Eur J Cancer, Vol. 26, No. 6, pp. 699–702, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00

Increased Incidence of Kaposi Sarcoma in Sweden before the AIDS Epidemic

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Clinical factors of possible importance for the greater than two-fold rise in the incidence of Kaposi sarcoma of the elderly in Sweden before the AIDS epidemic were reviewed in 63 regional patients. 5 patients had lymphoproliferative disease before or at the time of Kaposi sarcoma, and 4 patients had been receiving steroids (including 1 with lymphoma) at diagnosis. 2 of these 9 patients plus 2 additional patients had received blood transfusions 1–9 years before diagnosis. None of 17 patients tested was positive for HIV-1, and none had signs of an unexplained progressive immune defect. Of the evaluable cases, 27% had diabetes mellitus and 7% had had previous myocardial infarction. However, only the frequency of congestive heart failure (47%) was significantly greater than that of an ambulatory control group ($P = 0.001$) in the age group 75–84 years. Exposure to cytomegalovirus (CMV) was not more common in 15 Kaposi sarcoma patients than in an age and sex matched control group. No single factor could account for increased Kaposi sarcoma among the elderly. If the classical form has an infectious aetiology, the tumour could arise after effective transmission of the agent (as by a transfusion), especially combined with some degree of immune deficiency or perhaps congestive failure late in life.
Eur J Cancer, Vol. 26, No. 6, pp. 699—702, 1990.

INTRODUCTION

KAPOSI SARCOMA is a multicentred proliferation of endothelial cells, which in Western societies has typically affected the elderly. Since the middle of this century, Kaposi sarcoma has been described in new epidemiological settings, including patients with a variety of diseases treated with immunosuppression [1] and in recipients of organ transplants [2]. These observations were followed in 1981 by a sudden large increase in Kaposi sarcoma in AIDS [3]. Furthermore, general epidemiological patterns [4], reports of non-aggressive Kaposi sarcoma in males lacking HIV-1 [5, 6] and reports of HIV-negative post-transfusion Kaposi sarcoma [7, 8] imply an infectious agent transmitted separately from HIV.

The spread of HIV and a Kaposi sarcoma agent need not have begun at the same time. In an epidemiological study from Sweden [9], the incidence of Kaposi sarcoma in the elderly more than doubled during the 25 years preceding the country's first report of AIDS in 1982. Whether this clinical form of Kaposi sarcoma shares aetiological factors with the epidemic form is uncertain, however.

To assess whether transfusion therapy or increased use of immunosuppression in recent years might account for the change in incidence, we reviewed retrospectively and by questionnaire a regional group of patients with classical Kaposi sarcoma in whom HIV infection was excluded. Other clinical factors that have been previously associated with Kaposi sarcoma, including exposure to cytomegalovirus [10–12], malignant tumours [1], cardiac disease [13, 14] and diabetes mellitus [15], were also examined.

PATIENTS

Study group

Skin biopsy specimens were reviewed in a regional group of 53 consecutive patients with non-AIDS-related Kaposi sarcoma treated at the University of Lund Hospital between 1956 and 1988. 10 more patients, all alive, were studied from county hospitals in the southern part of the country. The mean age was 73 (range 42–94), there were 36 men and 27 women and 22 patients were alive. 5 cases (8%) had a lymphoid malignancy and 7 cases (11%) had another previous malignancy. Of the regional patients, 39 (62%) had been included among the previous registry study of 529 national cases (39/529, 7%) reported through 1982 [8].

Medical charts were reviewed to establish medication before diagnosis and any history of lymphoproliferative disease or other malignancy, diabetes mellitus, congestive heart failure, myocardial infarction or previous blood transfusion. A questionnaire on some of these factors and on gamma-globulin or cortisone treatment was answered by 21 of the 22 surviving patients. Denominators for the frequency of immunosuppressive therapy, myocardial infarction, cardiac failure and diabetes mellitus were based on specific answers. Unclear or absent

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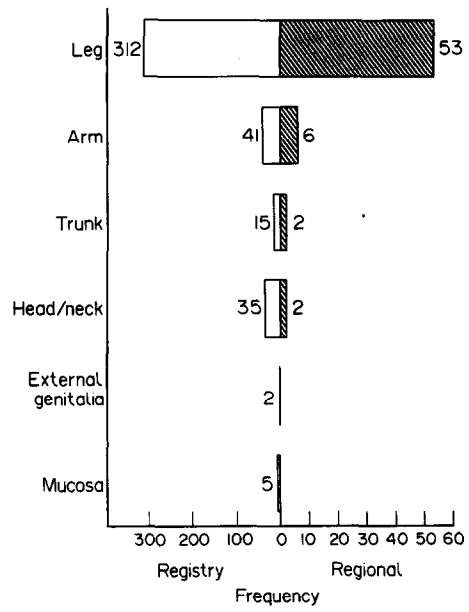

Fig. 1. Initial biopsy site in national and regional groups (ext = external). Site was not specified in 119 national cases.

statements were treated as missing observations and such cases were excluded from the calculation of frequency. Scatterplots of cases included in denominators were proportional to the annual accrual of Kaposi sarcoma.

Proportions of evaluable patients expected to have diabetes mellitus based on age and sex were taken from current prevalence data accumulated at the ambulatory health care centre in the district of Dalby [16], which lies within the study region and maintains close epidemiological surveillance of 21,262 inhabitants (three-quarters of whom visit the centre at least once every 4 years). The non-adjusted prevalence for each age interval and sex was multiplied by the corresponding number of study patients and the values summed. An ambulatory district group of 614 subjects aged 75–84 with a known frequency of myocardial infarction and congestive failure (P.-O. Bitzén, personal communication) was compared without breakdown by sex to the corresponding age group in our patients.

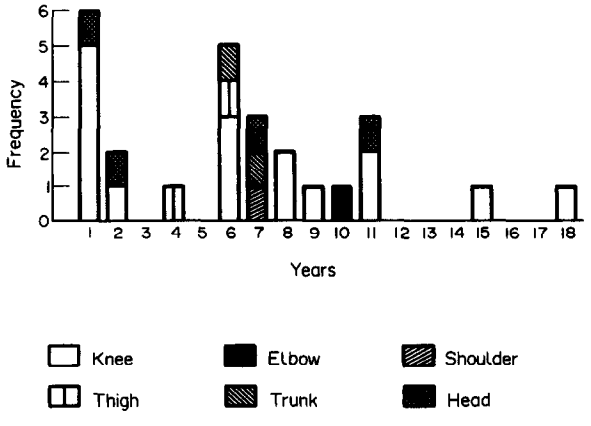

Fig. 2. Combined intervals to recurrences by site. Biopsy may not always have been done on recurrent distal lesions which may be underestimated. Note that legend indicates proximal boundaries of anatomical regions.

Table 1. Cases treated with immunosuppressive drugs or blood transfusion before diagnosis

Year of diagnosis	Age/sex	Steroid indication	Site of Kaposi sarcoma*	Transfusion
1968	69/F	Non-Hodgkin's lymphoma	Leg u/d	1966†
1976	76/F	Giant cell arteritis	Leg b/d	?
1979	69/M	Bronchial asthma	Leg b/d	None
1983	73/M	Autoimmune haemolytic Anaemia	Limbs b/d	1982
1987	90/F	—	Leg u/d	1978‡
1979	72/F	—	Thigh	1972**

*u = unilateral, b = bilateral and d = distal. Transfusion: †for anaemia, ‡before and after knee surgery and **after gastrectomy.

Serology

HIV was assayed prospectively by ELISA (Vironostica, Organon) in 15 of the survey respondents and 2 recently diagnosed when aged 56 and 66 years from outside the demographic region who were not otherwise included in the study. IgG anti-CMV antibodies were measured (Enzygnost, Behringewerke) in 13 respondents and the extra 2 patients (cases 9 and 12 in Table 4) and compared with age and sex matched controls.

Statistics

Serological results were compared between groups with the two-tailed Fisher exact probability test. Other statistical comparisons were based on χ^2 with Yates' correction. No significant difference in the presence of congestive failure or diabetes was found between patients answering questionnaires and those for whom medical records only were available.

RESULTS

The distribution of the specified initial biopsy site (Fig. 1) was analysed in the regional group by plotting the recurrence patterns for the entire sample, including recurrences at any site more than 1 year after the original diagnosis or progression to an axial skin site at any time after the first diagnosis (Fig. 2). 26 histologically sampled recurrences in 17 patients were thus detected during a follow-up of 2 months to 27 years. This does

Table 2. Associated lymphoproliferative disease

Year of diagnosis of Kaposi sarcoma	Age/sex	Disease
1964	61/M	Chronic lymphatic leukaemia in 1964
1968	69/F	NHL (inguinal) in 1966
1974	46/F	Hodgkin's disease in 1964
1973	79/F	NHL (orbital) in 1971
1987	69/M	NHL (in leukaemic phase) in 1987

NHL—non-Hodgkin's lymphoma.

Table 3. Other associated diseases

Disease	Mean age (range)	Observed frequency	Expected frequency	P
Diabetes mellitus	80 (59–91)	14/49 (29%)	5.8/49*	0.07
Congestive heart failure	77 (55–91)	12/44 (27%) 7/15 (47%)†	 84/614 (14%)†	0.001
Myocardial infarction	79 (71–88)	3/43 (7%) 1/12 (8%)†	 54/614 (9%)†	0.65

*Based on prevalence data in ref. [4].
†Limited to age 75–84 yr.

not include 1 patient with progression to angiosarcoma in subsequent biopsy specimens (an additional case with recurrence on the foot after 27 years was omitted from the graph).

4 patients (4/49, 8%) were receiving corticosteroids as the sole immunosuppressive treatment when Kaposi sarcoma was diagnosed. 1 of these patients was also among the 5 with lymphoproliferative disease. None had received an organ transplant. Table 1 shows the year of diagnosis of Kaposi sarcoma and indication for steroid, and includes patients with a known history of blood transfusion.

Cases of lymphoproliferative disease are shown in Table 2. The number of patients with diabetes, congestive heart failure or previous myocardial infarction is compared in Table 3 with the expected number. In the age range 75–84 years, only congestive failure was significantly increased ($P < 0.001$).

HIV was negative in all 17 patients studied. Moreover, no patient had clinical evidence of a progressive severe immune defect. Table 4 shows serum IgG anti-CMV levels compared with controls. No significant difference was found in the number in each group with past CMV exposure.

Table 4. CMV IgG absorbances in Kaposi sarcoma cases compared with sex and age matched controls

Case (Age/sex)	Active lesion	Absorbance	
		Patient	Control
1 (85/F)	–	1.71	1.20
2 (83/M)	+	1.27	1.90
3 (77/M)	+	1.45	2.00
4 (75/M)	+	1.21	1.30
5 (74/F)	+	2.01	2.30
6 (72/F)	–	1.21	1.20
7 (69/M)	+	1.53	1.10
8 (66/M)	–	1.70	1.60
9 (66/M)	+	1.64	1.60
10 (63/M)	+	1.82	0
11 (60/F)	+	1.04	0
12 (56/M)	+	1.85	1.00
13 (51/M)	+	1.57	2.10
14 (91/F)	+	1.56	0
15 (90/F)	+	1.51	1.40

Cases 12 and 15 received blood transfusions 5 and 3 years, respectively, before diagnosis.
Absorbance above 0.2 indicates past exposure.

DISCUSSION

In all epidemiological forms, Kaposi sarcoma is multicentred, but the aggressive growth and greater tendency for axial involvement seen in AIDS cases are probably secondary to the immune defect, since these features often occur in Kaposi sarcoma associated with iatrogenic immunosuppression [2, 17]. Analysis of primary and recurrent lesional sites did not indicate any shift towards axial involvement, as would be expected if undiagnosed HIV were the reason for the national increase in Kaposi sarcoma frequency before the AIDS epidemic. The likelihood of undiagnosed AIDS was diminished by consistently negative HIV tests and the lack of progressive immune defects.

If lymphoma patients were excluded, our study included 3 of 44 (7%) evaluable cases with Kaposi sarcoma that developed after the use of corticosteroids and, as in a similar series from Norway [18], none of the patients had received an organ transplant. The latter observation is in contrast to the frequent occurrence of post-transplantation Kaposi sarcoma in certain geographical areas [19]. In addition, the few steroid-related cases were diagnosed throughout the study rather than in a cluster during the large rise in the incidence of Kaposi sarcoma which occurred nationwide in the early 1970s. Thus the evidence does not support iatrogenic immunosuppression as a major cause of the rise in the age-adjusted incidence.

Kaposi sarcoma varies widely in frequency between populations with different causes of immunodeficiency and within populations with immunodeficiency of similar aetiology. Beral *et al.* [4] reported, for example, that transfusion recipients with AIDS were three times more likely to develop Kaposi sarcoma than patients with haemophilia and other clotting disorders (3% vs. 1%). Yet even these frequencies exceed the 3 patients out of hundreds at our institution treated with corticosteroids or other immunosuppressive agents during the years encompassed by our study. This is consistent with the finding of Beral *et al.* that immunosuppressed patients without AIDS are about one-twentieth as likely to develop Kaposi sarcoma as patients parenterally infected with HIV.

Previous transfusion is often poorly documented in medical records, and our 4 cases (Table 1) are probably an underestimate. The occurrence of Kaposi sarcoma in a patient with autoimmune haemolytic anaemia after having received blood transfusions and immunosuppressive therapy is reminiscent of a case reported from this institution in 1954 [20]. Isolated reports have described Kaposi sarcoma occurring subsequent to blood transfusion in patients who have remained negative for HIV antibodies [5, 6, 21]. The coincidence of initial reports of Kaposi sarcoma among renal transplant recipients with the introduction of routine multiple preoperative blood transfusions has been commented upon [22]. Clinical indications for transfusion often exist in other autoimmune diseases and may be particularly frequent in haematological disease, including lymphoproliferative disorders and thymoma associated with red cell aplasia [23]. Moreover, our study reaffirms the observation that Kaposi sarcoma occurs more often with or after rather than before such diseases [24]. Transfusion deserves further study as an aetiologic factor in Kaposi sarcoma.

Lothe [25] has summarized the evidence against clinical oedema as a predisposing factor in classical Kaposi sarcoma. In a separate pathological study (unpublished) based on our patients, initial skin lesions were small, solitary or few in number and rarely extended into the subcutis. This makes tumour growth an unlikely explanation for oedema of the foot. Oedema

has nonetheless varied in reported frequency from 15 to 43% [26] and was common in our patients, although a reliable estimate of its frequency was not possible. However, the number of cases with congestive heart failure, a major cause of oedema, exceeded that expected in the age range 75 to 84 years. This confirms previous impressions of increased cardiac disease in Kaposi sarcoma of the elderly [14] and suggests that the tendency we saw for increased diabetes mellitus may be related to the failure. 6 of the 12 patients with cardiac failure had diabetes mellitus. Congestive failure, by upsetting fluid balance at the capillary level in the distal extremities, could facilitate endothelial proliferation as a first step in the development of the tumour. This might imply that the multicentred process would affect dependent areas. We did not, however, see a relation between the presence or absence of congestive failure and a tendency for axial involvement (Fig. 2).

Giraldo *et al.* [27] have summarized evidence for CMV as an inducer of Kaposi sarcoma and proponents of this hypothesis have stressed multiple exposures to CMV as a possible critical factor, though applicable largely to homosexual men [28]. Multiple exposure would be difficult to demonstrate in our group of elderly patients who in any case did not differ significantly from controls in frequency of initial exposure to CMV. Studies have found no viral genomic DNA in the tumour by Southern blotting and *in situ* hybridization [29, 30].

Thus cardiac failure and lymphoproliferative disease [9, 24] are the only medical conditions found more often than expected in classic Kaposi sarcoma in Western countries. The rare occurrence of Kaposi sarcoma in steroid-treated patients indicates that immunodeficiency alone is an ineffective inducer of the tumour and that other cofactors, possibly including previous transfusion, are needed. Although none of our cases occurred in husband and wife, the evidence from the AIDS epidemic indicates that sexual transmission of Kaposi sarcoma is possible. Perhaps the potential to develop Kaposi sarcoma is acquired early in life.

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Acknowledgements—This work originated at the University of Lund Hospital and is supported by the John och Augusta Perssons Foundation for Scientific Medical Research, the Royal Physiographical Society of Lund, and the Medical Faculty of the University of Lund.