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<td>Author(s)</td>
<td>Millard, Peter R.</td>
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<tr>
<td>Citation</td>
<td>熱帯医学 38(8). p135-140, 1986</td>
</tr>
<tr>
<td>Issue Date</td>
<td>1986-08-31</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/4465">http://hdl.handle.net/10069/4465</a></td>
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Kaposi’s Sarcoma in Europe: Review and Pathology

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Kaposi’s sarcoma has been described as an opportunistic tumour. Kaposi’s life also reflected a similar facility for self preservation particularly with his marriage to the daughter of Ferdinand Hebra, the founder of Vienna’s foremost Dermatology Clinic, a clinic of which Kaposi was later to become the Head. Nevertheless, Moriz Kaposi made major contributions to venereology and dermatology and his descriptions of the sarcoma still apply (Kaposi, 1872). Although Kaposi’s first patients were examples of the focal benign form of the sarcoma, he was later to report progressive systemic involvement. Either type has remained rare in Europe and of the two the disseminated pattern is the least common (Hutt, 1984). This is in contrast to Kaposi’s sarcoma in central Africa where the tumour is endemic and invariably disseminated although with some examples spreading only amongst lymph nodes (Hutt, 1984). There is a striking preponderance amongst men and overall the commonest cutaneous site is the dependent parts of the limbs. Severe oedema is a common concomitant. Microscopically there are proliferating spindle cells separated by vascular spaces often enclosing red cells (Templeton, 1981). Macroscopically haemorrhagic lesions are the key to recognition. Distinguishing the tumour from either inflammatory reactions or vascular neoplasms can at times be extremely difficult but cytoplasmic eosinophilic inclusions within some tumour cells are a unique feature (O’Connell, 1977). The origin of these inclusions is unclear but the current hypothesis is that they are the residue of phagocytosed red cells.

A further variant of Kaposi’s sarcoma emerged following the introduction of organ transplantation for the treatment of end stage renal disease. The tumour was seen 400-500 times more commonly amongst graft recipients than expected (Penn, 1983) (Table 1) and differed in age and sex distribution, the latter both reflecting the allograft population rather than any property of the tumour. Although the localised and the disseminated form occurred there was often an overlap between the two with a mixed pattern predominating. This phenomenon is repeated amongst AIDS sufferers where the tumour has an even higher incidence (Fauci, 1984) (Table 1).

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<thead>
<tr>
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<th>KAPOSI SARCOMA</th>
<th>B-LYMPHOMA</th>
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<tbody>
<tr>
<td>General population</td>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>Central Africa</td>
<td>9.0</td>
<td>50</td>
</tr>
<tr>
<td>1° Immunodeficiency</td>
<td>0</td>
<td>10-35</td>
</tr>
<tr>
<td>Allograft recipients</td>
<td>4.9</td>
<td>33</td>
</tr>
<tr>
<td>AIDS patients</td>
<td>27</td>
<td>3-4</td>
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TABLE 1 TUMOURS (%) and IMMUNE DEFICIENCY

Kaposi’s sarcoma is an integral part of the definition of AIDS and its
distribution amongst these patients in Europe mimics that in the United States (CDC, 1985; CDC, 1986) (Table 2). Thus in Europe isolated Kaposi's sarcoma provides the second form of presentation and patients with Kaposi's sarcoma alone have a longer life expectancy than those with infection, accompanied or unaccompanied by tumour. In either environment it is often unclear exactly how the tumour contributes to death.

<table>
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<tr>
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<th>PATIENTS(%)</th>
<th>DEATHS(%)</th>
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<tr>
<td>Opportunistic infection</td>
<td>64.1</td>
<td>53.7</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>20.0</td>
<td>24.4</td>
</tr>
<tr>
<td>Infection and sarcoma</td>
<td>15.2</td>
<td>65.0</td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
<td>83.3</td>
</tr>
<tr>
<td>Total number</td>
<td>940</td>
<td>468</td>
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**TABLE 2 AIDS IN EUROPE:17 COUNTRIES (CDC, 1985)**

**THE ROLE OF IMMUNODEFICIENCY**

A link between Kaposi's sarcoma in transplant recipients and in those with AIDS is immunodeficiency. This is predominantly a cellular defect with an emphasis on a reduction of the T-helper cells. Lasting regression of the tumour has resulted amongst transplant recipients when immunocompetence is restored (Penn, 1983) but since a similar manipulation is not possible in AIDS, equivalent regression has yet to be recorded. Depressed cellular responses have been found amongst Africans with Kaposi's sarcoma although not uniformly (Kestens et al, 1985) and there is spontaneous regression in both the sporadic and endemic forms of the disorder (Templeton, 1981). A common phenotype is shared by those with the spontaneous disease and by some homosexuals with AIDS (Friedman-Kien et al, 1982) but this has not been described within the allografted patients. The development of the tumour in the T-regions of lymph nodes and the appearance of lymphomas amongst these patients (Ziegler et al, 1984) may also be pointers towards a role for the immune system. The sarcoma most often appears either simultaneously with the lymphoma or following its recognition (Safai et al, 1980) and at either of these times immunodepression is probably established.

If immunodeficiency is important in the pathogenesis of Kaposi's sarcoma the marked variation in the incidence of this tumour amongst the immunodeficient population (Table 1) has to be explained. The tumour has neither been recognised amongst the primary immunodeficiency syndromes nor amongst those with secondary immunodeficiency other than that following allografting or AIDS. Secondary immunodeficiency is however poorly reported. The absence in primary and most secondary immunodeficiency could relate to these patients' short life span although the tumour appears on average sixteen and a half months after grafting and has developed within two and a half months (Penn, 1983). The life span of those with primary immunodeficiency is nevertheless sufficient for the growth of lymphomas (Frizzera et al, 1980) and the variation between the incidence of lymphomas and Kaposi's sarcoma amongst the graft and AIDS patients (Table 1) cannot be clearly explained either in terms of life expectancy or immunodeficiency.

An alternate or related pathogenic factor is persistent antigenic
stimulation. This may either produce immunodeficiency so permitting tumour expression or be directly involved in tumour genesis. Chronic malaria is the antigen specifically incriminated in Kaposi's sarcoma in Africa (Hutt, 1984) and donor antigens in those with grafts (Penn, 1983). The multiple infections experienced by AIDS patients may individually or collectively have a role but especial attention has been directed to the cytomegalovirus (CMV) (Giraldo, Beth and Huang, 1980).

**THE ROLE OF INFECTION**

An association between CMV and Kaposi's sarcoma is a distinct possibility (Giraldo, Beth and Huang, 1980). There is a high frequency of CMV in allografted and many AIDS patients, populations both subject to Kaposi's sarcoma. A similar high rate of infection is however found within the entire population of the United Kingdom but without any increased risk of Kaposi's sarcoma. The demonstration of CMV-DNA and RNA in Kaposi tumour cells strengthened the possibility of a relationship (Giraldo, Beth and Huang, 1980) until it was appreciated that homologies existed between the genomes of CMV and human DNA (Peden, Mounts and Hayward, 1982). Preliminary studies incorporating specific viral DNA fragments failed to reveal CMV-DNA sequences in Kaposi tumours. The place of CMV in the aetiology of Kaposi's sarcoma therefore remains unproven.

There is no reason to suppose that either the Epstein-Barr or the Hepatitis B viruses, both potential oncogenic agents and commonly found in many with Kaposi’s sarcoma (Penn, 1983; Fauci, 1984), are involved in this tumour’s formation. HTLVIII/LAV although widespread in Africa and the common denominator to those with AIDS is similarly unrelated. Nevertheless, despite the failure to identify a putative agent there are observations which suggest some forms of Kaposi’s sarcoma may indeed be infective. The striking localisation of the tumour in Central Africa (Hutt, 1984) is the most convincing. Further support comes from the restriction of the tumour to the indigenous populations of these regions and the absence amongst immigrants from and to these areas. The high incidence of Kaposi’s sarcoma in AIDS is a further factor (CDC, 1986).

**THE CELL OF ORIGIN**

Ignorance of the cause of Kaposi's sarcoma mirrors the confusion over the cell of origin. A wide range of cells has been incriminated mainly relying upon electron microscopy studies (Templeton, 1981). Many of these cells are common to the tissues in which the tumour is found and there is no conclusive evidence that any one is the stem cell. The present hypothesis is that the tumour arises from vascular endothelium although in none of the studies were Weibel-Palade bodies, the ultrastructural marker of vascular endothelium, found. The gross and microscopic appearances have clear analogies with vascular tumours and immunocytological studies incorporating peroxidase labelling and polyclonal Factor VIII related antigen (FVIII:RA) may provide evidence in support of this concept (Millard and Heryet, 1985). A smaller number of studies using lectins are similarly supportive (Ordonez and Batsakis, 1984). The peroxidase studies include reports of staining confined to the cells lining the spaces within the tumour and of staining of the intervening spindle cells (Millard and Heryet, 1985). The results are inconsistent and this in part may have arisen from variations in technique. Commercially obtainable polyclonal antibodies were used and these can vary in their specificity and purity.
Different fixatives as well as enzyme digestion were other variables but common to most studies was the absence of a clear description of what constituted positive staining. Background staining with this antibody is often difficult to eliminate and can obviously provide a source of observer error. False positivity can also arise from the use of Freund's adjuvant in the preparation of polyclonal antibodies if the tissues under study include mycobacteria (Kahn et al, 1985) (Fig 1). This potential cross reactivity may apply particularly to AIDS patients infected with atypical mycobacteria. Further, FVIIIRA is not confined to endothelial cells but occurs in a range of other cells (Millard and Heryet, 1985) many of which are found in the skin, the most commonly studied tissue. Staining of cells other than tumour cells is therefore possible. Conversely, not all endothelial cells even within normal tissues display the antigen and absent staining does not prove that a cell is not endothelial. The protein forms part of the plasma and if cryostat tissue is used, this and the haemorrhagic component of the tumour contribute to diffuse staining. Enzyme digestion can in turn add to difficulties in antigen demonstration as well as in the reproducibility of results.

**FIGURE 1** Mediastinal lymph node exposed to polyclonal FVIIIRA. There is positive staining of the endothelium of the vessel (right) and of the macrophages within the lymph node (left). The macrophages included large numbers of Mycobacteria. The patient was a homosexual with AIDS. Diaminobenzidine x 320.

In an attempt to resolve these difficulties we studied six Kaposi's sarcomas with two commercially obtainable polyclonal antibodies and four monoclonal antibodies to FVIIIRA all with and without trypsin and protease (Millard and Heryet, 1985). Positive labelling of tumour cells was only accepted when it matched that in labelled endothelial cells in vessels unrelated to the tumour. Acceptable and reproducible staining was provided by both type of antibody (Fig 2). Within the tumour staining was confined to some cells lining the spaces and was absent within the intervening spindle cells, a result that was consistent with all previous studies where paraffin sections were used and positive staining defined.
The view that Kaposi's sarcoma arises from vascular endothelium is not firmly substantiated and attention has now reverted to the possibility of an origin from lymphatic endothelium (Dorfman, 1984). The lymphoedema frequently found with the tumour and the earliest histological appearances when the spindle cell component is sparsely represented are compatible with the idea as is the rarity of Kaposi's sarcoma within the brain (Templeton, 1981), an organ devoid of lymphatics. Histochemical studies too provide some support for this viewpoint (Beckstead, Wood and Fletcher, 1986). Monoclonal antibodies to lymphatic endothelium have been used in a study of early and late lesions and the results also suggested that the cell of origin is from lymphatic endothelium (Jones et al, 1986). The study, however, largely depended upon a single monoclonal antibody, not unique to lymphatic endothelium, and panels of these antibodies are to be preferred before conclusive claims are made.

CONCLUSION

Kaposi's sarcoma remains an enigma. Despite the appearance of AIDS and the increased number of examples for study there is still uncertainty over the role of the immune responses, the role of infective agents, especially cytomegalovirus, and the cell of origin. The striking male predominance, highlighted in AIDS, and yet absent amongst haemophiliacs with AIDS is also unexplained.

REFERENCES


