, over half of pediatric cases showed generalized lymphadenopathy. With regard to the male to female ratio, the adult type KS showed a much higher incidence in males than in females. On the other hand, the pediatric type KS showed a higher female incidence than the adult type KS. These findings suggest that there are certain etiological differences between the pediatric type and adult type KS in Western Kenya. It has been postulated that some infections with a transmissible agent in young non-immune children lead to proliferation of KS in the lymph node (Slavin *et al.*, 1969). Both pediatric and adult type KS showed similar ethnic and geographic distribution (Taylor *et al.*, 1971; Schmid, 1973; Toriyama *et al.*, 1987a, b). A high incidence of KS was observed in the Luo ethnic group living around Lake Victoria, which is a relatively moist tropical savanna. However, there were only a few cases in dry areas where other ethnic groups including the Luo group reside. These findings are consistent with those of previous reports (Davies, 1959; Davies and Lothe, 1962) and suggest that climatic conditions such as high temperature and humidity play an important role in the causation of KS. In Colombia, South America, where KS showed histological patterns similar to those of African endemic type KS, there were no pediatric patients with KS and the lymph node-type KS (Garcia *et al.*, 1989). In classical type KS, there were very few pediatric cases and lymph node cases (Bluefarb, 1957; Bisceglia *et al.*, 1988). These reports indicate that genetic factors and environmental factors such as life style, living conditions and aging differ among the various types of KS.

KS cells developed at the paracortical area of the lymph nodes and gradually proliferated along the reticulin network originating from the trabeculae. KS cells were composed of several elements, that is, spindle-shaped cells without any differentiation, spindle-shaped cells with slit-like structures and immature endothelial cell-like cells. Immunohistochemically these cells were only positive for Vimentin, which is a marker for mesenchymal cells, while other markers for differentiated cells were negative. These results suggest that KS cells

originated from pluripotential cells near the reticulin network, that is, mesenchymal cells which become immature and mature endothelial cells, and showed the features of undifferentiated spindle-shaped cells. Although previous reports have expressed different opinions about the histogenesis of KS, such as vascular endothelial cell (Rutgers *et al.*, 1986; Hashimoto *et al.*, 1987), lymphatic endothelial cell (Bechstead *et al.*, 1985; Dictor, 1986; Russelljones *et al.*, 1986), Schwann cell (Pepler, 1959) and fibroblast (Mottaz and Zelickson, 1966), there may be no contradiction if the stage of differentiation from mesenchymal cell to each of the components is regarded as a spectrum of differentiation. It is thought that macrophage-like cells are one of the components of KS lesions, but it is still obscure whether the macrophage-like cells are part of the spectrum of mesenchymal cells, or of the stromal reaction around KS tissues.

From the histological findings of the lymph node-type KS in children, that is, coexistence of spindle-shaped cells, immature endothelial cell-like cells, macrophage-like cells, and relatively well differentiated small blood and lymphatic vessels, KS seems to be an independent disease with histological features differing from those of 1) Castleman's disease, which shows marked hyperplasia and hyalinization of intra- and extrafollicular blood vessels in tumor tissue (Kessler and Beer, 1983); 2) angioimmunoblastic lymphadenopathy with dysproteinemia, which is characterized by bifurcated hyperplasia of PAS-positive, thick-walled small blood vessels and proliferation of immunoblasts and plasma cells (Frizzera *et al.*, 1974); and 3) vascular transformation of lymph node sinuses, which is characterized by hyperplasia of small blood vessels localized in the sinus or trabeculae without any association of spindle-shaped cells (Michal and Koza, 1989).

The histological features of KS also differ from those of 1) spindle cell hemangioendothelioma, which shows the coexistence of cavernous hemangioma with spindle cells (Weiss and Enzinger, 1986); 2) angiosarcoma, which is composed of Factor-VIIIRa positive endothelial cells with atypia (Enzinger and Weiss, 1988a); and 3) fibrosarcoma, which is surrounded by enormous collagen fibers with a herring-bone pattern of spindle cells but no slit-like lumens (Enzinger and Weiss, 1988b).

Several reports have suggested that the pediatric type KS is a malignant or low-grade malignant tumor (Master *et al.*, 1970; Taylor *et al.*, 1971) because of its clinical and histological features, that is, rapid growth and short period leading to death, generalized invasion to organs, necroses, some abnormal mitoses and atypism of proliferating cells. In our histological results, however, there are no abnormal mitoses, primary necroses, cellular atypia or invasive growth. Some cases with poor prognosis showed a potential for misdiagnosis as malignant tumors such as angiosarcoma. In classical KS, KS associated with immunosuppressive therapy and Acquired immunodeficiency syndrome-related KS, some cases showed spontaneous remission, and lesions of the patients who had been treated with steroid therapy appeared or disappeared depending on variation in immunosuppressive status (Zisbrod *et al.*, 1980; Real and Krown, 1985). These results indicate that KS might not be a malignant tumor, but rather a benign neoplasm, tumor-like lesion or reactive hyperplasia.

Our findings indicate that: 1) there are certain differences in the etiological co-factors of KS between the endemic lymph node-type KS in children and the endemic cutaneous type KS in adults, 2) KS cells originate from pluripotent mesenchymal cells, and 3) KS might not be a malignant tumor, but rather a benign neoplasm, tumor-like lesion or reactive hyperplasia.

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西部ケニアにおける小児の風土病型リンパ節型カポシ肉腫

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風土病型カポシ肉腫（KS）は赤道アフリカに多く見られ，比較的小児にも好発し，また，リンパ節に発生するものも多く認められてきた。今までの我々の調査でも，小児に発生するKSは，主にリンパ節に初発していた。しかし，これらのKSに関する組織学的検討は，ほとんどなされていない。今回我々は，小児KSのうちリンパ節に初発した症例22例を用いて，地理病理学的，組織学的，免疫組織学的な検索を行い，その民族，地理的分布，組織学的形態像，細胞の由来，発生機序に関して検討した。その結果1）風土病型KSの好発年齢には，小児期と中高年齢期の二峰性が見られ，初発部位は小児では主にリンパ節で，多発する傾向が見られ，中高年齢期では四肢の皮膚に多く見られた。2）小児リンパ節型KSは，成人皮膚型KSと同様にLuo族に多く見られ，高温で多湿なビクトリア湖周辺に多く，乾燥した地域にはまれであった。3）KSはリンパ節のpara-cortical areaより発生し，reticulin networkに沿って増生していた。4）KSの病変部はspindle-shaped cell, macrophage-like cell, immature endothelial cell-like cell, mature blood vessel, lymphatic vessel, postcapillary venuleなどの細胞からなっていた。5）悪性を示唆する細胞異型，異型核分裂像，腫瘍による増殖性壊死，リンパ節被膜外への浸潤像などは認められなかった。6）免疫染色およびレクチン染色では，内皮細胞のマーカーであるFactor-VIIIRa, UEA-1はmature blood vesselなどのendothelial cellに陽性で，spindle-shaped cell, macrophage-like cell, immature endothelial cell-like cellは陰性であった。間葉系細胞のマーカーであるVimentinは，spindle-shaped cell, immature endothelial cell-like cell, mature blood vesselなどのendothelial cellに陽性であった。macrophage-like cellはFactor-XIIIRaのみ陽性で，KSの病変部に多く見られたが，KSの構成成分の一種であるか，反応性の増生であるかは不明であった。これらの結果より，KSの発生には自然環境，生活様式などの因子とともに遺伝因子など，いくつかの因子が強い影響を与えていると考えられた。また，KSはparacortical areaのreticulin network近傍の多潜能なmesenchymal cellより発生し，悪性腫瘍というよりは良性腫瘍，あるいは反応性疾患と考えられた。

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