# Lymphoproliferative disorders in non-AIDS-associated Kaposi's sarcoma

## The Johannesburg Hospital experience, 1980 - 1992

**M. E. Stein, D. Spencer, R. Dansey, Y. Perner, K. Gunther, W. R. Bezwoda**

**The association of the non-AIDS-related, classic form of Kaposi's sarcoma (KS) with secondary malignancies, especially lymphoproliferative disorders, has frequently been noted. However, in endemic African-type KS, such an association has been reported only rarely. A review of 62 non-AIDS-related cases of KS treated and followed up at Johannesburg General Hospital between 1980 and 1992 revealed 8 patients (13%) in whom KS was associated with malignant lymphoproliferative disorders. The prevalence of secondary lymphoproliferative disorders was not significantly different among patients with classic KS (3/15; 20%) when compared with those who had African KS (4/47; 8%). In both forms of KS subtle disturbances of immunity have been described which may play a role in the pathogenesis of secondary lymphoproliferative disorders, although the factors responsible and the pathogenetic mechanisms involved in malignant lymphoid transformation in these patients have not been fully elucidated.**

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Non-AIDS-associated Kaposi's sarcoma (KS) is a rare vascular tumour, affecting mainly the skin but also involving regional lymph nodes and internal organs. The disease has a high incidence among Jews of eastern European descent[1] and is the most common neoplastic disease in the sub-Saharan black population.[2]

**Department of Medical Oncology and Haematology, Johannesburg Hospital**

**M. E. Stein**, M.D.

**D. Spencer**, F.C.P. (S.A.)

**R. Dansey**, F.C.P. (S.A.)

**W. R. Bezwoda**, PH.D.

**Department of Pathology, South African Institute for Medical Research, Johannesburg**

**Y. Perner**, F.C.PATH. (S.A.)

**Department of Laboratory Haematology, University of the Witwatersrand, Johannesburg**

**K. Gunther**, F.C.PATH. (S.A.)

An association between the classic type of KS and lymphoproliferative disorders has been reported with a frequency ranging between 17% and 60%.[3] The lymphoproliferative disorders are mostly of B-cell origin and include non-Hodgkin's lymphoma, chronic lymphatic leukaemia and multiple myeloma.[4,5] An association with lymphoid disorders of undefined status, but which may be premalignant, such as Castleman's disease (angiofollicular lymph node hyperplasia) and angio-immunoblastic lymphadenopathy, has also been described.[6,7] Impaired immune function appears to be the underlying factor predisposing to either KS, lymphoproliferative disorders or both.[8]

While classic KS is frequently associated with lymphoproliferative disorders, only a few instances of an association between the endemic, African-type of KS and other malignancies have been reported.[9-11] The scarcity of reported cases may be due to short follow-up of non-compliant patients, lack of appropriate medical facilities in many underdeveloped countries and shorter survival due to accompanying infectious events.[11,12]

In this retrospective analysis, 8 patients with non-AIDS-associated KS and lymphoproliferative disorders are reported. The current literature is reviewed.

## Patients and methods

The records of all patients with non-AIDS-related KS (negative HIV enzyme-linked immunosorbent assay (ELISA), no history of opportunistic infection), treated at Johannesburg General Hospital from 1980 to 1992, were reviewed. All patients underwent physical examination, haematological and biochemical studies and chest radiography. Where clinically appropriate, gastro-intestinal radiography or endoscopy, abdominal sonography or computed tomography was performed. Tumour stage was established according to the Mitsuyasu classification system.[13] Patients were treated with various radio- and chemotherapeutic regimens.

## Results

### *Classic KS*

There were 15 patients with the classic form of KS. Ten (67%) were male and 5 (33%) were female. The age at diagnosis of KS ranged from 26 to 81 years with a mean age of 70 years. The majority (71%) of the patients were Jews of eastern European descent. One patient was Italian born and the rest were white South Africans.

Six patients (40%) had stage I disease (KS limited to one anatomical region), 6 patients stage II disease (multiple skin lesions) and 3 patients (20%) presented with stage IV disease (disseminated skin lesions, lymphadenopathy and/or involvement of the gastro-intestinal tract).

#### Associated lymphoproliferative disorders (Table I)

Three patients had a diagnosis of lymphoproliferative disorders preceding the diagnosis of KS. One patient had a 6-year history of Waldenström's macroglobulinaemia before presenting with KS of the lower limbs. This patient had

asymptomatic biclonal IGM (kappa) paraproteinaemia, low IgA titre, Bence Jones proteinuria and mild renal dysfunction. One patient developed KS 3 years after the diagnosis of stage IVB Hodgkin's disease. This patient had been treated with various chemotherapeutic regimens for the lymphoma. Complete remission was never achieved and he died of progressive Hodgkin's disease 3 years after diagnosis with minimal evidence of KS. The third patient developed KS of the right thigh 2 years after the diagnosis of a follicular low-grade stage IV non-Hodgkin's lymphoma. This patient was not treated initially either for the lymphoma or the KS but 3 years later, following progression of the lymphoma, she received chlorambucil and prednisone and achieved near-complete remission both of the KS and the malignant lymphoma.

One patient developed Castleman's disease 54 months after the diagnosis of KS. The Castleman's disease involved the mediastinal lymph nodes, adjacent pericardium and pleura and the patient died of complications related to this involvement with stable KS confined to the skin.

## *Endemic, African KS*

Forty-seven HIV-1-negative black men domiciled in the southern African region, including South Africa, Mozambique, Botswana, Namibia and Malawi were included in this study. Their mean age was 53 years (range 24 - 82 years). Thirty-seven patients (80%) presented with disease limited to skin only and 10 patients (20%) with extensive disease involving the skin and gastro-intestinal tract as well as lymphadenopathy and/or pulmonary involvement.

### Associated lymphoproliferative disorders (Table II)

Three patients had a non-Hodgkin's lymphoma (1 high-grade, peripheral T-cell lymphoma; 1 low-grade follicular non-Hodgkin's lymphoma; 1 large-cell immunoblastic lymphoma) as well as KS. All the lymphomas were diagnosed at the same time as the KS. The lymphoma was limited to the peripheral lymph nodes in each case and responded significantly, though incompletely, to chemotherapy. All three patients died of progressive KS. A fourth patient presented with advanced KS, involving the

**Table I. Association of classic KS with lymphoproliferative disorders**

| Patient no. | Age/sex | Stage of KS | Treatment of KS | Lympho-proliferative disorder | Stage | Treatment of lymphoproliferative disorder | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 76/F | II | Interferon | Waldenström's macroglo-bulinaemia | | Nil | Died of heart failure; unrelated to KS |
| 2 | 65/M | I | Radiation therapy | Hodgkin's disease | IVB | MOPP; bleomycin, vinblastine; radiation therapy | Died of advanced Hodgkin's disease; minimal KS |
| 3 | 70/F | I | Radiation therapy | Low-grade lymphoma | IV | Chlorambucil and steroids | Near-complete remission; death unrelated to KS |
| 4 | 69/M | I | Radiation therapy | Castleman's disease | Lymph-adenopathy | Corticosteroids | Died of complications of Castleman's disease |

MOPP = mustine (nitrogen mustard), oncovin (vincristine), procarbazine, prednisolone.

**Table II. Association of endemic, African KS with lymphoproliferative disorders**

| Patient no. | Age | Stage/ localisa-tion of KS | Treatment of KS | Lympho-proliferative disorder | Stage | Treatment of lymphoprolifera-tive disorder | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 60 | I; lower limbs | Radiation therapy; local field; 2 400 cGy | Low-grade lymphoma (well differentiated lymphocytic lymphoma) | Peripheral lymphadenopathy (stage I or stage II disease) | COPP | Lymphoma responded; died of progressive KS |
| 2 | 78 | I; right leg | Radiation therapy; local fields; 2 400 cGy | High-grade, peripheral T-cell lymphoma | III peripheral mediastinal para-aortic lymphadenopathy | COPP | Regression of lymphoma; died of progressive KS |
| 3 | 34 | IV; disseminated skin lesions; lymphadeno-pathy | Vinblastine, etoposide; radiotherapy | Immunoblastic lymphoma | Lymphadenopathy (stage II or III disease) | CHOP | Incomplete response of lymphoma; died of progressive KS |
| 4 | 23 | IV; disseminated skin and peripheral lymph node involvement | | Diffuse large cell lymphoma | IV (bone marrow involved) (?liver/ ?spleen) | Cytosar + interferon; CHOP | Partial response; died following massive relapse and neutropenic sepsis |

All patients were male. COPP = cyclophosphamide, oncovin, prednisone, procarbazine.

skin and peripheral lymph nodes (Figs 1 and 2) as well as hepatosplenomegaly, ascites and pleural effusion. Immune function tests showed an absolute T-cell lymphopenia with a low T4/T8 ratio (0,78:1). Bone marrow trephine biopsy revealed infiltration by B-cell lymphoma (Figs 3 and 4). After chemotherapy consisting of cytosar and interferon-alpha, a partial reduction in tumour bulk was achieved together with marked symptomatic improvement. This patient was continuing with the CHOP regimen (cyclophosphamide, epidoxorubicin, oncovin, prednisone) with a very good initial response. The patient, however, relapsed and died about 3 months after the start of CHOP therapy, with a rapidly enlarging liver, pancytopenia and extensive bone marrow involvement. Permission for autopsy was refused.

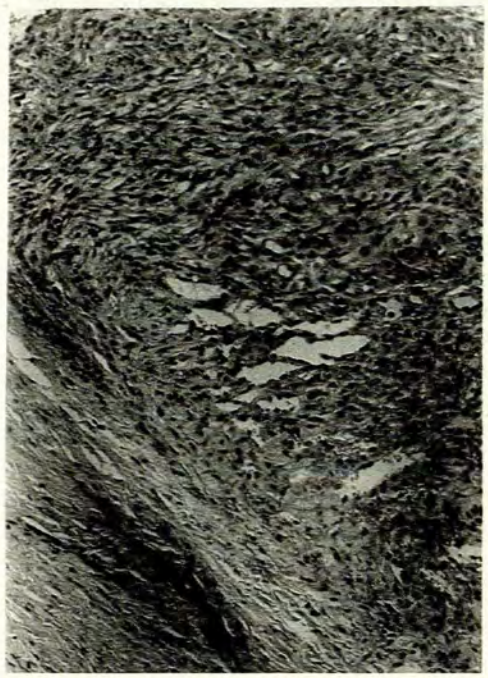

**Fig. 1. Lymph node, including capsule, showing effacement of normal nodal architecture as a result of KS (low power magnification; H & E).**

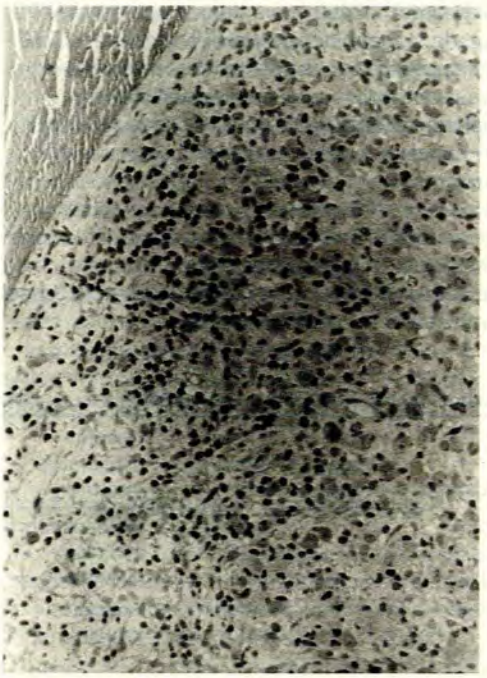

**Fig. 3. Bony trabeculum with adjacent marrow cavity showing diffuse, marked hypercellularity caused by involvement of non-Hodgkin's lymphoma (low power magnification; H & E).**

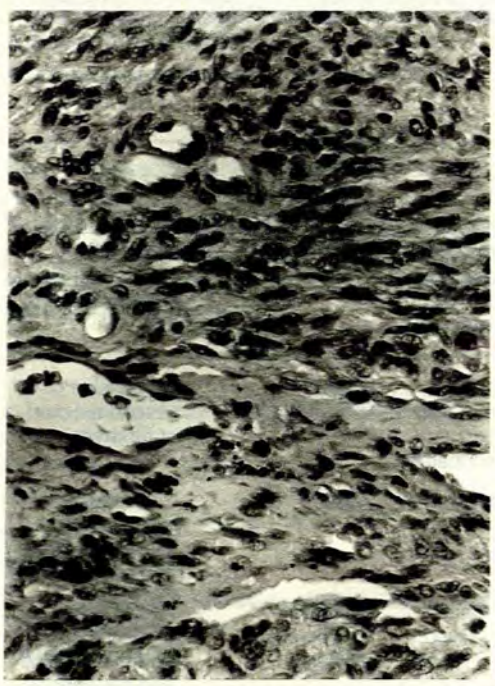

**Fig. 2. KS with numerous slit-like spaces. Nuclear pleomorphism and increased mitotic activity are readily discernible (10 x 40; H & E).**

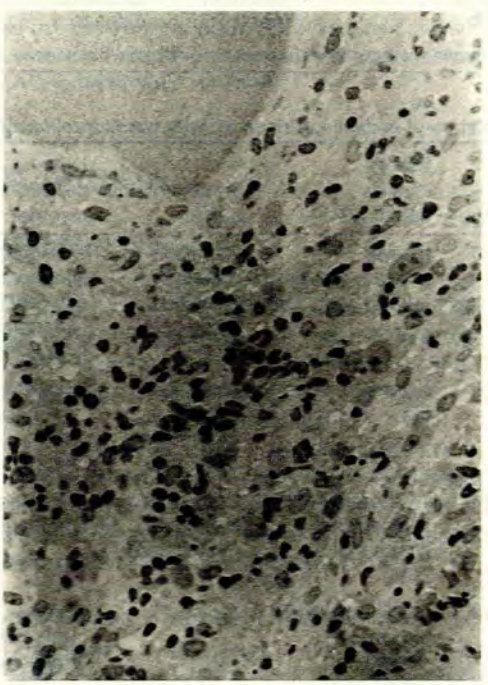

**Fig. 4. Polymorphous infiltration of lymphoma cells of B-lineage within the marrow cavity. Large binucleate cell identified in centre of the field (10 x 40; H & E).**

## Discussion

A close association between classic KS and secondary malignancies was appreciated as early as 1954.[11,14] In 1966 Moertel[15] reported KS appearing as a second primary cancer in 51 of 565 patients with lymphoreticular tumours — an incidence of 9%. Other authors[16-19] found an association between KS and lymphoma ranging between 6% and 14%. Safai *et al.*,[10] reviewing the Memorial Sloan Kettering Cancer Center experience (1949 - 1975), found 92 patients with classic KS, of whom 34 (37%) developed a second primary malignancy. In these patients, the second malignancy involved the lymphoreticular system in 58%. By contrast, only 8% of *all* patients with primary malignancies other than KS developed lymphoid tumours as second malignancies. In the light of tumour registry data from Connecticut and New York,[3] the age- and sex-adjusted rates for lymphoproliferative malignancies in KS patients was found to be 20-fold greater than in the general population. In a recent review, Friedman-Kien and co-workers[20] found that about one-third of patients with KS have a history of, or later develop, malignancies of reticulo-endothelial origin, including B-cell lymphoma, chronic lymphatic leukaemia, multiple myeloma and thymoma.

Little is known about the pathogenesis of lymphoproliferative disorders in non-AIDS-related KS. Moertel and Hagendrom[21] even proposed a common progenitor cell for KS and lymphoma. Recent studies of the pathogenesis of KS make this unlikely.[13,22,23] More probable is impaired immune surveillance and T-cell regulatory dysfunction in patients with KS leading to unopposed proliferation of abnormal B-cells.[1,4,22] The aggressive course of KS in immune-suppressed patients as well as the more widespread and rapidly progressive form of epidemic, AIDS-related KS, also suggest a significant role for impaired immunity in the aetiology and pathogenesis of KS.[20,23]

In addition, the prolonged use of chemotherapy, particularly alkylating agents and immunosuppressive drugs, has also been associated with an increased frequency and more aggressive course of KS. Examples include the development of KS in patients who have undergone organ transplants, patients with auto-immune diseases and patients with thymoma. Total cumulative dose and length of exposure appear to be important in determining the frequency of malignancy in such patients.[11,24] In the present study only 1 patient with classic KS had received any chemotherapy prior to diagnosis. The other 2 patients with lymphoma had received no chemotherapy before the diagnosis. Prolonged use of chemotherapy was thus unlikely to be a major factor in our patients.

Of special interest with regard to the lymphoproliferative disorders associated with KS is the patient who developed Castleman's disease (angiofollicular lymph node hyperplasia) 54 months after the diagnosis of KS. Castleman's disease is characterised histologically by prominent vascular proliferation, resembling that of KS. Chronic antigenic stimulation is thought to result in lymphoreticular and endothelial cell proliferation which in turn lead to T-cell regulatory dysfunction and excessive proliferation of B-cells.[6,25]

Castleman's disease resembles classic KS in respect of immune function disturbances. Low natural killer cell activity, cutaneous anergy, low suppressor T-cell activity and increased levels of the lymphokine, IL-6,[6,22,26] have been found in both conditions. Both KS and Castleman's disease respond to radio- and chemotherapy and in both diseases treatment results in partial restoration of immune responses following regression of disease.[27,28] However, while the similarities between the two diseases are striking, less than 20 cases of Castleman's disease in association with KS have been reported so far.[6,25-30] The majority of the cases were related to the multicentric angiofollicular lymph node hyperplasia (plasma cell type) group which is a more aggressive variant of Castleman's disease.[6,29,30] This type of Castleman's disease is associated with severe impairment of immune regulation and transition to lymphoproliferative disorders or KS has been described.[31-33]

With regard to the association of the African endemic form of KS and second malignancy, early reports seemed to suggest that African KS might also be associated with increased risk of lymphoproliferative disorders.[9-12] In 1962 Murray and Lothe[34] described Hodgkin's disease in association with KS. Uys and Bennet,[35] McKinney[36] and Kungu and Gatei[37] described sporadic cases of KS with associated lymphoproliferative disorders. However, in a series of 117 cases of KS in Tanzania, only 1 patient had Hodgkin's disease while in another series only 2 of 339 patients with African KS had lymphoma.[9,11]

Endemic African KS has generally not been considered to be associated with severe immune deficiency.[38] Recent reports have, however, demonstrated alteration in cell-mediated immunity and lymphocyte function in the endemic variant of KS.[2,39] In Africa, the co-existence of malnutrition and chronic infections such as malaria, chronic helminthic infestations and hepatitis may also result in impaired cellular immunity.[23] The emergence of a very aggressive form of African KS[38] and the occurrence of KS in childhood[8,13] with its fulminant course, suggest that immune suppression may also play a role in this variant of KS.[40,41] It is possible that the younger age of patients with African KS, as well as the shorter survival of such patients compared with those with classic KS, might be responsible for the lower frequency of lymphoproliferative disorders in African KS.[11] Additional reasons may be underreporting due to limited medical facilities and lack of follow-up of such patients in the African context.[2,38] However, in the current series 4 of 47 patients (8%) with African KS had associated lymphoproliferative disorders, a prevalence not significantly different from that seen among patients with classic KS (3/15, 20%). While these figures are lower than those described by Safai and co-workers,[10] they appear to be more in keeping with the prevalence found by other investigators.

While both forms of KS thus appear to be associated with lymphoproliferative disorders, it is necessary to ascertain which influences which, since there is no consistency regarding which illness occurs first. The association with lymphoma may be due to a common pathogenetic mechanism rather than a directly causal relationship. KS and Burkitt's lymphoma have the same geographical distribution and may be related to Epstein-Barr virus infection, which is endemic in Africa.[10] Other antigenic stimuli may also result in chronic proliferative stimuli both to lymphoid and vascular endothelial cells which, in the presence of immune dysfunction, result in malignant transformation. This possibility is suggested by the occurrence of as yet ill-defined entities, such as Castleman's disease which appears to share a number of features with both KS and lymphoproliferative

disorders and which has on occasion been associated with the progressive development of one or other malignancy. Further investigation of patients may well show the occurrence of common pathogenetic mechanisms.


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# The value of abrasive cytology in the early detection of oesophageal carcinoma

## A pilot survey in Ciskei


**C. Lazarus, K. Jaskiewicz, H. A. Southall, R. A. Sumeruk, J. Nainkin**



**The use of abrasive cytology as a screening procedure in the diagnosis of early cancer of the oesophagus among asymptomatic rural Ciskeians was assessed. An inexpensive, locally manufactured brush biopsy capsule was used to obtain cytological material from 1 336 subjects. The technique gives a high yield, has a high predictive value and identifies a high prevalence of sufferers at the detectable preclinical phase of the disease.**



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Squamous cancer of the oesophagus is the commonest cancer among black men in southern Africa. Only cancer of the cervix among black women is more prevalent.[1] It was especially common among rural Transkeians,[2] but is now also found increasingly in urban populations of the region.[2-6]

As a rule, patients with oesophageal cancer present at an advanced stage of relentless progression. While patients' symptoms are usually of recent origin, their period of survival is short.[7,8] This cancer therefore seems to fulfil many of the criteria necessary for it to be suitable for screening. These include: *(i)* a high prevalence in a susceptible population; *(ii)* its recognition as a serious disease in the community; *(iii)* effectiveness of cancer therapy, either by means of surgery or radiotherapy; and *(iv)* a well-documented, prolonged 'detectable pre-clinical phase' (DPCP) when effective therapy could lead to a cure.[9]

Abrasive brush cytology as a screening technique for oesophageal cancer has been used for many years in high-incidence areas of China. Early diagnosis and many long-term survivors have been reported.[10,11] In southern Africa,


**Departments of Surgery, Gastro-enterology and Pathology, Cecilia Makiwane Hospital, Mdantsane, Ciskei**

**C. Lazarus**, M.D., F.R.C.S.

**R. A. Sumeruk**, M.D.

**J. Nainkin**, M.D., M.R.C.P. (LOND.)

**Department of Pathology, Groote Schuur Hospital and University of Cape Town**

**K. Jaskiewicz**, M.D., M.MED., PH.D., M.R.C. PATH. (LOND.)

**Institute of Social and Economic Research, Rhodes University, Grahamstown, CP**

**H. A. Southall**, PH.D.