

**TITLE: SOME CLINICO-HISTOPATHOLOGIC ASPECTS OF KAPOSI'S
SARCOMA IN PATIENTS WITH AND WITHOUT THE ACQUIRED
IMMUNE DEFICIENCY SYNDROME**

**A Dissertation presented in part fulfillment for the degree of
Master of Medicine in Pathology of the University of Nairobi.**

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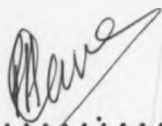
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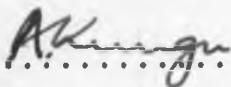
DECLARATION

I certify that this is my original work and has not been
presented for a degree in any other university.



.....
Dr. Paresh A. Dave M.B; chB

This dissertation has been submitted for examination with my
approval as University supervisor.



.....
Prof. A. Kungu M.B; chB, F.R.C. Path(U.K)

DEDICATION

I dedicate this book in loving memory of my late mother.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
KS	Kaposi's sarcoma
KNH	Kenyatta National Hospital
M:F	Male:Female ratio
CMV	Cytomegalo Virus
HIV	Human Immunodeficiency Virus
HTLV III	Human T-Lymphocyte Virus
HPF	High Power Field
HLA	Human Leucocyte Antigen
ELISA	Enzyme Linked Immunoabsorbent Assay

ACKNOWLEDGEMENT

I am indebted to the following without whose assistance this dissertation would not have been possible.

1. My most sincere gratitude to my supervisor Prof. A. Kungu for his invaluable assistance and guidance.
2. Prof. D.G. Gatei for his review and opinion on some of the difficult KS lesions on histology.
3. The technical staff and especially Mr. P. Shuja, Mrs Wangechi, Susan and John for the preparation of the slides and special stains.
4. My family for their understanding and patience during this period.
5. My fellow colleagues for their moral support.
6. Miss Peres Ongewe for her secretarial; computer services.
7. All those who may have helped in the completion of this dissertation and who I have regrettably not mentioned.

SUMMARY

This is a five year retrospective study of Kaposi's Sarcoma as seen at Kenyatta National Hospital. A dramatic change in epidemiology and clinical presentation is observed. This include a lower M:F ratio of 4.5:1, a younger age group, changes in ethnic distribution and an increase in the lymphadenopathic form of the disease.

There is a diversity of clinical presentation in AIDS-Kaposi's Sarcoma patients with the neoplasm being widely disseminated, however limb involvement is not uncommon. All forms of Kaposi's Sarcoma were seen during this period. Histologically slit forming type predominated in AIDS-Kaposi's Sarcoma lesions. Other significant differences on histology include the degree of inflammatory cell infiltrate ($p < 0.05$), presence of sclerosis ($p < 0.01$) and the presence of necrosis or ulceration ($p < 0.05$).

KAPOSI'S SARCOMA

INTRODUCTION:

Kaposi's sarcoma by definition is a multicentric malignant neoplastic process characterized by a proliferation of spindle cells and vascular structures. This proliferation typically occurs in multiple sites most frequently in the dermis and results in the production of nodules or plaques possessing a characteristic violaceous appearance(1,2).

Kaposi's sarcoma was first described in 1872 by Moritz Kaposi in a paper entitled "Idiopathic multiple pigmented sarcoma of the skin"(3).

Kaposi's sarcoma is considered to be an obscure tumour with an interesting epidemiology and an unknown histogenesis. KS has recently come to the forefront because of its frequent occurrence in patients with the Acquired Immune Deficiency Syndrome (AIDS).

Since its original description by Moritz Kaposi, four forms of KS are recognised.(4) These are:-

- 1) The CLASSIC or European form: This was first described in 1872 and was endemic to older men of Eastern European or Mediterranean descent.
- 2) The AFRICAN form: This is an endemic form of KS recognised

from Central Africa, occurring in a younger age group and occasionally associated with generalized involvement of lymph nodes.

- 3) KS associated with RENAL TRANSPLANT: This occurs in transplant recipients undergoing immunosuppressive therapy.
- 4) Epidemic form of Kaposi's sarcoma associated with AIDS: This is the most recent form of the disease described initially in male homosexuals and found in varying proportions of AIDS patients.

REVIEW OF LITERATURE

In 1897, DeCaricis described 12 patients seen in Northern Italy. This high frequency in people of Italian extraction was confirmed by later reports. Dorfell reported 15 cases and reviewed existing European literature where it was noted that there was a higher incidence among Ashkenazit Jews and Italians. By contrast fewer cases were reported in the United Kingdom, Scandinavia and parts of Northern and Western Europe. In all regions the disease occurred predominantly in elderly males. In the United States, KS occurred sporadically and accounted for only 0.02% of all malignancies. The disease was seen in both American Jews and blacks and occurred predominantly in elderly men. In Asia, KS occurred sporadically and the incidence was extremely low despite similar etiological conditions as sub-Saharan Africa. Sporadic cases have also been reported from

South America and Australia(5).

In Africa although cancer in general was thought to be rare, a large number of cases of Kaposi's sarcoma were described especially from Central and South Africa.(6).

In Tanzania KS occurred frequently and accounted for 4% of all malignancies. The M:F ratio was 12:1 with the disease occurring in all ages but most frequently in the 4th to 7th decade.(7)

In Uganda KS was the 7th commonest tumour with an annual incidence of 0.7/100,000 in Kampala and a M:F ratio of 9:1.(8)

In Malawi KS formed 4.2% of all malignant tumours.(9)

In 1980 a symposium on KS was held in Makerere Medical College, Kampala Uganda. At this symposium the experience of KS had been enhanced by the reporting of over 1000 new cases. The highest proportional rates were found in North Eastern and Eastern Zaire, Rwanda and Burundi followed by French Equatorial Africa, Uganda, Malawi, Tanzania, Zimbabwe and Kenya. There was also a localized distribution within some of these countries. The high incidence however was limited to sub-Saharan Africa.(10)

In all endemic areas the tumour occurs mainly in males but the M:F ratio increases with age from 1.7:1 in the first decade to 15:1 in those over 60 years of age.(5)

The earliest indication associating KS with cellular

immunosuppression came from its sporadic occurrence in patients who had undergone renal transplantation. Hardwood et al described 4 renal transplant recipients developing KS on the lower limbs from 3 months to 4 years after transplant. In their review of literature the age of the patients ranged from 24 years to 61 years with a mean age of 43 years and a M:F ratio of 2:1. 4 cases of KS in renal transplant recipients were of similar ethnic background (Jewish or Mediterranean ancestry). These patients had been immunosuppressed with corticosteroids and azathioprine and regression of the lesions were not uncommon following discontinuation of immunosuppressive therapy.(11)

In the two year before January 1981, an epidemic involving 73 homosexual men with a disseminated type of Kaposi's sarcoma had been reported to the Centre of Disease Control Atlanta, Georgia. These patients had been seen primarily in New York and California. The clinical features, natural history and mortality of the disease in homosexual men was similar to the lymphadenopathic form of Kaposi's sarcoma seen in Africa and in immunosuppressed renal transplant patients.(12)

Epidemiologic and Immunologic data later suggested that these patients with KS were part of a wider spectrum of AIDS that includes patients which present clinically with various other opportunistic infections.(13)

KS is an epiphenomenon of AIDS, with a varying distribution among the risk groups. Homosexual men have a 46% incidence of KS at

their initial diagnoses of AIDS, while the incidence amongst heterosexual intravenous drug abusers is 3.8%. (14) The incidence of KS in AIDS varies from region to region. In United Kingdom, KS is the presenting feature in 21% of AIDS patients. (15) The centre of Disease Control estimate that nearly 34% of AIDS patients develop KS. (16)

In Uganda this figure is found to be 10% while the incidence of KS in AIDS patients was found to be 10% at Kenyatta National Hospital. In Zaire, KS was seen in 16% of AIDS patients. (17,18,19)

As a result of this high incidence KS remains a diagnostic presentation of AIDS in high risk population. (16)

The clinical features of endemic and European KS are variable but can be divided into three patterns. (1)

- 1) Nodular disease: This presents subcutaneous nodules on the lower limbs usually around the ankles. The nodules are in the dermis and may be accompanied by oedema. The prognosis is good with survival from 8-10 years or even longer.
- 2) Locally aggressive disease which presents as lobulated solitary lesions. There may arise de novo or more commonly from pre-existing lesions. The tumour ulcerates and may erode local structures.

- 3) Generalized disease: The disease may be widespread from the beginning or it may present as nodular disease in which the tempo of the disease accelerates after a period of slow progression. This form also includes the lymphadenopathic form of KS seen in African children in which there is involvement of lymph nodes without cutaneous manifestation. It also includes patients who have nodal, visceral and cutaneous involvement with rapid development of widespread oedema and fleshy nodules of short duration.

In AIDS patients there exists a diversity of clinical presentation. In AIDS, the disease manifests as a multicentric neoplastic process that manifests with a single or more frequently multiple pink, red or violet macules, papules or nodules on the skin or oral cavity. The lesions are detected frequently on the trunk, arms, head and neck. The tip of the nose is a common and unique location. Lesions of the legs are less common than in the classical form of KS. Involvement of the upper and lower gastrointestinal tract is infrequently reported. The visceral lesions are usually asymptomatic although gastrointestinal lesions may occasionally result in haemorrhage and malabsorption. Pulmonary involvement is ominous and may present with insidious dyspnoea or haemoptysis. The cutaneous lesions are non blanching, pink to red, non tender and generally non-pruritic. (12,16,20,21,37)

Post-mortem studies on AIDS patients have revealed widespread dissemination of KS lesions involving all internal tissues except

the brain. Furthermore KS may be disseminated without cutaneous involvement in approximately 5% of AIDS patients. (22,23,24)

At Kenyatta National Hospital, C. Mwangi found 20% of AIDS patients had cutaneous involvement while 80% had visceral involvement without cutaneous involvement at post mortem examination. The lesions of KS were found in the lungs, trachea, oesophagus and spleen. (25)

The aetiology and pathogenesis of Kaposi's sarcoma is unknown. Several mechanisms have been suggested and include the effects of an oncogenic virus, an immunosuppressed state resulting in impaired immune tolerance or a combination of both. (26,27) The role of immunosuppression is supported by the high incidence of KS in renal transplant recipients and in patients receiving corticosteroids or cytotoxic drugs. (11,28) The evidence of a viral ecology includes the high prevalence of CMV antibodies among patients with KS. (29) Other possible aetiologies under investigation, due to the clinical importance of AIDS related KS, include the use of potentially carcinogenic recreational drugs, a direct association with and cellular transformation by human immune deficiency virus (HIV) and the presence of circulating factor(s) responsible for endothelial proliferation. (30,31,32)

The diagnosis of KS depends on the recognition of the two elements, the spindle cell and the vascular component. In the majority of cases these components are in equal proportions. The characteristic element is the small clear space surrounded by the

processes of a single endothelial like cell.(33)

The spindle cell resembles a fibroblast with the nucleus centrally placed and elongated with rounded ends and staining darkly. The mitotic rate is low. In a few tumours the cells are plumper with more rounded nuclei, prominent nucleoli and many mitoses. The vascular component of the tumour is usually well marked. Mature vessels of homogenises and lymphatic type are seen at the periphery of the nodule and are though to be reactive in nature. Red cells are found in both the vascular slits and between the spindle cells. Inflammatory cells are usually found in and around the tumour nodules.(20)

Apart from the mixed cell type described above, there are two other histological variants. The monomorphic tumour pattern is diagnosed when a single cell type predominates. However the spindle cells are shorter and plumper with a higher mitotic index than that of mixed cellularity.

The other variant exhibits a rather pleomorphic or anaplastic appearance. There is a high degree of mitoses and marked pleomorphism. Diagnosis may be difficult as the tumour resembles haemangioendothelioma and some pleomorphic rhabdomyosarcomas.

A relationship has been observed between histological type and clinical characteristics. Nodular disease usually shows mixed cell appearance. Generalized Kaposi's sarcoma also shows a similar pattern while the aggressive form show the monomorphic

or anaplastic types.(34)

Kungu and Gatei reviewed 357 cases in Kenya and classified the histological patterns into 3 types.(35) These are as follows:-

- (a) SLIT forming type:- Featuring mainly slits between and within spindle cells with little pleomorphism, low mitotic index and lymphocyte infiltration.
- (b) SOLID type:- featuring marked pleomorphism and absence of slits. Numerous mitotic figures were observed with mainly a plasma cell infiltration.
- (c) MIXED type:- where both slit forming and solid types are seen in different areas of the tissue. However one pattern usually predominates.

Kaposi's sarcoma in AIDS patients is generally thought to be histologically no different from the classical form.(24,36) However patients with AIDS and Kaposi's sarcoma tend to have a more angiomatous appearance with a more progressive disease and multiple organ involvement. Histological appearances of autopsy specimens show the lesions as having taken a more aggressive angiosarcomatous pattern with spindle cell proliferation.(14,37)

D. Serwadda et al described 4 AIDS patients with KS having generalized lymphadenopathy oral lesions and visceral involvement. Histologically the disease was of the mixed

cellularity type except in one case where monomorphic KS was seen in a lymph node, thus indicating a difference in pathology.(38)

McNutt et al found the light microscopic appearance of AIDS and Non-AIDS KS to be similar except that necrotic endothelial cells were seen more in the AIDS KS. The KS lesions from male homosexuals showed abundant entrapped erythrocytes with small amounts of haemosiderin present. Few clusters of plasma cell were seen within the lesions. Mitoses were sparse with only 0-1 per 10 high power field and in only 2 cases were there upto 2 mitoses per 10 HPF.(39)

C. Mwangi found KS lesions in AIDS patients at postmortem to be of the Slit forming type.(26)

The question relating to histopathology is whether KS in AIDS patients can be distinguished microscopically from Non AIDS KS.

A more stringent comparison would be between AIDS related and Non-AIDS KS with similar microscopic appearance. Such a study would be possible only in Africa because of the prevalence of both types of KS.(40)

The histogenesis of KS remains a subject of dispute. Early histochemical and microscopic studies ascribed the cellular origins of KS variously to reticuloendothelial proliferation, neural (schwann) cell origin, a combination of endothelial and perithelial proliferation and multipotent perivascular

mesenchymal cells. Current theories about the origin of KS favour either vascular or lymphatic endothelium.(41)

KAPOSI'S SARCOMA IN KENYA

The first case of KS in Kenya was described by N. Maclean in 1939 in a 42 year old Kikuyu male who presented with painful nodules on the skin of the foot. The lesions were histologically reported as haemorrhagic pigment sarcoma of Kaposi's. (42)

Rogoff Studied 206 cases of KS diagnosed on biopsy material between 1957 and 1966. He classified the disease according to age and tribe. 20 of their cases involved patients under the age of 21 years. The M:F ratio was 7.2:1. 85% of their cases were composed of single lesions, 76% of which affected the limbs while the rest occurred elsewhere. KS comprised 2.9% of all malignant tumours and the incidence was highest amongst the Kikuyu-Embu-Meru group followed by the Luo.(43)

Kungu and Gatei studied 425 cases of KS diagnosed histologically between 1968 and 1978. 81% of the patients were from the Kikuyu, Meru, Luhya and Kamba tribes. The largest number of KS patients were in the 41-50 years age group. The M:F ratio was 8.5:1. 78% of cases affected the upper and lower limbs and the lymphadenopathic form was seen mainly in the younger age group.(35)

GENERAL OBJECTIVE:

The general objective of this retrospective study was to review Kaposi's sarcoma as seen at Kenyatta National Hospital during the five year period from January 1987 to December 1991.

SPECIFIC OBJECTIVES

The specific objective were to:-

- 1) To study and analyze the presentation of Kaposi's sarcoma in terms of age, sex, tribal distribution and HIV status.
- 2) To study the clinical presentation of AIDS and Non-AIDS Kaposi's sarcoma in terms of symptomatology, duration of symptoms in relation to development of diagnostic features and the distribution of lesions.
- 3) To study the histological features and patterns of Kaposi's sarcoma in AIDS patients and compare these features with the histological features of Non-AIDS Kaposi's sarcoma.

MATERIALS AND METHODS

Paraffin blocks of all specimens diagnosed on histology as Kaposi's sarcoma were retrieved using the file records of the request forms in the department of Human Pathology at Kenyatta

National Hospital. New slides were prepared from the blocks that were retrieved and stained by the Haematoxylin and Eosin method. The slides were also stained for haemosiderin using Perls prussian blue stain.

The In-patient record files were traced from the records department of KNH using the In-patient numbers written on the request forms. Information regarding the age, sex, tribe, clinical presentation and HIV status (in terms of ELISA) were retrieved and entered on a performa sheet.

The histological appearances of the lesions were studied and classified into 3 types (Kungu and Gatei classification)

- 1) SOLID type
- 2) SLIT type
- 3) MIXED type

The following histological features were also studied.

- 1) Degree of pleomorphism: This was graded as follows

Mild:- nuclei appeared fairly uniform and slender

Moderate:- variation in size of nuclei, slender and occasional plump nuclei were seen in some areas of the lesion.

Marked:- Plump round vesicular nuclei, large bizarre cells and prominent mitoses. These features were seen throughout the lesion.

2) Mitotic Index:- These were the number of mitoses per 10 HPF in each biopsy, graded as follows 0-5, 6-10, >10

3) Degree of Inflammatory cell infiltrate

This parameter was studied in skin lesions only and graded as follows:-

Mild:- Inflammatory infiltrate covering less than 25% of the HPF (x40 objective) in the areas of aggregation/distribution of the infiltrate.

Moderate:- Inflammatory infiltrate covering between 25-50% of HPF (x40 objective).

Intense:- Inflammatory infiltrate covering more than 50% of HPF (x40 objective).

4) Type of infiltrate:- This parameter was studied in skin lesions only and was described as being either LYMPHOCYTE predominant or PLASMA cell predominant)

5) Ulceration/necrosis:- This was described as being present or absent.

6) Degree of haemorrhage:- This was graded as follows:-

Mild:- extravasated RBCs covering less than 25% of the observed lesion.

Moderate:- extravasated RBCs covering between 25% to 50% of the observed lesion.

Extensive:- extravasated RBCs covering more than 50% of the observed lesion.

7) Degree of Haemosiderin deposition:- This was graded as mild, moderate or extensive depending on the intensity, and area covered by haemosiderin deposition.

8) Fibrosis:- This was graded as being absent or present.

To avoid any form of observer bias the slides were reviewed histologically and the various parameters studied first before the insertion of the HIV status.

INCLUSION CRITERIA

- (1) All blocks with adequate tissue for histology were included
- (2) Patients whose files were traced and whose HIV statuses were available.

EXCLUSION CRITERIA

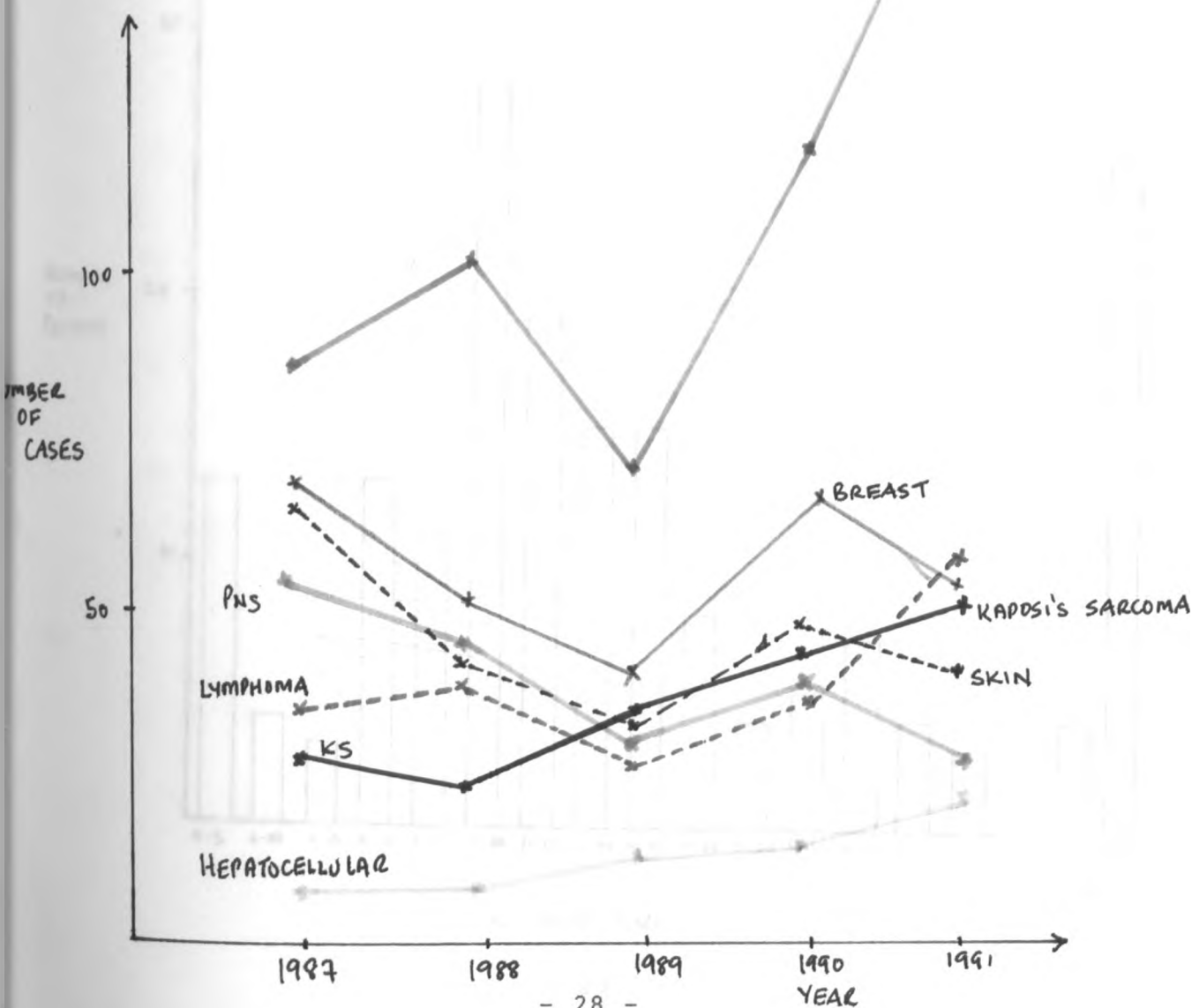
- (1) Block with inadequate tissue were excluded
- (2) Patients with missing files and/or having no HIV results.

RESULTS

Between January 1987 and December 1991, one hundred and eighty two cases (182) of Kaposi's sarcoma were diagnosed on histology in the Department of Human Pathology, Kenyatta National Hospital. This is an average of 36 cases per year.

FIG 1: NUMBER OF CASES/YEAR OF KAPOSI'S SARCOMA AND OTHER COMMON MALIGNANCIES

SOURCE: KENYATTA NATIONAL HOSPITAL
CANCER REGISTRY

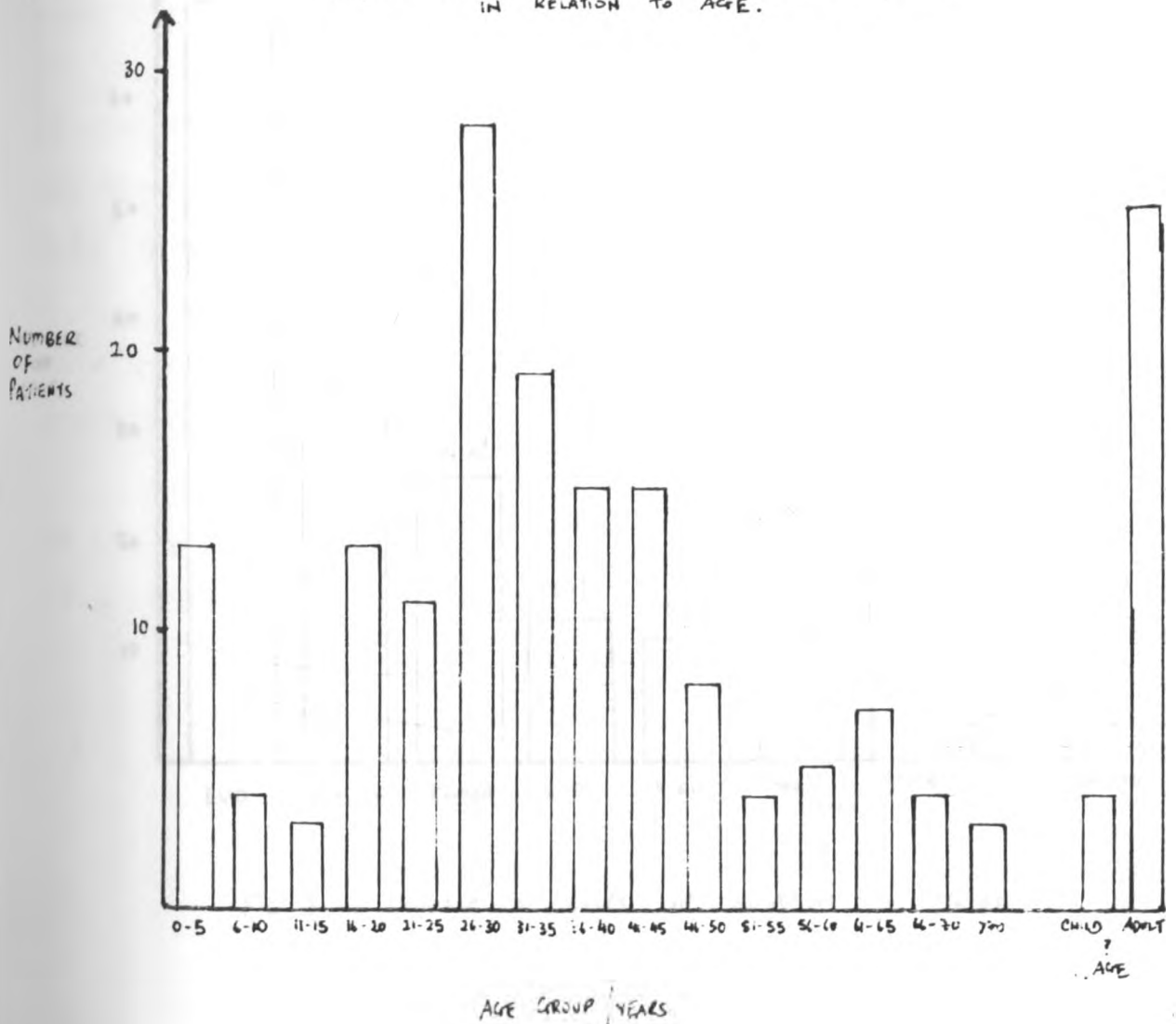


AGE AND SEX DISTRIBUTION

The youngest patient was 1 year old and the oldest was 90 years of age. There were 22 children (≤ 15 yrs of age) and 160 adults. The age distribution of the patients is shown in Fig 2. The largest number of the patients were those in their 3rd decade. (26-30 years Age group)

There were 148 males and 34 females, giving an overall male to female ratio of 4.3:1

FIG 2 : NUMBER OF CASES OF KAPOSI SARCOMA IN RELATION TO AGE.



TRIBAL DISTRIBUTION

The largest number of cases were seen in patients of the Luo community. Patients from this group comprised 37.3% of all cases of Kaposi's sarcoma.

Overall 50.5% of the patients came from tribes that originate from the Western part of the country.

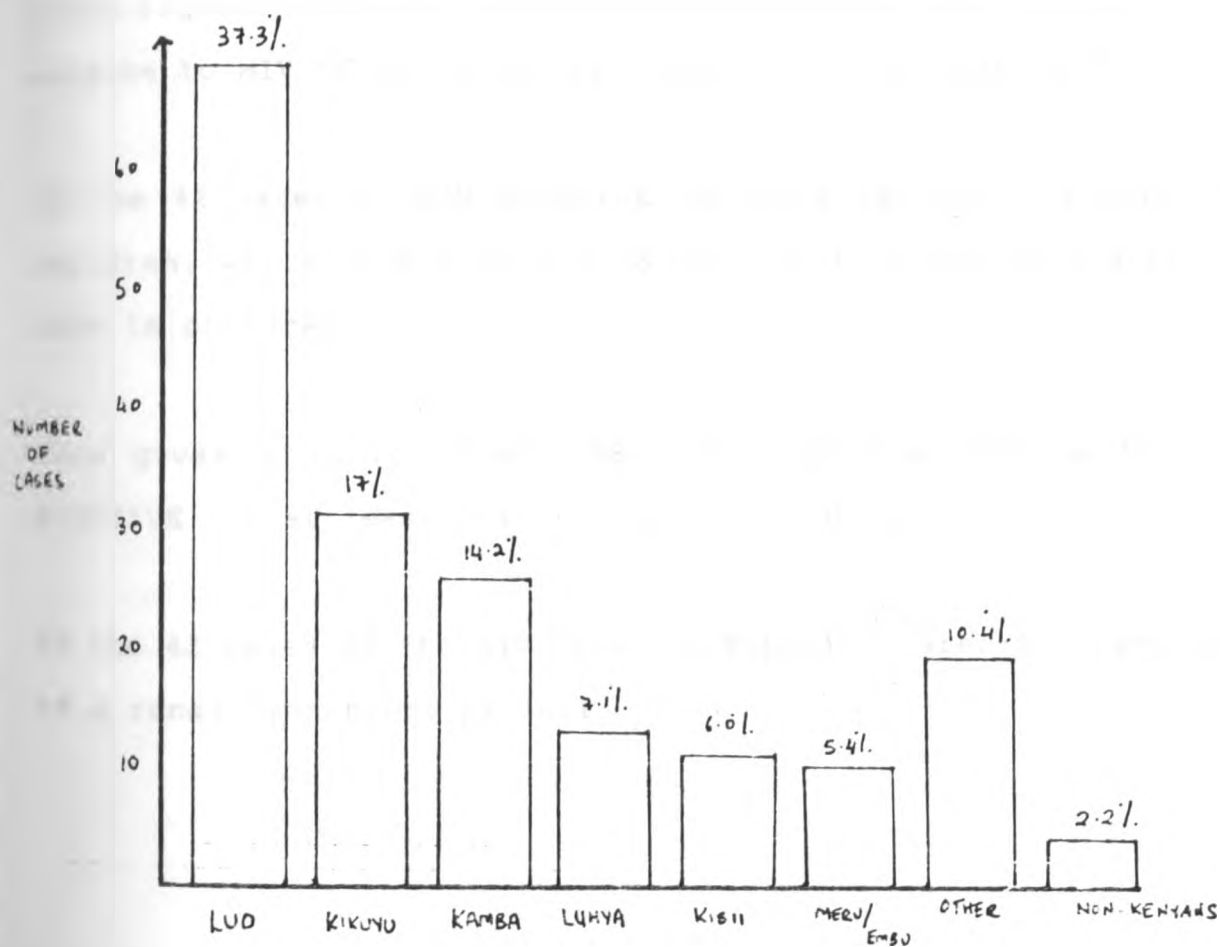


FIG 3 : NUMBER OF CASES IN RELATION TO TRIBE

KAPOSI'S SARCOMA IN RELATION TO HIV STATUS

110 patients had their HIV status declared by the ELISA method. 68 of these were POSITIVE and 42 were NEGATIVE. From the history and clinical presentation a further 12 patients were likely to be positive while 10 others were likely to be negative. It was not possible to determine the HIV status in the remaining 50 patients due to inadequate history and clinical information on the request forms.

These figures indicate that the ration of HIV POSITIVE Kaposi's sarcoma to HIV NEGATIVE Kaposi's sarcoma is at least 1.6:1

Of the 42 cases of HIV Negative Kaposi's sarcoma, 14 were in children, while only 2 of the 68 HIV positive Kaposi's sarcoma were in children.

This gives a ratio of HIV NEGATIVE Kaposi's sarcoma to HIV POSITIVE of at least 7:1 in the childhood age group.

Of the 42 cases of the HIV Negative Kaposi's sarcoma 1 case was of a renal transplant patient.

BIOPSY SITES

Of the 182 cases, there were 130 skin biopsies, 35 lymphnode biopsies, 11 muco-cutaneous (oral) and 6 from the respiratory tract (Nasal, Nasopharynx; Larynx). The site of 1 biopsy was not known. These findings are summarized in the table below:-

Table 1: BIOPSY SITES IN KAPOSI'S SARCOMA LESIONS

SITE	NUMBER	%
CUTANEOUS	130	71.4
LYMPHNODE	35	19.2
MUCO-CUTANEOUS	11	6
RESPIRATORY	6	3
NOT KNOWN	1	0.4

Lymphnode presentation was seen in 14 children and in 21 Adults That is 40% of lymphnode presentation is seen in children and 60% is seen in Adults.

It was not possible to classify the biopsy sites as belonging to HIV positive or negative patients. This is because the HIV statuses were not declared on the majority of the request forms.

CLINICAL FEATURES

Case record files of 63 HIV POSITIVE Kaposi's sarcoma patients and 37 HIV NEGATIVE Kaposi's sarcoma patients were studied. Table II and Table III show some of the major symptoms in HIV positive and HIV negative Kaposi's sarcoma respectively.

Table II: MAJOR SYMPTOMS OF HIV POSITIVE KAPOSI'S SARCOMA

SYMPTOMS	NUMBER OF PATIENTS	%
Development of skin - Non pruritic 30 nodules Pruritic 12	42	56.7
Lymph Node enlargement	9	12.2
Persistent diarrhoea	9	12.1
cough (non productive)	7	9.4
Dysphagia	4	5.4
Cough (non productive)	1	1.4
Epistaxis	1	1.4
Breathing difficulties	1	1.4
TOTAL	74	100

3 patients in this group had no symptoms. Their lesions were observed on physical examination of HIV positive patients who had been admitted for other illness. 13 patients from the above group also had proven pulmonary tuberculosis.

Table III: MAJOR SYMPTOMS OF HIV NEGATIVE KAPOSI'S SARCOMA

SYMPTOMS	NUMBER OF PATIENTS	%
Development of SKIN Nodules Non pruritic 20 Pruritic 3	23	60.5
Lymphnode enlargement	8	21.1
Hoarseness of the voice	2	5.3
Breathing difficulties	2	5.3
Development of ORAL lesions	1	2.6
Development of Nasal masses	1	2.6
Nasal discharge	1	2.6
TOTAL	38	100

3 patients in this group had no complaints related to Kaposi's sarcoma. There included 1 patient who had renal transplantation and was on immunosuppressive therapy. The lesions were noted on routine follow up of the patients. 1 patient was being treated for HODGKIN disease and another patient was being treated for chronic lymphocytic leukaemia.

DURATION OF SYMPTOMS

Table IV shows the duration of symptoms in months in the two groups.

Table IV: Duration of symptoms (months)

	0-6	7-12	13-18	19-24	25-30	31-36	>36
HIV+	42	12	3	1	0	0	0
HIV-	16	2	3	2	0	6	2

ANATOMICAL SITES OF KAPOSI'S SARCOMA LESIONS

The distribution of lesions in relation to the anatomical sites is illustrated in Table V for the HIV positive patients and Table VI for HIV negative lesions.

Table V: DISTRIBUTION OF LESIONS IN HIV POSITIVE KAPOSI'S SARCOMA

ANATOMICAL SITE	NUMBER OF PATIENTS	%
MULTIPLE SITES	21	33
LOWER LIMBS ONLY	17	27
LYMPH NODE	11	17.4
ORAL LESIONS ONLY	4	6.3
LOWER LIMB + UPPER LIMB	3	4.8
UPPER LIMB ONLY	3	4.8
FACE ONLY	2	3.2
TRUNK ONLY	1	1.6
LARYNX	1	1.6
TOTAL	63	100

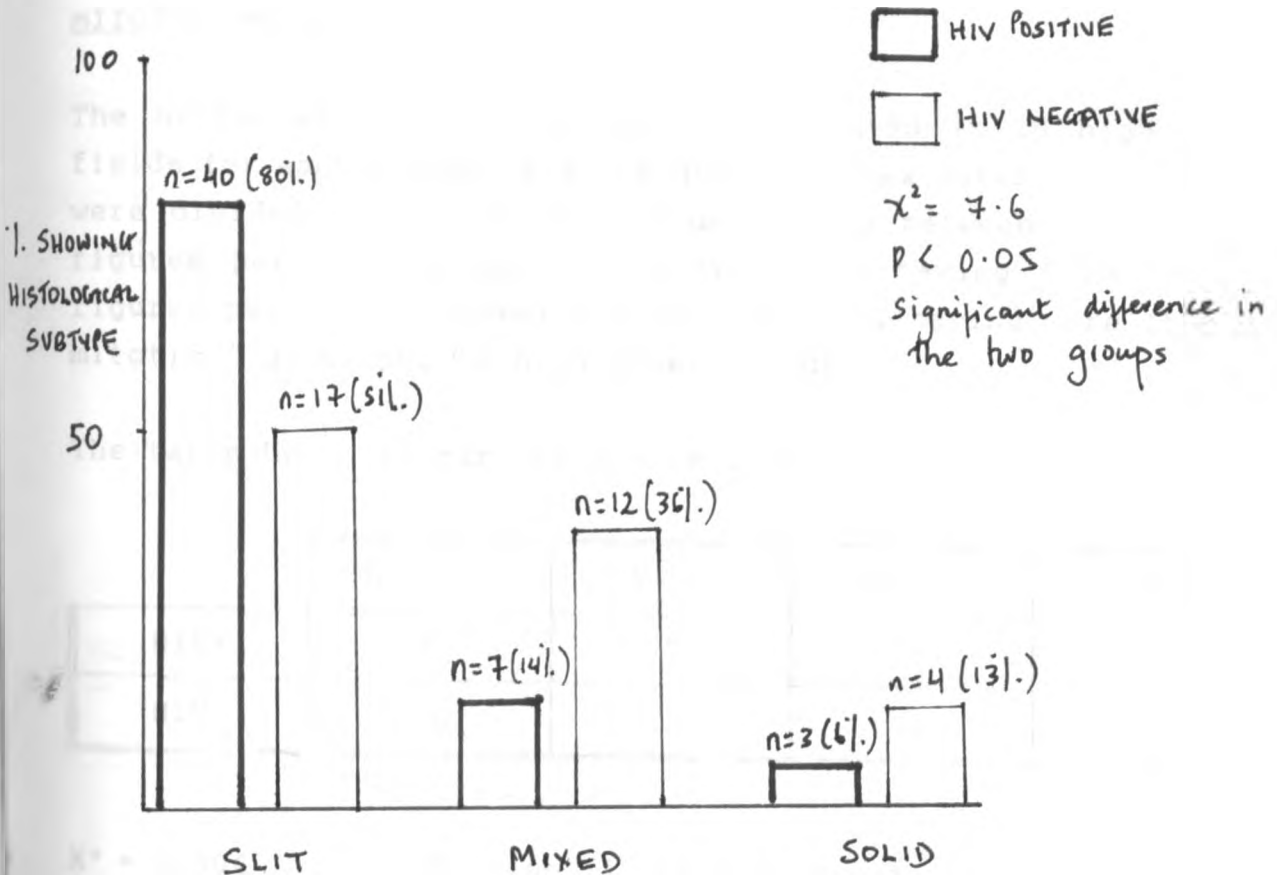
Oral lesions were noted to be present in 16 other patients. 9 of these had multiple lesions, 4 had lymph node involvement only and 3 patients with involvement of lower limbs only.

Table VI: DISTRIBUTION OF LESIONS IN HIV NEGATIVE KAPOSI'S SARCOMA

ANATOMICAL SITE	NUMBER OF PATIENTS	%
LOWER LIMB ONLY	14	37.8
UPPER LIMB + LOWER LIMB	9	24.4
LYMPH NODE ENLARGEMENT	7	18.9
ORAL LESIONS	2	5.4
POSTNASAL SPACE/NASAL CAVITY	2	5.4
LARYNX	1	2.7
CONJUNCTIVA	1	2.7
UPPER LIMB ONLY	1	2.4
TOTAL	37	100

HISTOPATHOLOGY:

Histopathological studies were performed on biopsies from 83 patients. These were biopsies that fulfilled the inclusion criteria. There were 50 HIV positive Kaposi's sarcoma lesions studied and 33 HIV Negative Kaposi's. 65 Biopsies were from the skin and 18 biopsies were from lymph nodes. Results for the different parameters are shown below:-



DEGREE OF PLEOMORPHISM:

The degree of pleomorphism was divided into 3 categories mild, moderate and marked. The table below shows the number of biopsies showing the degree of pleomorphism in the two groups.

	MILD	MODERATE	MARKED	TOTAL
HIV+	21	16	13	50
HIV-	13	13	7	33

$X^2 = 0.533$ $p > 0.05$ No significant difference in the two groups.

MITOTIC INDEX

The number of mitotic figures were counted in 10 high power fields for each biopsy, and the mitotic index determined. These were divided into 3 groups, those having between 0-5 mitotic figures per 10 high power fields, those having 6-10 mitotic figures per 10 high power fields and those having more than 10 mitotic figures per 10 high power fields.

The table below summarizes the results.

	0-5	6-10	>10	TOTAL
HIV+	37	7	6	50
HIV-	26	5	2	33

$X^2 = 0.806$ $p > 0.05$ No significant differences in the two groups.

DEGREE OF INFLAMMATORY CELL INFILTRATE

This parameter was studied only in the skin lesions and excluded lymph node lesions. Thus 65 skin biopsies were studied for this parameter. The results are shown below. This parameter was graded as Mild, Moderate or Intense.

	MILD	MODERATE	INTENSE	TOTAL
HIV+	19	14	5	38
HIV-	7	10	10	27

$$\chi^2 = 6.187 \quad 0.02 < p < 0.05$$

significant difference exist in the two groups

TYPE OF INFILTRATE

This parameter was studied only in skin lesions and was described as being either lymphocyte predominant or plasma cell predominant. Results for two groups are shown below:-

	LYMPHOCYTE	PLASMA CELL	TOTAL
HIV+	21	17	38
HIV-	17	10	27

$$\chi^2 = 0.385 \quad p > 0.05 \quad \text{No significant differences in the two groups.}$$

ULCERATION OR NECROSIS IN LESIONS

This was described as being either present or absent. The results are summarized below:-

	PRESENT	ABSENT	TOTAL
HIV+	5	45	50
HIV-	9	24	33

$\chi^2 = 4.230$ $p < 0.05$ significant difference at 95% confidence level.

DEGREE OF HAEMORRHAGE AND VASCULARITY

This was categorized into 3 groups: Mild, Moderate and Extensive Results are shown below:-

	MILD	MODERATE	EXTENSIVE	TOTAL
HIV+	20	13	17	50
HIV-	17	8	8	33

$\chi^2 = 1.244$ $p > 0.1$ No significant difference in the two groups

FIBROSIS

This parameter was recorded as being either present or absent for the two groups. Results are shown below:-

	PRESENT	ABSENT	TOTAL
HIV+	15	35	50
HIV-	25	8	33

$\chi^2 = 16.67$ $p < 0.01$ significant differences present between the two groups

DISCUSSION

An average of 36 cases per year of Kaposi's sarcoma were seen between January 1987 and December 1991, with an increase of over 40% between 1988 and 1989.

The largest number of patients were in their 3rd decade of life and were specifically in the 26-30 yrs age group. This is a younger age group when compared to the study by Kungu and Gatei in which the majority of the patients were in the 5th decade. (35)

There was a male preponderance with a male to female ratio of 4.5:1. This is a much lower ratio than that of the study by Kungu and Gatei in which the male to female ratio was 8.5:1. (35) This ratio is also much lower than the earliest study by Rogoff in which the M:F ratio was 7.2:1. Thus although there is a male predominance, this change in M:F ratio indicates an increasing incidence of the disease amongst females which may be attributed to the emergence of AIDS in this environment.

With regard to tribal distribution, the largest number of cases were seen amongst members of the Luo community. Slightly over 50% of the total number of patients originated from the Western sector of the country. In the earlier studies by Kungu and Gatei as well as the earliest study by Rogoff, the majority of the patients were from the Kikuyu, Embu and Meru group (35,43). This "tribal" shift may be related to the emergence of AIDS related Kaposi's sarcoma and the tribal distribution of HIV disease. Statistics from the Kenya National AIDS control programme indicate that approximately 43% of AIDS cases classified by district of birth are from Nyanza and Western province together. This high ethnic prevalence may suggest a genetic predisposition.

This ethnic predisposition to the disease has been supported by the relatively high prevalence of the disease in certain ethnic groups in the United States and in whom there is a distinct

association with particular HLA-DR phenotypes and principally HLA-DR5(12,44). This association also supports the findings that within certain geographical areas, members of a particular ethnic group showed a considerably higher incidence of KS than others living in the same location.(45) Early in the AIDS epidemic, there was an frequency of HLA-DR5 in KS patients of European, Jewish or Italian background, while KS patients of Northern European background had a higher than expected frequency of HLA DR2.(46)

110 patients had serology results for HIV antibodies performed by the ELISA method. Of these 68 were positive and 42 were negative for HIV. This gives an overall ratio of HIV positive to HIV negative as 1.6:1. However in the childhood group the ratio of HIV positive Kaposi's sarcoma to HIV negative Kaposi's sarcoma is 1:7. This ratio for the adult group is 2.4:1. These ratios suggest that the major impact of AIDS on the incidence of Kaposi's sarcoma has been on the adult age groups. The ratio for the adult group is a bare minimum. This ratio could be much higher because many AIDS patients with Kaposi's sarcoma are not biopsied as they may be extremely moribund and may die before investigations are performed. Furthermore some patients may have the diagnosis made on clinical grounds only. In some patients the lesions may be missed altogether. Furthermore AIDS patients may have visceral KS without cutaneous lesions.(22,23,24,25) Of the HIV negative cases of Kaposi's sarcoma, there was one case of a renal transplant patient who was on immunosuppressive drugs. This patient was a 28 year old Kamba male who developed the lesions 3 years after transplant surgery. To date only 3 renal transplants have been performed at Kenyatta National Hospital, out of which one patient developed Kaposi's sarcoma. This is a relatively high incidence, even though the numbers are few. In Western countries the incidence of Kaposi's sarcoma in recipients of renal transplants is approximately 0.4%.(47) Despite identical management protocols, this high incidence suggests the presence of some etiologic agent in this environment which is yet to be identified.

Although skin lesions were the commonest presentation (71.4%), lymph node presentation was not infrequent. Indeed 19.2% of the lesions were in lymph nodes. This incidence of lymph node involvement is more than twice that reported in the study by Kungu and Gatei. Furthermore 60% of Kaposi's sarcoma in lymph nodes were seen in adults, while only 40% were seen in children. In the earlier study the majority of lymph node presentation were seen in children below 10 years of age. KS involving the lymph nodes is seen in a large number of AIDS patients.(48) The lymphadenopathic form of KS is rather intriguing. Bhana et al suggest two forms of lymph node involvement.(49) One occurs in younger patients and involves many groups of nodes and probably develops in situ. The other lymphadenopathic form is as a result of metastases from an aggressive tumour to the regional lymph node. It is not clear from this study into which group the lymphadenopathic form seen in adult patients (and especially those with AIDS), fall into since there were no follow up studies or post-mortem studies done. However the lymph node involvement in childhood KS probably fall into the former group.

The clinical features were studied from data retrieved from case record files of 100 patients. There were 63 HIV positive Kaposi's sarcoma patients and 37 HIV negative patients. Most of the patients in the two groups presented with the development of nodules preceded by swelling. 29% of these patients in the HIV positive group described the lesions as being pruritic. In Western literature, Safai et al and other authors mention the lesions of Kaposi's sarcoma as being generally non pruritic.(12,16,20,21,36) This feature may be due to secondary fungal infections of the skin which are commonly present in HIV positive patients in this environment.

Other symptoms present in HIV positive Kaposi's sarcoma patients include cough, persistent diarrhoea and dysphagia. Their symptoms may be due to involvement of these sites by Kaposi's sarcoma lesions. 3 Patients with HIV positive Kaposi's sarcoma were asymptomatic. This emphasizes the need for clinicians to

look actively for lesions of Kaposi's sarcoma in AIDS patients.

71% of patients in the HIV positive group had duration of symptoms lasting less than 6 months while only 51% of HIV negative Kaposi's sarcoma patients had symptoms lasting less than 6 months. 25% of HIV negative Kaposi's sarcoma had symptoms lasting more than 2 years. There were no patients with AIDS KS having symptoms lasting more than 2 years. This observation suggests that the lesions develop more rapidly in HIV positive patients and could be related to the rate of development of immune dysfunction and the degree of immunodeficiency.

In the HIV positive group 33.3% of the patients presented with multiple lesions, 27% had lesions involving the lower limbs only and 17.4% of the patients presented with lymphnode involvement 25% of the patients were noted to have oral lesions. There were no patients with visceral involvement seen, neither were there any PM follow up done to confirm visceral involvement, PM studies may have shown visceral involvement. C. Mwangi showed visceral involvement is cutaneous form in 80% of HIV positive patients. In the HIV negative group the lower limbs were involved in 62% of the cases while lymphnode enlargement was seen in 18.9% of the patients. The clinical features of HIV positive Kaposi's sarcoma differ from those described in Western literature by Safai et al and Amberson et al in which involvement of the lower limb is less common.(36,54) In this study involvement of the lower limbs is seen frequently in HIV positive Kaposi's sarcoma patients and may not be clinically distinguished from the classical type of Kaposi's sarcoma. This observation has also been expressed by A.C. Bayley et al in which endemic form of KS was distinguished from atypical KS by HTLV III serology.(50) KS has been associated with other malignancies, especially lymphomas are also seen in AIDS. In this study No associated malignancies were observed occurring with AIDS-KS.

Histological studies were performed on 50 HIV positive KS lesions and 33 HIV negative KS lesions.

Slit forming type was seen in 80% of HIV positive patients while mixed and solid types were seen in 14% and 6% respectively. Slit forming type was seen in 51% of HIV negative KS lesions. This difference was statically significant at p value of less than 0.05. This observation has also been expressed by C. Mwangi at KNH, D. Servadda et al, in Uganda and in Western literature by Heyer, Kahn and Volberding.(25,29,37) This slit forming type is synonymous with the mixed cell variant expressed by other authors. This variant is associated with nodular non aggressive lesions and thus may have better prognosis.(33) Meyer et al emphasize that HIV patients with KS live longer than those dagnosed with other HIV related illnesses.(37) Furthermore, Kaposi sarcoma lesions in iatrogenically immunosuppressed patients, such as renal transplant patients, have been known to regress upon withdrawing therapy.(11) It can therefore be hypothetically inferred that KS lesions in HIV positive patients may regress if the immunosuppressed state is reversed. Currently no such treatment modality exist.

50% of HIV positive KS lesions showed a mild degree of mononuclear cell infiltration. In the HIV negative group 75% showed moderate to intense degree of infiltration while 25% showed mild degree of infiltration, around the lesions. These differences were statistically significant and may be explained by the relative differences in the degree of immunosuppression. Some histological features that suggest most immunity include the infiltration of the tumour by lymphocytes and plasma cells.(7,53) A number of immunological studies have been done on KS. Masters et al found that antibody responses and immunoglobulin levels were normal but there was a striking impairment in delayed hypersensitivity in patients with aggressive lesions only.(51) Kestens et al found no evidence of immune suppression among patients with endemic African KS as compared with normal controls.(52)

Ulceration or necrosis was observed to be present in 10% of HIV positive lesions and 28% of HIV negative lesions. These

differences were statically significant. This observed difference may be explained as an immune response to the lesions of Kaposi's sarcoma and which are dimished in HIV positive patients.

Fibrosis was present in 30% of HIV positive biopsies and in 75% of HIV negative biopsies. This difference is statistically significant and may again be explained on the basis of the impaired immunity in AIDS patients.

There were no statistical difference observed with respect to the degree of pleomorphism, mitotic index, degree of vascularity and haemorrhage, the degree of haemosiderin deposition and the type of infiltrate. Thus in this respect the two groups are essentially similar. There observation differs from those of Heyer et al in which AIDS-KS lesions are described as being more angiosarcomatous, (37) and other studies in which plasma cells, extravasated erythrocyte and haemosiderin deposition and cells with bizzare nuclei were seen. (55)

CONCLUSIONS

1. The full spectrum of Kaposi's sarcoma is present in this environment.
2. Major changes noted in the epidemiology of Kaposi's sarcoma. These are:-
 - (a) Younger age group with the largest number of patients in 26-30 years age group.
 - (b) Lower M:F ratio of 4.5:1
 - (c) Shift in tribal distribution with majority of patients from Luo community.

These changes in pattern of Kaposi's sarcoma may be attributed to the emergence of AIDS in this setup.

3. Although skin presentation is the commonest form of manifestation, there has been an increase in the lymphadenopathic form of Kaposi's sarcoma and specifically in the adult age group.
4. The disease is widespread in the patients with HIV, with a shorter duration of symptoms. Leg involvement is not uncommon and may be indistinguishable clinically from the endemic and classical form of the disease.
5. Slit forming type predominates in HIV positive Kaposi's sarcoma.
6. Minor differences exist histologically and include the absences or presence of Necrosis/ulceration, sclerosis and the degree of lymphocyte or plasma cell infiltration.

MAJOR CONSTRAINTS

1. The retrieval of paraffin blocks was extremely cumbersome and time consuming as there was no organized filing system and because of this a number of blocks could not be traced.
2. A number of patient record files could not be traced because there was no monitoring system as to the movement of files from the records department. In others although the IP numbers corresponded, the files were for different patients.
3. The data presented on the request forms by the clinicians was in most cases grossly inadequate with regard to the clinical picture presented by the patient.

RECOMMENDATIONS

1. There is an urgent need to reorganize the filing system for the paraffin blocks so that retrospective histopathological studies such as this one can be made more convenient and easier.
2. There is an urgent need for computerization of the entire records department at Kenyatta National Hospital.
3. There is need to carry out studies to identify the aetiologic agents, if any, that are implicated in the pathogenesis of Kaposi's sarcoma.
4. There is a need to carry out immunogenetic studies to identify high risk populations in the environment.
5. Transplant recipient patients may be prone to develop Kaposi's sarcoma and early recognition and therapeutic intervention may lead to a more favourable outcome.



CHILDHOOD LYMPHADENOPATHIC KS
(HIV NEGATIVE)



ENDEMIC KS INVOLVING LOWER LIMBS
(HIV NEGATIVE)



KS LESIONS IN RENAL TRANSPLANT PATIENT



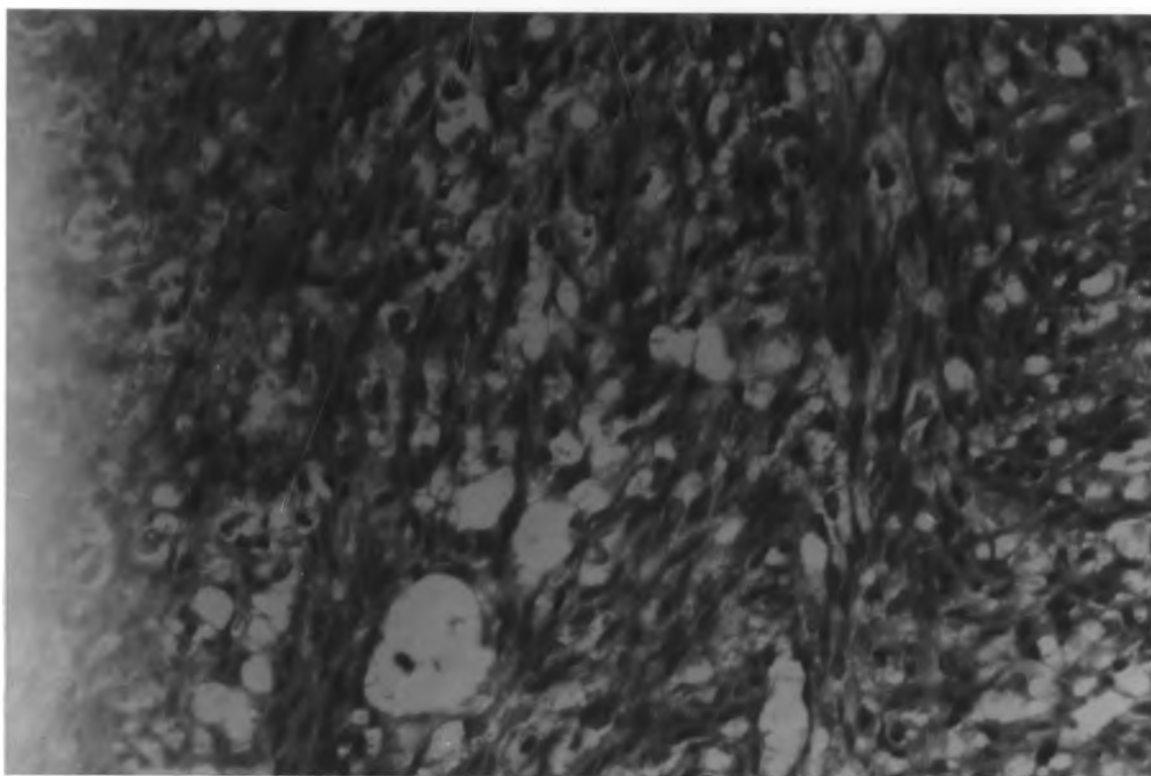
FLORID ORAL KS LESIONS IN HIV POSITIVE PATIENT



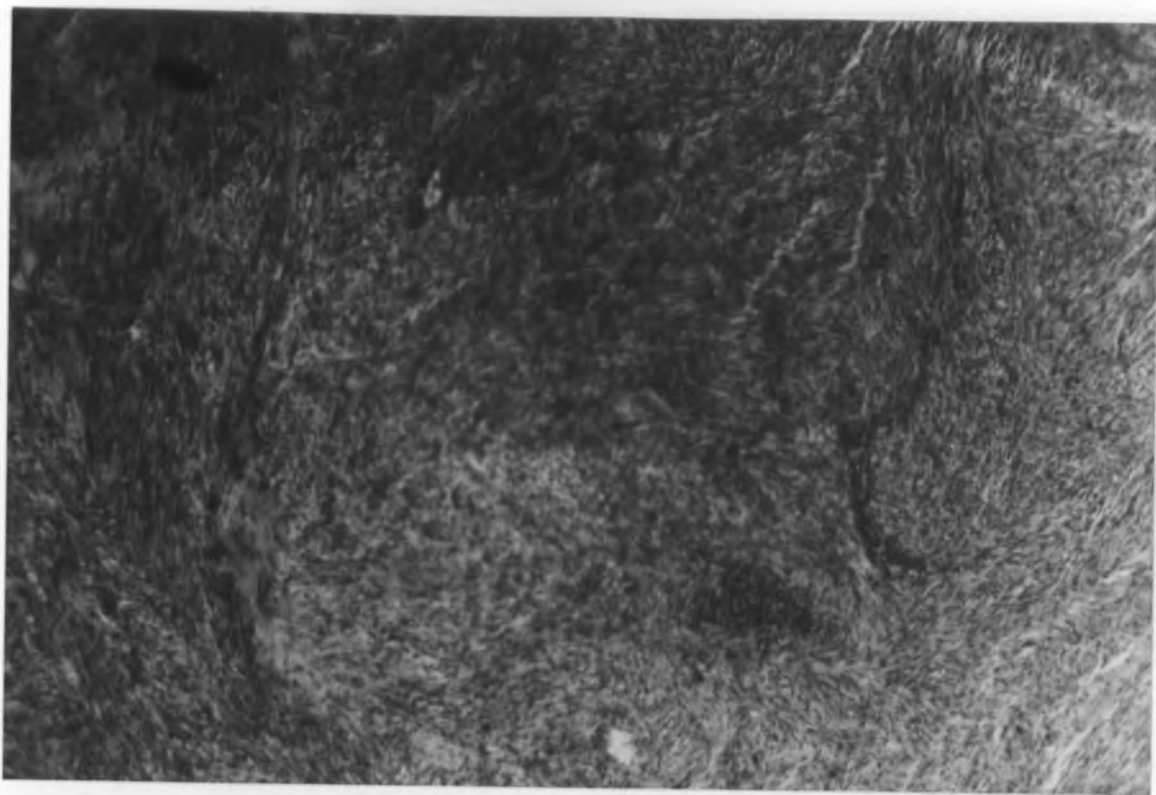
DISSEMINATED KS LESIONS IN HIV POSITIVE PATIENT



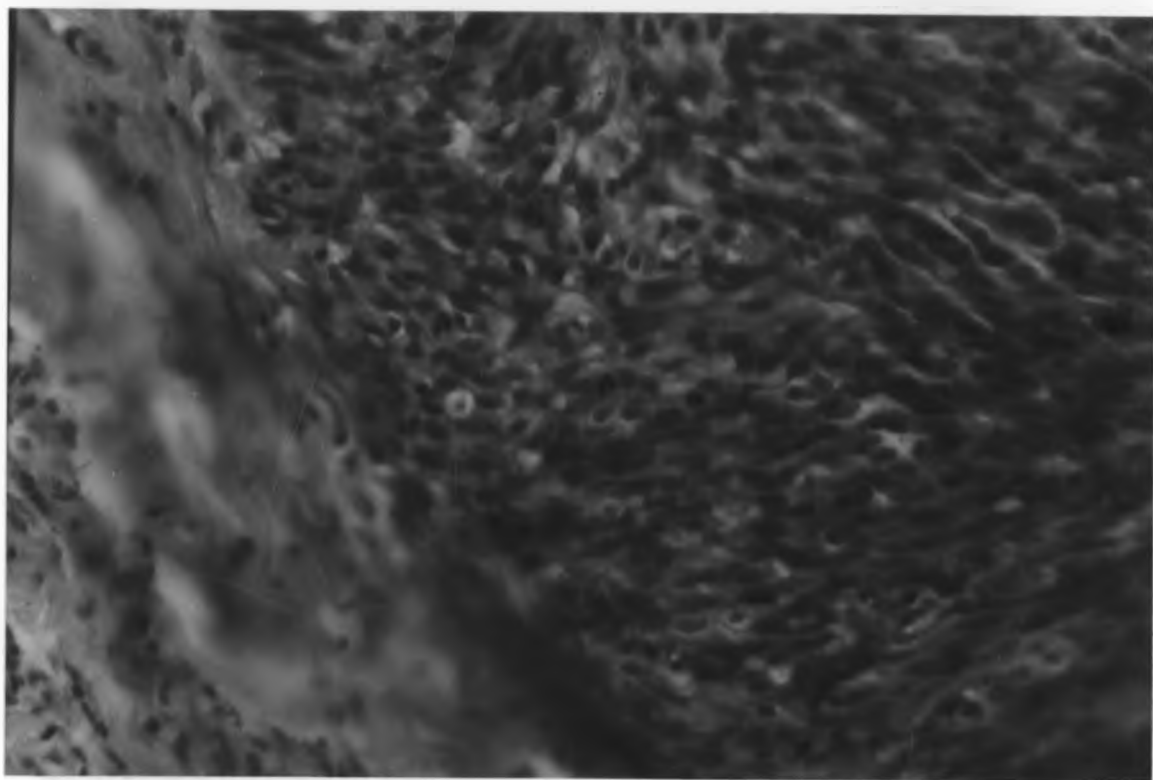
FLORID KS LESION ON LOWER LIMBS OF HIV POSITIVE PATIENT



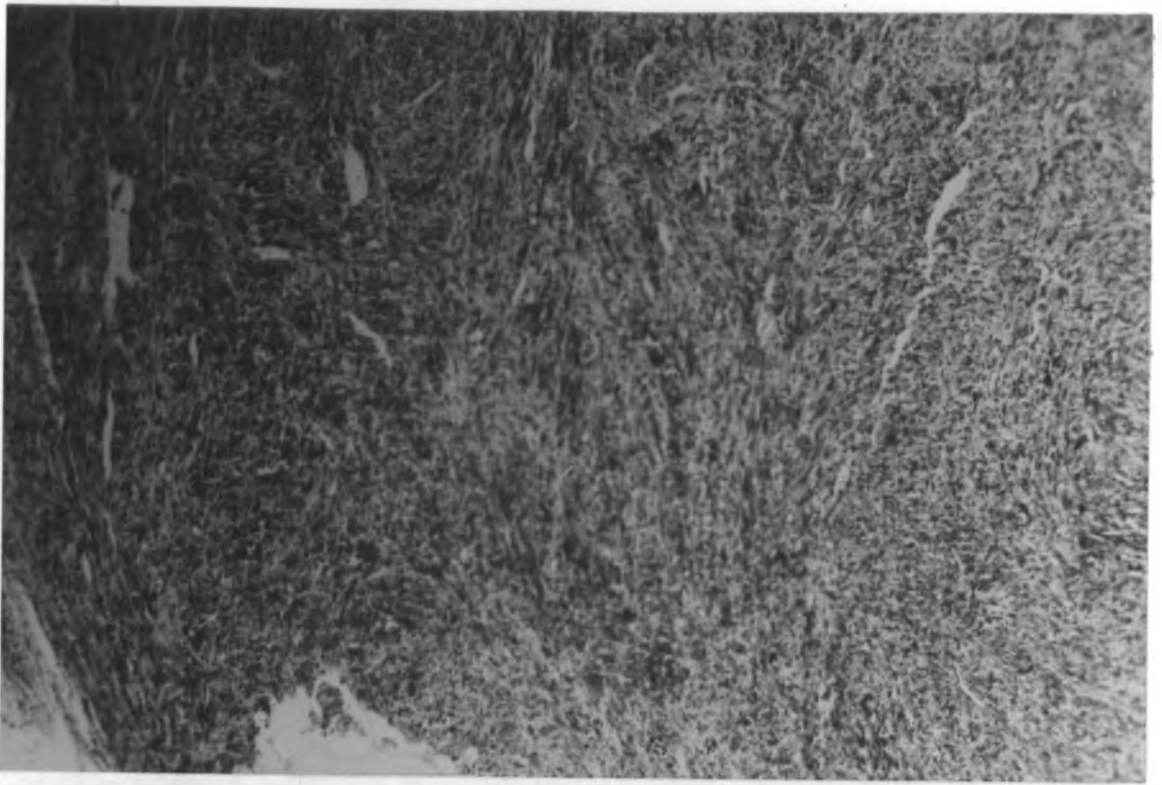
KS: SLIT FORMING TYPE WITH MILD DEGREE OF PLEOMORPHISM (HE x 400)



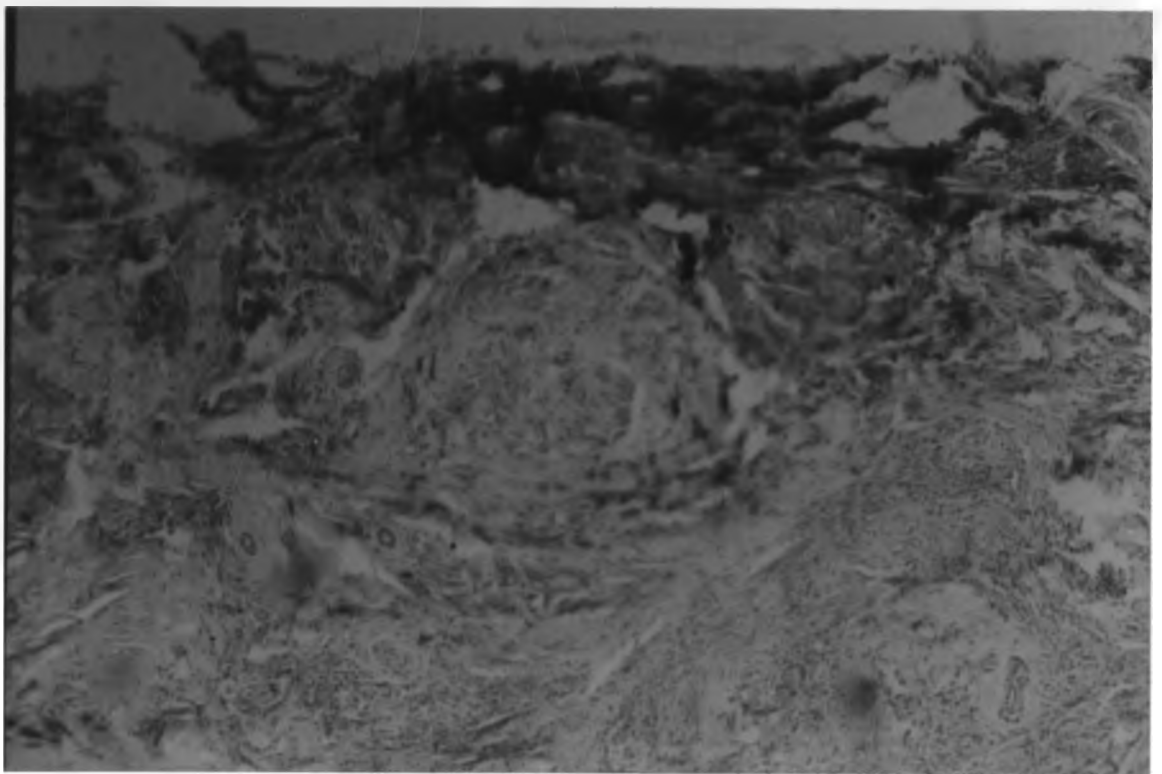
KS: MIXED TYPE (HE x 100)



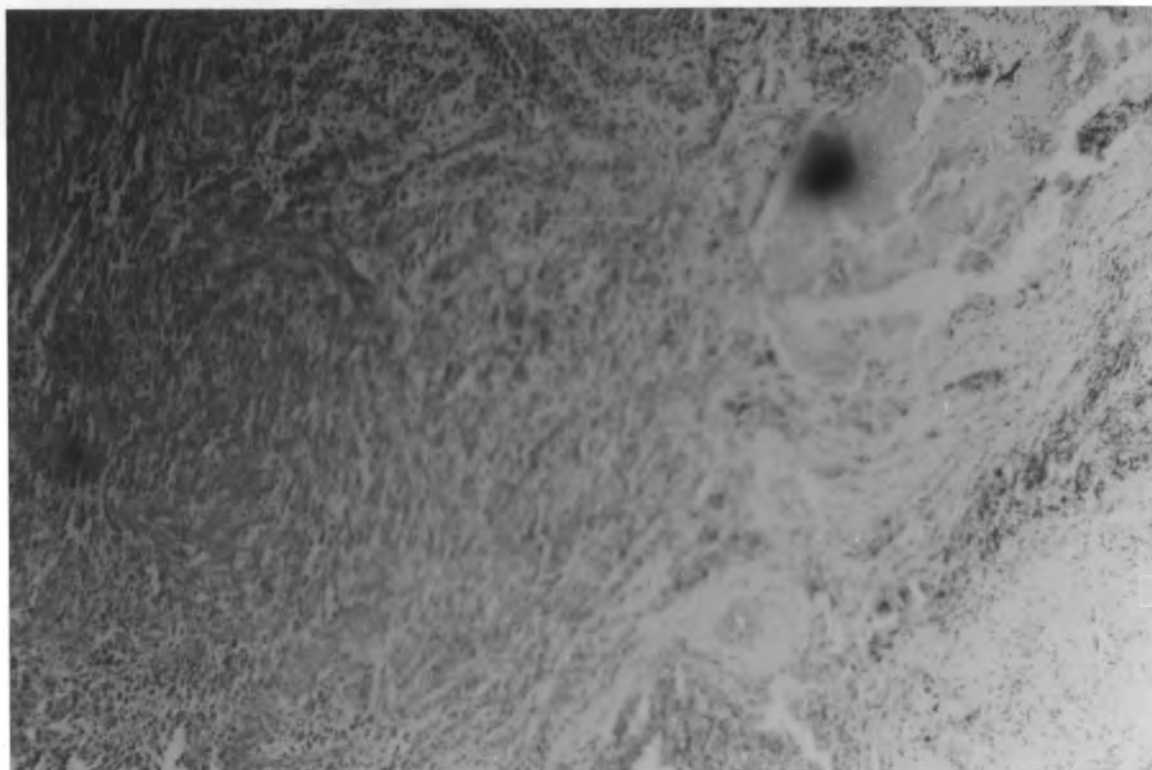
KS: SOLID TYPE SHOWING MARKED DEGREE OF PLEOMORPHISM
(HE x 400)



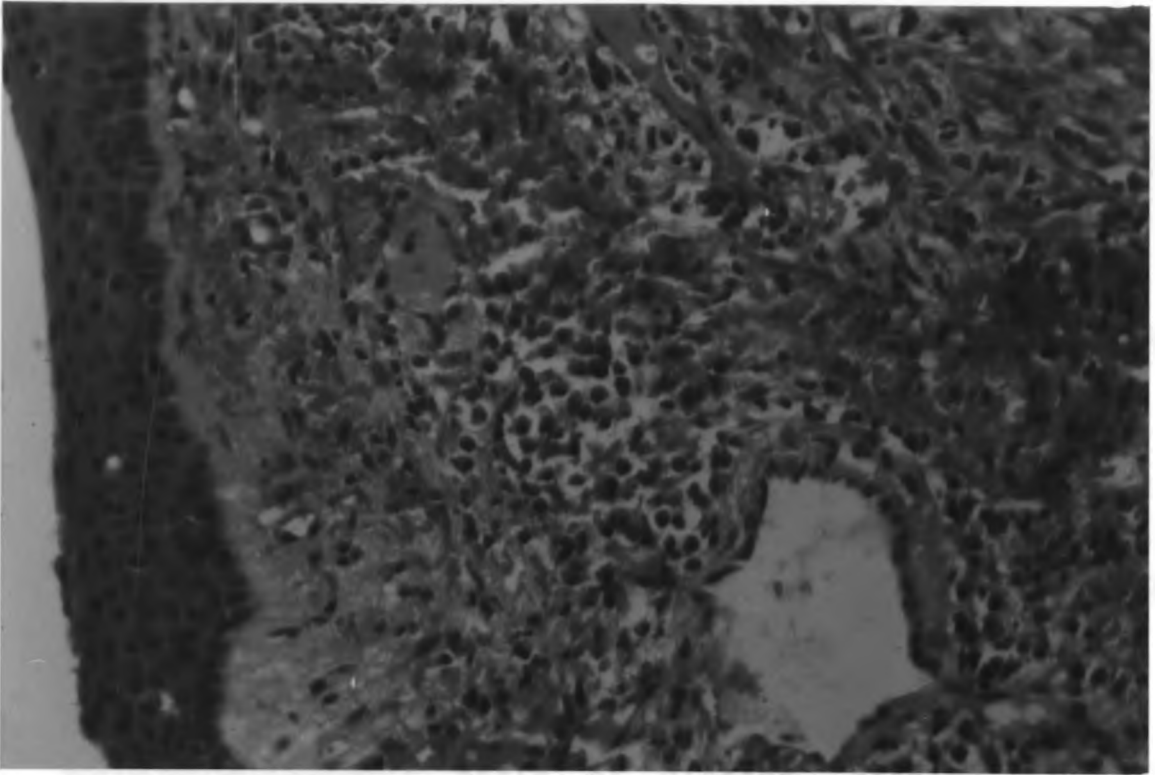
KS: INTENSE DEGREE OF HAEMORRHAGE (HE x 100)



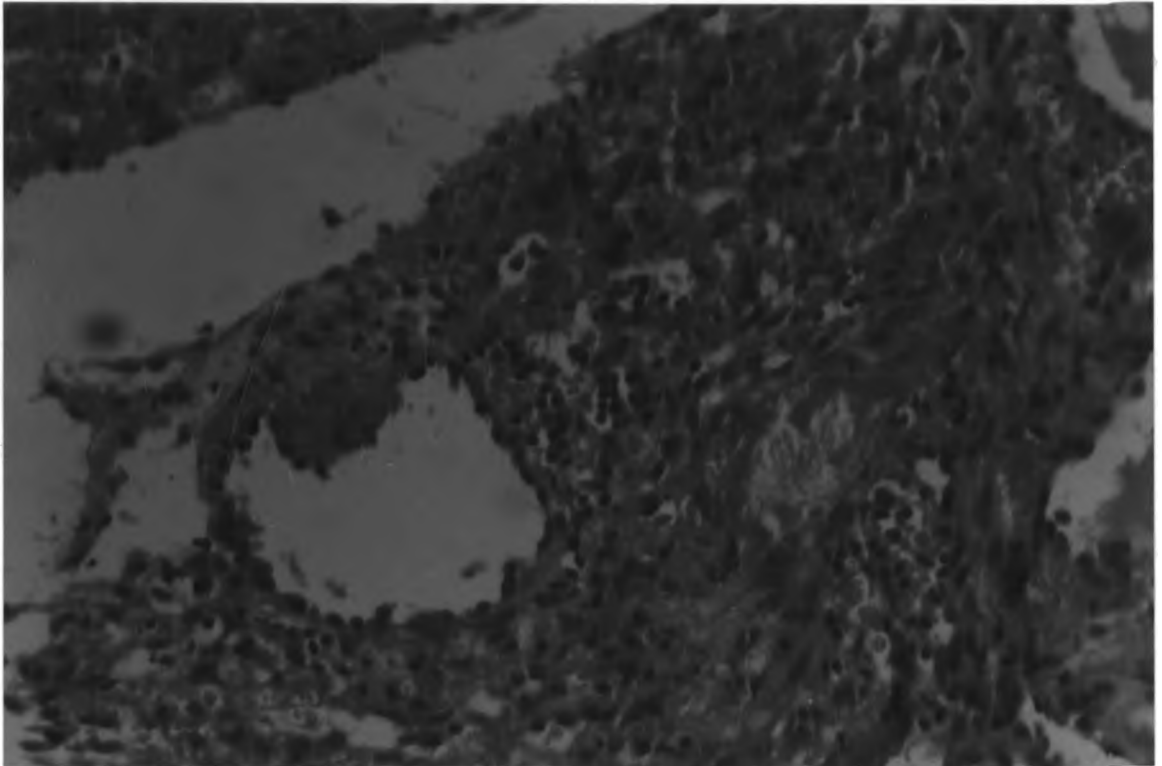
KS: INTENSE HAEMOSIDERIN DEPOSITION
(PERL'S PRUSSIAN BLUE STAIN x 100)



KS: MILD DEGREE OF HAEMOSIDERIN DEPOSITION
(PERL'S PRUSSIAN BLUE STAIN x 100)



PREDOMINANT PLASMA CELL INFILTRATION (HE x 400)



PREDOMINANT LYMPHOCYTE INFILTRATION (HE x 400)

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APPENDIX A
PROFORMA SHEET.

BIOPSY NUMBER: _____

IN-PATIENT NUMBER: _____

AGE: _____

SEX: _____ TRIBE: _____

HIV STATUS: _____

HISTORY: _____

CLINICAL EXAMINATION

GENERAL EXAMINATION: _____

DISTRIBUTION OF LESIONS: _____

OTHER CLINICAL FEATURES: _____

APPENDIX C

Staining by Haematoxylin and Eosin Procedure:-

- 1) Dewax and hydrate paraffin sections
- 2) Stain in Mayers haemalum for 5 minutes
- 3) Rinse and Blue tap water
- 4) Immerse slides in Eosin for 30s - 1min with agitation
- 5) Wash in tap water
- 6) Dehydrate in 70%, 95% and two changes of absolute alcohol
- 7) Clear in Xylene and mount with DPX

APPENDIX D

STAINING METHOD FOR HAEMOSIDERIN

PERLS PRUSSIAN BLUE REACTION

Procedure:-

1. Bring reactions to water
2. Rinse with distilled water
3. Flood section with a mixture of equal parts of 4% aqueous potassium ferrocyanide and 4% aqueous hydrochloric acid (freshly prepared)
4. Rinse in distilled water
5. Counterstain with 0.5% neutral red for 30 seconds
6. Rinse in distilled water
7. Dehydrate in 3 changes of absolute ethanol
8. Clear in 3 changes of Xylene and mount in DPX



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Our Ref:

Your Ref:

Dr. P. Dave,
Dept. of Pathology,
University of Nairobi.

19th May, 1992.

Re: Research Proposal entitled "Some clinical histopatho-
logical aspects of kaposi sarcoma in patients with
and without the acquired immuno deficiency syndrome"
(P221/1/92 Revised)

I am pleased to inform you that the KNH-ERC has reviewed
and approved the revised version of your above cited
research proposal.

On behalf of the Committee, I wish you luck in carrying out
your study and in addition request you to submit a summary
of your research findings and recommendations (if any)
for future reference by the Committee.

Thank you.

Dr. Anastasia N. Guantai
SECRETARY - KNH-ERC

cc. Prof. F.E. Onyango - Chairman - KNH-ERC
Prof. Kungu - Dept. of Pathology
Director - KNH