

Leading Article**African Kaposi's sarcoma**

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Much has been written in recent times on the condition first described by Moritz Kaposi as 'idiopathic multiple pigmented sarcoma of the skin'. This surge of interest stems from its remarkable association with the acquired immunodeficiency syndrome (AIDS). In Africa, human immunodeficiency virus (HIV) infections have resulted in the emergence of a second clinical pattern of the disease.

The classical endemic Kaposi's sarcoma (KS), seen in parts of tropical Africa, was initially recognized during the early part of this century and accounts for up to 9% of all recorded malignancies in parts of eastern Zaire. As one moves away from this epicentre, the frequencies decrease. However, even in these endemic regions, variation in the disease pattern is observed over short distances. Clustering of cases has been observed. In the West Nile/Madi districts, KS accounts for 18.2% of all registered tumours, whereas the other districts record frequencies of between 3-7% (HUTT & BURKITT, 1965). Endemic African KS is also characterized by its occurrence in 2 age peaks: in early childhood between the ages of 2 and 3 years and in the adult population in which the numbers increase gradually after the age of 25 years. The sex ratio in the young is almost one, whereas in adults there is a high male preponderance. The childhood disease tends to involve mainly the lymph nodes and pursues a more rapidly fatal course (SLAVIN *et al.*, 1970). The disease in the adult population may be more indolent with cutaneous nodules or plaques on the extremities, though a more aggressive pattern with florid, infiltrative or lymphadenopathic lesions has been described. Most of the endemic disease patients have low income occupations. The disease appears to have a multicentric origin and lesions are often seen in clusters over the hands and feet. The lesions may coalesce and result in a non-pitting oedematous limb or may even spontaneously disappear. The clustering of lesions on the limbs and the geographical distribution of cases raises the possibility that there is some environmental agent inducing the disease. The amelioration in severity of disease with age suggests that some degree of immunity to a possible infective process can be developed, and this may also explain the spontaneous resolution of lesions in some patients. A question that remains unanswered is why is there a male preponderance in endemic African KS?

The second group of atypical African Kaposi's sarcoma (AAKS) patients was described in Zambia by BAYLEY *et al.* (1985). This group consists of younger patients with atypical lesions such as generalized symmetrical lymphadenopathy, oropharyngeal and gastrointestinal tract lesions, respiratory distress and gross weight loss. Skin lesions were seen in unusual sites such as the face, trunk and genitalia. This group of KS patients had a slightly higher number of female patients and was also characterized by a relatively

poor response to conventional chemotherapy and early deaths. Subsequently, 91% (20/22) of Zambian and 100% (4/4) of Ugandan AAKS patients, and 24% (4/17) of Zambian and 8% (1/13) of Ugandan patients with the classic endemic disease were found to be HIV positive (BAYLEY *et al.*, 1985). Several other reports followed later, describing a change in the epidemiology of KS in other parts of Africa. There was a definite increase in total numbers as well as an increase in the number of female patients (COKER & WOOD, 1986). It appears therefore that the association of AIDS and KS in most, though not all, patients has resulted in the increased expression of a more severe form of disease.

To understand the peculiar geographical distribution and the nature of KS, studies have been carried out to identify a genetic basis for the disease, and to isolate a possible infective agent. MELBYE *et al.* (1987) studied immunogenetic markers in 23 histologically proven Zairean KS patients, and compared them with unrelated sex- and tribe-matched controls. They found no definite association between any of the HLA antigens, including DR5 and DR3, with KS. Further comparison with results from a cohort of Nigerian subjects also did not reveal any significant association. All attempts to isolate or detect any virus or its antigens using serological and *in situ* hybridization techniques have not revealed any definite association between KS and any of the common human viral pathogens. DELLI BOVI *et al.* (1986) investigated tissues from 13 KS patients for the presence of DNA sequences from hepatitis B virus (HBV), human cytomegalovirus (CMV) and the AIDS-related virus. They did not find any evidence of either the AIDS virus or HBV, but found CMV-DNA sequences in 2 of 13 specimens. The levels of positivity of CMV-DNA were said to reflect the presence of CMV in the cells and not as specific transforming genes. The findings by AMBINDER *et al.* (1987) of a total lack of CMV-DNA in biopsy specimens from 19 Zairean patients militates against any direct causative role of CMV in KS.

Immunosuppression has been postulated as a potential cofactor in the development of KS. Whilst some degree of immunosuppression is observed in AIDS-associated KS, it is not so evident in the endemic disease. The study by KESTENS *et al.* (1985) in 27 Zairean patients with KS and 41 age-, sex- and tribe-matched controls indicated no significant difference in the immune status of patients and controls, irrespective of the extent of disease. The authors did, however, note that, in comparison to healthy Belgian controls, the African patients and controls had slightly increased suppressor T-cells resulting in a lower T4/T8 ratio. The most conclusive evidence in favour of the role of depressed immunity in the pathogenesis of KS comes from the finding that KS

accounts for 3.7% of all *de-novo* malignancies developing amongst patients receiving immunosuppressive therapy for organ transplant procedures. The KS in some of these patients improves or regresses totally on withdrawal, or reduction in the administration, of immunosuppressive therapy (BHOOPCHAND *et al.*, 1986).

The histology of KS lesions has been well described by ACKERMAN (1988) as a chronological sequence of three clinico-pathological stages. The early macule/patch lesions consist of dilated thin-walled vascular spaces with jagged outlines in the dermis and involved viscera. These lesions may be sparsely infiltrated with lymphocytes and plasma cells. The endothelial cells do not show any mitoses. The plaque/patch stage exhibits both features of the early patch stages as well as spindle cell proliferation. The last, nodular stage is the variety most commonly seen in endemic African KS and consists of the classical picture of well circumscribed collections of spindle cells with slits containing a few red cells. These cells may show some mitoses. It is generally accepted that the histology of AIDS and non-AIDS related KS is essentially the same (LUCAS *et al.*, 1988). A difference between endemic and AIDS-related disease is that the latter consists predominantly of maculo-papular lesions, possibly because the more obvious clinical presentation of widespread lesions and oedema results in an early biopsy.

The general consensus is that the KS cell is of endothelial origin; whether vascular or lymphatic remains a matter of dispute. DICTOR (1986) suggested that KS arises from aberrant lymphaticovenous connections and this may explain the oedema that is associated with these lesions and the discordant immunocytochemical studies.

There are limited data available on the cytogenetics of KS cells. SAIKEYCH *et al.* (1988) report the presence of some random abnormalities in the chromosomal arrangements, particularly of chromosome numbers 7, 10 & 12. The most frequent karyotype is 46XY. This karyotypic picture does not suggest that KS is a true sarcoma, but this remains inconclusive until verified by greater numbers of such studies.

More recent molecular biological investigations have revealed the mechanism by which KS lesions proliferate. By transfecting high molecular weight DNA from KS cells into murine NIH 3T3 cells, DELLI BOVI & BASILICO (1987) were able to identify and clone a set of human DNA sequences capable of inducing tumorigenicity in experimental animals. Subsequently it was shown that the mRNA transcribed from the KS oncogene encodes a growth factor homologous to both acidic and basic bovine fibroblast growth factors. Of great interest is the finding by NAKAMURA *et al.* (1988) that cells from AIDS-KS lesions could be maintained in long-term culture in the presence of CD4+ T-cells infected with HTLV-I/II or HIV-1/2. These findings highlight 2 important facts. The first is the indirect role of HIV and possibly of other infections in stimulating growth of KS cells. The second is that KS cells have the capacity to produce self-stimulating growth factors and thereby achieve autonomy characteristic of tumour cells. The critical unanswered question is what triggers growth factor expression and whether this event reflects a multicentric vascular/lymphatic reactive phenomenon

(BROOKS, 1986) to a possible infective process, or whether it is a true neoplastic process. The lack of true metastases in KS points strongly against its being a true sarcoma.

Any hypotheses on the aetiopathogenesis of KS must account for all the different clinical and epidemiological presentations of the condition. It appears that an infective aetiology of KS could most probably explain the variations in presentation of KS. The consistent chronological progression of lesions through stages of macules, papules, and nodules, and the chronic inflammation in the early stage lesions, support such a hypothesis. An infective aetiology would also explain the clustering of cases in certain areas, as well as the symmetrical distribution and clustering of lesions. In the presence of immunodeficiency, any such infection becomes systemic, hence the more aggressive spread and poor resolution in AIDS. The improvement in KS observed on withdrawal of immunosuppressive therapy in organ transplant recipients is consistent with the hypothesis of an infective aetiology of KS. The role of immunodeficiency is evidently vital, but we have not yet defined the exact immune feature in which a defect would predispose to the genesis of KS, especially in endemic KS patients who do not appear to be clinically immunocompromised. Perhaps the transient immunodeficiency associated with diseases such as measles and malaria facilitates infection with the KS agent.

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tant, as may variations in disease patterns. There is no clear evidence of reversals in mortality rate decline in the data examined by Dr Blacker, though he stresses that the quality of the data may not be good enough to demonstrate small changes even if they existed.

In the second paper, Professor Carlos Monteiro presented evidence from several studies in São Paulo, Brazil, to show a strong association between declines in infant mortality rates and improvements in basic sanitation and health services. Data from child health surveys revealed that this reduction in mortality was achieved despite any measurable improvement in the socio-economic conditions or nutritional status of children in the city.

The first of 3 papers on strategies for improving infant and child health reviewed the potential success of targeted preventive interventions and reductions in infant and child mortality rates. Ms Hermione Lovel presented detailed information on the progress and shortfalls for each intervention considered: female education, fertility, food supplementation, growth monitoring, immunization, oral rehydration, and breast feeding.

In a case study from Nepal, Dr Tony Costello examined the possibilities and limitations for improving infant health through strengthening primary health care systems. He concluded that, with relatively little investment, district-level health systems can be supported to provide better antenatal, perinatal and infant health care. This permits long-term improvements in primary health care and sustainable reduction in infant mortality rates.

In the last of these papers, Dr Lerberghe emphasized that reduction in mortality rates should not be used as the main criterion for assessing whether child health care at district level is appropriate, effective and acceptable. He found that in Zaire people were happy to support some of the running costs of a health system which met their demands and needs.

Four papers were concerned with policies for improving infant health under conditions of economic hardship. In the first, Dr Issaka-Tinorghah described

the way in which structural adjustment and the economic recovery programme affected the vulnerable groups in Ghana. He proposed ways in which government policies and actions must attack deprivation and protect child health from the effects of economic recession. In the second paper, Dr Frances Stewart presented an analysis of the effect of economic recession and adjustment policies on child health, drawing on data from the UNICEF 10 country study. She described the elements necessary to achieve adjustment with a human face, adjustment which protects the vulnerable and promotes growth.

Dr David Sanders continued this theme with a presentation on economic adjustment and child survival in Zimbabwe, where reductions in infant and child mortality were maintained through reorganization of health care provision: this did not, however, reduce malnutrition levels associated with recession and drought.

The symposium concluded with a presentation by Professor Kenneth Newell on the implications and determinants of infant mortality. With the advent of specific technologies capable of reducing infant mortality rates in the absence of social or economic change, he questioned the validity of infant mortality rates as an indicator of change in social development. He emphasized that the primary factors influencing infant death also have significant effects on survivors. Health workers need to ensure that strategies for improving child health permit the optimal development of survivors as well as the prevention of death.

Seven of the papers presented are published in this report. We also include a résumé of the paper by Dr David Sanders.

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