Kaposi’s sarcoma:
A review of 136 Rhodesian African cases

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Kaposi’s syndrome was originally described by Moricz Kaposi, Professor of Dermatology in the University of Vienna in 1872. The condition was thought to be rare and virtually confined to Central European Jews, although later it was also described in Mediterranean peoples. There was even evidence that amongst the Jews the condition was confined to the Ashkenazi sect (Rothman, 1962). Early reports were often based on small series of cases, rarely numbering more than a dozen.

Since the original masterly description of the disease (Kaposi, 1872) there has been much confused discussion on all aspects of the tumour. Today it is recognized that Kaposi’s sarcoma is more common than was at first thought, particularly in some parts of Africa. The realization of the importance of the disease led to a symposium on Kaposi’s sarcoma held at Makerere College, Uganda, in May 1961. It is to this symposium that the current upsurge of interest and increase in research is primarily due.

Incidence
At the Harari Hospital histological laboratory, Rhodesia, Ross (1966) found 136 cases which conformed to the criteria of Kaposi’s sarcoma and which represented 3·3% of all malignant tumours seen between 1955 and 1965. Between 1961 and 1966 the author, a general surgeon, observed thirteen cases of the disease at Harari Central Hospital. Cook (1966) quotes an incidence in the Congo of 12% of all cancers and Davies & Lothe (1962) in Uganda found a figure of 3% of all cancers or 6·4% of all tumour cases in males. This is in contrast with the experience among the white races. For example, the records of the radiotherapy unit, Westminster Hospital, reveal only three cases from 1949 to 1965, during which time nearly 16,000 patients were treated for malignant disease, and Rothman (1962) reported that search of the University of Chicago cancer registry from 1946 to 1960 showed eight cases of Kaposi’s sarcoma in 13,700 malignancies.

Age
The original and subsequent ‘European’ description stressed that the patient would be in the sixth or seventh decades. However, Oettle (1962) found that the African patients were between 35 and 44 years. At Harari Hospital some difficulty has been experienced in establishing ages but none in the series was over 50 years and this seems to correspond closely with Oettle’s figures though at least one patient was 24 years of age.

In contrast, at the Westminster Hospital, the three patients were 76, 78 and 83 years old, respectively.

Sex
Males predominate in all series and Ross (1966) reported 128 males, four females and four where no sex was indicated in his 136 records.

Race
All the Harari patients were Bantu. At Westminster there were two Jews of Central European origin. The third case occurred in an Englishman born of an English father and a Welsh mother. Series from Europe and America conform to the original description of a preponderance of Central European Jews or Mediterranean peoples. Of great interest is the fact that the disease is unusual in the Jews of Israel but is becoming commoner in Germany where the Jewish population is greatly reduced (Oettle, 1962).

Clinical features
The Harari Bantu cases were typical of the original description of European patients given by Kaposi. The skin changes were not as obvious in the dark skin, and patients tended to present rather
later in the course of the disease. One hundred and twenty-eight cases in the series were males who were surprisingly young, appearing to be in their later thirties or early forties. Age is still a difficult thing to determine in the African and one has to obtain an approximation on past events in many people over 35.

The history was of nodules developing upon the limbs accompanied by some discomfort in the form of itching or pricking. Swelling and sometimes haemorrhage from the nodule after slight trauma was also noted.

The nodule of Kaposi's sarcoma in our patients occurred on the hands or feet and often further nodules were found over the forearms or lower leg. These varied in size from a few millimetres to a centimetre, but large nodules were encountered of 2–3 cm in size. Ulceration occurred in the nodules often irrespective of size, and might spread to involve other nodules.

The skin around the nodule and the skin in apparently uninvolved areas may show interesting sequential changes. It may become turgid and shiny, often resembling watered silk in the early stages and eventually the skin becomes coarse and pachydermatous. Elephantiasis may be the final result. These changes are probably due to the enormously increased lymph flow in the involved area. With the multicentric sarcomatous changes occurring in the soft tissues, and the inordinate increase in lymph flow, it would be logical to expect tissue changes from simple oedema through to a form of elephantiasis.

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Differential diagnosis

The clinical diagnosis should always be confirmed by biopsy. Kaposi's sarcoma may be confused with a simple ganglion, an angioma, neurofibromatosis, melanoma (often found on the sole of the foot in Africans), nodular leprosy, granuloma pyogenicum, lymphangiosarcoma, onchocerciasis, filarial elephantiasis, maduramyositis, syphilis, sarcoidosis of the skin and post-mastectomy lymphangiosarcoma.
Kaposi's Sarcoma

Fig. 3. A nodule in Kaposi's sarcoma in cross section. This figure demonstrates the epithelium stretched over the tumour. On each side are normal rete pegs. The tumour has not involved the epithelium but is obviously malignant on the deep aspect.

Fig. 4. High-power magnification (x 1600) of Kaposi's sarcoma. Note the strands of mature connective tissue, the vascularity and the malignant fibroblasts. (Section by kind permission of Dr C. M. D. Ross.)
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further areas of involvement appeared, all of which required repeated therapy. One has died at 83 years of age while two still attend the follow-up clinic, 2 years after being diagnosed.

Radiological features
Soft tissue films may reveal extensive changes that are not clinically obvious. Palmer (1962) has made an extensive study of the radiological changes in Kaposi's sarcoma and has shown that the nodule is merely the 'tip of the malignant iceberg'. Further, there may be bone changes associated with soft tissue involvement. There may be generalized rarefaction and the head or base of a phalanx or metacarpal or metatarsal may appear to have been 'rubbed out'.

Localized rarefaction with a loss of trabeculation of the bone or cortical erosion may occur in some, while infiltration of the bone can produce 'cysts' as opposed to rarefaction which is due to local hyperaemia.

Angiography
This is a most interesting investigation since it demonstrates the surprisingly extensive involvement of the soft tissues. The skin nodule is merely a small part of extensive tissue change. The arteries to involved tissues may demonstrate a sharp 'cut off' effect.

Spontaneous regression
Cook (1966) has suggested that spontaneous regression may be expected in perhaps 2% of patients. No patient in this series has shown complete regression.

The Westminster cases
The three elderly males treated at Westminster Hospital were typical examples of Kaposi's sarcoma. Two were Central European Jews. The lesions demonstrated slow progression with extensive tissue involvement. There was a satisfactory response to radiotherapy and chemotherapy, but

Fig. 5. Radiograph of the foot in a patient with Kaposi's sarcoma. The metatarsal heads appear to have been 'rubbed out.' There is generalized rarefaction due to gross soft tissue oedema and poor blood supply in the foot. There is increased density of the shafts of the bone together with small soft tissue nodules, rarefaction of the tarsus, metatarsal heads and phalanges. Some cortical destruction and central deposits are present. (Professor P. Palmer's case: by kind permission of Professor Palmer and S. Karger AG, Basel.)

Fig. 6. Soft tissue tumours of the foot and ankle in advanced Kaposi's sarcoma. Note the extent of the soft tissue involvement. (By kind permission of Professor P. Palmer and S. Karger AG, Basel.)
Histology

Microscopic examination shows large spindle cells with numerous mitotic figures associated with a varying proportion of new blood vessels. Strands of mature connective tissue penetrate the tumour and there is a sparse infiltration of plasma cells and histocytes in these strands. The lymphatics may show a striking dilatation, indicating increased lymphatic flow in keeping with Palmer's lymphangiographic observations. Over a typical nodule the epidermis may be stretched with flattening of the rete pegs or there may be infiltration of the dermis with direct extension of the tumour and the blood vessels may show invasion by the tumour.

The examination of multiple sections taken at widely separated sites demonstrates the multifocal origin of the tumour. The maturity and autonomy of the tumour in each section favours a multicentric origin rather than direct or metastatic involvement.

Treatment

In the treatment of Kaposi's sarcoma radiotherapy, chemotherapy or a combination of both methods has been employed. Both methods are available in Rhodesia, but in Uganda there is no radiotherapy unit and it is to the credit of clinicians there that such excellent results have been obtained by chemotherapy alone. Kaposi's sarcoma is extremely radiosensitive and radiotherapy, coupled with the long natural history of the disease, has proved to be the most effective weapon in treatment.

Where facilities for radiotherapy are available, all obviously involved areas are treated and it may be necessary subsequently to treat any other area that becomes involved later in the disease. It must be borne in mind that the apparently superficial lesion is only a small part of the disease and that superficial therapy will be inadequate.

Chemotherapy

It has been the author's practice to use nitrogen mustard to treat Kaposi's sarcoma, which corresponds to the technique used at Mulago. Eight patients were treated in this manner where there was either a very localized lesion and one had time to review the treatment and employ subsequent radiotherapy if necessary, or where the patient had very extensive disease and it was felt that a systemic drug would be preferable to very extensive radiotherapy.

The route of the nitrogen mustard administration was both arterial and intravenous. Isolated perfusion of a limb was considered but rejected on the following grounds:

(i) The disease is multicentric and cytotoxic agents must reach involved areas not as yet clinically or radiologically apparent. The danger to the haemopoietic tissue was considered to be outweighed by the gravity of the condition. Always provided that careful clinical and laboratory monitoring was carried out before, during and after cytotoxic therapy.

(ii) The rapidity with which nitrogen mustard is fixed within the tissues favours intra-arterial injection of the drug without involving a major vascular dissection.

After the initial arterial injection the drug was administered by the intravenous route in an attempt to deal with active cellular division occurring after the initial injection.

Nitrogen mustard was administered at an initial dosage of 0.4 mg/kg body weight using a percutaneous arterial puncture into the major artery of the limb. This was always carried out under anaesthesia to ensure the patient's comfort and to facilitate the procedure. The injection was made over about 10 min using a dilution of 1 mg mustine hydrochloride in 1 ml normal saline. At this dilution the average volume given was 20 ml containing 20 mg mustine hydrochloride. It is now our policy to use percutaneous arterial cannulation rather than direct arterial puncture, injecting the drug into the lumen of the artery at a distance of 5-10 cm from the puncture wound, thus avoiding the possibility of perivascular spill of the drug.

Following the initial dosage mustine hydrochloride, 10 mg twice weekly, is administered by the intravenous route in dilution of 20 ml by slow injection. Should the patient not tolerate the drug a higher dilution of 10 mg in 200 ml saline is used. All cases are given thiethylperuzine dihydrogen maleate (10 mg three times a day) or similar antiemetic prior to therapy and for the day of therapy. A full blood count including platelet count is carried out before administering mustine hydrochloride. If the haemoglobin falls below 80% (11.6 g/100 ml), the white blood count below 3000 cells/mm² or the lymphocytes below 10% of the differential count or the platelet count below 100,000/mm² treatment is suspended. The treatment is continued until clinical regression is evident, usually within 2 or 3 weeks. Our policy is to wait 2-3 months before repeating the course unless new lesions appear.

At Mulago, Cook (1966), using nitrogen mustard, reported that 82% of his series showed complete regression and 42% showed some improvement. Follow-up of Harari patients left much to be desired as most patients returned to their own districts and, despite an out-patient appointment, would not re-attend unless there was further progression of the tumour.
Theoretically the most effective therapy would appear to be radiotherapy and cytotoxic drugs. All overt lesions are treated by radiotherapy and the patient is given a course of mustine hydrochloride to treat the deep-seated and as yet unapparent areas. However, cytotoxic drugs may interfere with the response to radiotherapy. This therapy has been used in two of the author's cases with apparent initial success.

At the Harari Hospital from 1957 to 1966, forty-nine cases have been treated by radiotherapy (Greig) in the following annual distribution:

1 1 6 6 8 7 2 6 11 1

These patients were given radiotherapy for 6 weeks at a dose rate of 150 r/week on a 50-kV unit. There has been a response to therapy with the disappearance of local lesions. O'Brien & Brasfield (1966) treated the superficial lesions with low voltage radiotherapy on a 50–80-kV machine, giving a total of 500–2000 r. For deeper lesions they used 200–250-kV orthovoltage equipment. At the Westminster Hospital therapy is given on an 80-kV unit, giving 3000–3500 r over 3–4 weeks, the dosage being dependent upon the volume of the limb or anatomical site receiving therapy.

Where radiotherapy has been combined with nitrogen mustard therapy at Harari Hospital the dose of radiotherapy has been cut to 50 r on a 50-kV machine to clinically involved areas.

McWhirter (1967, personal communication) describes a case with involvement of both legs in which he treated the whole thickness of the left leg by the use of two opposed fields and gave a dosage of 1250 rad in a period of 1 week using 250 kV. This limb has remained free from recurrence for 1 year. The patient's right leg was perfused with 30 mg nitrogen mustard. A transient response was obtained and radiotherapy was used at the same dosage as in the left leg with a less dramatic result. There seems to be little doubt that the nitrogen mustard therapy has interfered with the response to radiotherapy.

Discussion

The interest in Kaposi's sarcoma was initially due to its rarity and to its apparent confinement to Mediterranean or Central European Jews. The current interest in the disease centres upon the multicentric origin, the racial differences and the fact that it is far commoner than expected. There is a high incidence in Bantu, and the Congolese have the highest incidence of the disease, while the Bantu of Kenya, Rhodesia and South Africa have a lower incidence than in the Congo. This variation is also geographical, the incidence being greatest in hot, humid climates and tending to decrease towards temperate zones. It may thus be that there is no racial variation but an environmental factor. This theory is further enhanced by the low incidence among Jews in Israel and the rising incidence among German Jews.

The diagnosis of Kaposi's sarcoma is being made with greater frequency in African territories. The disease has only recently been investigated in Africa and there are insufficient records upon which to form an opinion of the apparently rising incidence. Accurate records are now being kept and trends in incidence will become apparent in the near future.

There are at present few pointers to the aetiology. It would appear that some environmental factor is of major importance while genetic factors are far less important than at first thought. The possibility of a geographical factor is greatly diminished when it is realized that the immigrant communities of Africa are not liable to develop Kaposi's sarcoma. It occurs in the African but not to any extent in the Asian or European immigrants to Africa.

Trauma (Oettle, 1962) has been said to have no part in the aetiology of the disease nor has ultraviolet irradiation, as Kaposi's sarcoma is not seen in the albino or in association with xeroderma pigmentosum. The sites affected do not correspond with those usually involved in basal cell carcinoma or squamous cell carcinoma. Infective causes such as a virus, unless one postulates an associated hygienic factor, are not likely as the immigrant community is free of the disease. The fact that males are numerically at risk leaves the avenue of hormonal factors open to investigation.

It is certain that the lymphoedema associated with Kaposi's sarcoma occurs as part of the disease and there is no question of its being a sarcomatous change occurring in previously lymphangiomatosus tissue similar to the lymphangiosarcoma of the post-mastectomy case.

O'Brien & Brasfield (1966) have reviewed a series of sixty-three patients with Kaposi's sarcoma in which eighteen died of a second primary neoplasm. Included were five cases of Hodgkin's disease, three lymphosarcoma, three carcinoma of the colon and one each of multiple myeloma, malignant melanoma, carcinoma of the prostate, carcinoma of the tongue, carcinoma of the tonsil, carcinoma of the pancreas and carcinoma of the breast. These authors state that the mortality from these second primary neoplasms was higher than that of the Kaposi sarcoma. No second primary neoplasms have been reported in the Rhodesian cases and the author had not encountered any case with a second primary neoplasm among his patients.
Kaposi's sarcoma

The presence of angiomatous vessels has led to the belief that the disease is a form of angiosarcoma (Roulet, 1962; Dupont, 1951), but the work of Cook and his associates had centred attention upon the spindle cell component. Cook (1962) considers the spindle cell to be the prime element and, by a process of exclusion, suggests that this cell originates in the connective tissue rather than the vascular endothelium, smooth muscle or neural sheath. In his tissue cultures the spindle cell behaved as a fibroblast, and it could produce reticulin and collagen but did not differentiate into any distinctive cells such as the Schwann cell. The current view is therefore that the spindle cell of Kaposi's sarcoma is a malignant fibroblast arising with new vessels from a primitive mesenchymal cell which may be located in the loose adventitial cost of small blood vessels. Histiocytes which are very commonly associated with the tumour may be part of the stromal reaction of the tumour or have arisen from the original mesenchymal cell.

Interest in this tumour is increasing in view of the success of various forms of therapy and because of its potential in the field of research. Links must be sought in racial, environmental and geographical influence on this tumour.

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Summary

Kaposi's sarcoma is a well-documented tumour. It was thought to be rare and confined to Middle European Jews and Mediterraneans. It has, however, been found to be surprisingly common in certain parts of Africa.

Attention is drawn to the early changes in the skin of the African, manifest as a shiny watered silk appearance, which will progress to elephantiasis. The nodule is typical but is seen later in the African. Radiology is of interest in the detection of soft tissue and typical bony change.

Recent research into the origin of the tumour suggests that the malignant fibroblast originates in the adventitia of small blood vessels and that the tumour is a fibrosarcoma rather than a haemangiosarcoma.

The current view on therapy is that radiotherapy is curative but may have to be used at multiple sites. Chemotherapy has been successfully employed where radiotherapy has not been available and in Salisbury, Rhodesia, chemotherapy has proved to be of value.

References


