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Short Communication

Soft Tissue Sarcomas in HIV-infected Adult Patients

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Clinical and biological features of three HIV-infected adults with soft tissue sarcoma are reported. Epstein-Barr Virus (EBV) detection was negative using *in situ* hybridisation, PCR analysis and Southern blot analysis in the two cases for which tumour samples were available, contrary to all previously reported paediatric cases. All three patients developed metastases. Chemotherapy was feasible but only afforded tumour stabilisation. The cause of death in all three cases was distant spread and not AIDS. Soft tissue sarcomas associated with HIV infection are not exclusively found in children, do not appear to be EBV-related in adult patients, and fare dismally despite vigorous therapy.

Key words: sarcoma, leiomyosarcoma, rhabdomyosarcoma, human immunodeficiency virus, acquired immunodeficiency syndrome, Epstein-Barr virus, biology, chemotherapy, neoplasms
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INTRODUCTION

It is well established that HIV-infected patients are at increased risk from several neoplasms including Kaposi's sarcoma, high-grade non-Hodgkin's lymphoma and primary lymphoma of the brain [1]. Paediatric malignant and benign smooth muscle tumours have been also reported to be HIV-associated [2] and association between these tumours and Epstein-Barr Virus (EBV) have been documented recently [3]. This article reports the first clinical and biological description of three HIV-infected adult patients with soft tissue sarcomas.

PATIENTS AND METHODS

Three HIV-infected patients presented with soft tissue sarcomas. Their details are described in the Results section. However, tumour specimens from 2 patients were examined by *in situ* hybridisation (ISH), PCR analysis and Southern blot analysis for EBV detection. ISH was performed on paraffin-embedded sections with an oligonucleotide complementary to fragments of nuclear EBV encoded RNA1 (EBER-1, Dakopatts®). For PCR analysis, the EBNA1 gene was amplified [4]. The specificity of the PCR product was assessed after Southern blot analysis using an internal oligonucleotide. Southern-blot analysis was performed using a random primed ^{32}P-labelled probe specific for the Bam H1 W internal repeats of the virus. Raji and DG75 cell lines were used as EBV-positive controls.

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RESULTS

Patient 1

In 1989, a 39-year-old homosexual man was admitted to hospital with a painful abdominal mass. A small bowel leiomyoma was surgically removed. Serology was positive for HIV, as determined by both enzyme-linked immunosorbent assay (ELISA) and Western blot analysis. The CD4 lymphocyte count was 440/mm^3. He remained disease-free until 1991, when a local recurrence associated with liver metastases was noted. Biopsy revealed a grade 3 leiomyosarcoma (Table 1). CD4 lymphocyte count was 360/mm^3. The patient received six courses of doxorubicin (60 mg/m^2), ifosfamide (4500 mg/m^2), dacarbazine (750 mg/m^2) and vincristine (1 mg/m^2), every 4 weeks, and showed good clinical tolerance, except one episode of grade IV anaemia; the CD4 lymphocyte count fell to 200/mm^3. Only tumour stabilisation was achieved. The patient died of progressive disease in October 1993.

Patient 2

A 52-year-old homosexual man was known to be HIV-positive since 1990. He was not taking Zidovudine. In June 1992, a wide excision of a grade 3 pleomorphic rhabdomyosarcoma of his left upper arm was performed. The surgical

Table 1. Biological data from two HIV-infected adults with muscular sarcomas

	Patient 1	Patient 2
Immunochemistry		
S-100 protein	+	−
Alpha-smooth-actin	+	−
Myoglobin	+	ND
Actin (HFF35)	ND	+
Vimentine	ND	+
Desmine	ND	+
KP1	ND	+
KL1	ND	−
Histological grade	Grade 3	Grade 3
Karyotype	ND	48,XY,+5,+5
CD4 cell count	360/mm^3	200/mm^3
CD4:CD8 ratio	0.88	0.1
p24 antigen serology	Negative	Negative
EBV detection in tumour	Negative	Negative

ND, not done.

margin was wide. At this time, the CD4 lymphocyte count was 200/mm^3. The biological data are described in Table 1. Two months later, the patient underwent a wide myomectomy for a local recurrence. Pleural and lung metastases were detected during the postoperative course. The patient received doxorubicin (50 mg/m^2) and ifosfamide (5000 mg/m^2), every 3 weeks, in combination with G-CSF started from the second cycle because of grade IV haematological toxicity. A significant clinical improvement and radiological stabilisation were obtained for 5 months. He developed brain and epidural metastases and died in February 1993.

Patient 3

In 1985, a 19-year-old man was admitted for a paratesticular tumour. A radical orchidectomy showed an embryonal rhabdomyosarcoma. He received eight cycles of an adjuvant vindesine/mitomycin C/methotrexate regimen. However, treatment compliance was poor because the patient was very difficult to manage. In 1987, pulmonary metastases were detected. He admitted using intravenous drugs since 1981, and evidence of HIV infection was documented by ELISA and Western blot. The CD4 lymphocyte count was unknown. Chemotherapy, consisting of doxorubicin (30 mg/m^2), vindesine (2 mg/m^2), dacarbazine (750 mg/m^2) and cisplatinum (100 mg/m^2), was initiated for 5 courses, 1 cycle every 4 weeks. It only produced disease stabilisation, with mild toxicity. The patient died of progressive disease in April 1988. A sufficiently large tumour specimen was not available for subsequent biological investigation.

Detection of EBV

Tumour samples from patient 1 (leiomyosarcoma) and patient 2 (pleomorphic rhabdomyosarcoma) were negative for EBV, whatever the method employed: PCR, ISH or Southern blot. These results were confirmed twice using each detection method.

DISCUSSION

Certain tumours are now considered indicative of AIDS according to the US Centers for Disease Control [5]. The classification of muscular sarcomas in HIV-infected patients is ambiguous: whereas leiomyosarcomas have been reported both in children [2] and in epidemiological studies in adults [1], this neoplasm has not been added to the definition of AIDS. In a recent series of HIV-seropositive males, the incidence of leiomyosarcoma was moderately increased with a ratio of 2.5 [1]. Clinical descriptions of sarcomas other than Kaposi's sarcoma in adults with AIDS are quite rare and we only found one case of renal angiosarcoma with an unfavourable outcome [6]. By contrast, a number of HIV-infected children who developed leiomyosarcoma or rhabdomyosarcoma have been described [2, 7–11]. Their clinical characteristics are occurrence in both visceral and soft tissue locations, possible concurrent leiomyoma, early dissemination, a low CD4 lymphocyte count at diagnosis and a very poor outcome.

Immunodepression could not explain the occurrence of these sarcomas: the 1.2% incidence found in immunosuppressed patients seems comparable with that of general population [12]. It is well established that retroviruses can naturally and experimentally induce sarcomas in animal models, but not in humans. Other viruses are not linked to human sarcomas, although a recent study found an increased risk of developing sarcomas in cases of viral infection during childhood [13]. HIV is not considered directly oncogenic, as lentiviruses are not endowed with transforming properties. However, the *tat* gene of the virus has been shown to induce neoplasms including leiomyosarcomas in transgenic mice [14], and could be a plausible explanation for AIDS-associated tumours. As the presence of both a leiomyoma and a leiomyosarcoma is rare in one and the same patient and insofar as this situation exists in HIV-infected patients [2, 8, patient 2], it is tempting to suspect that a covirus infectious agent is involved in their development. Recently, McClain and colleagues [3] showed that high levels of the EBV genome was present in leiomyosarcomas and leiomyomas from HIV-infected young patients, whereas it was never present in HIV-negative case-controls, suggesting a major role of EBV in the oncogenic transformation of myocytes. Unlike McClain's cases, we found no evidence indicating the presence of EBV in our patients. Concerning patient 2, this might be a consequence of the rhabdomyosarcoma histology, as the EBV-positive sarcomas reported had smooth-muscle differentiation. The absence of the EBV in the tumour from patient 1 may reflect the difference between paediatric and adult cases of leiomyosarcomas occurring in HIV-infected individuals. Other transforming factors could be incriminated in the occurrence of myogenic sarcomas in adults, such as a new herpesvirus (KSHV), which was recently found in Kaposi's sarcoma from patients with AIDS [15].

The prognosis of muscular sarcomas in HIV-infected patients, both adults and children, is dismal compared with that of non-infected patients. The cause of death is sarcoma for the majority, not AIDS, indicating a putative role of the virus in the unfavourable outcome of cancer [2, 7–9]. Chemotherapy can be administered if carefully monitored in such patients, but it only affords a slight improvement in our experience.

The surveillance of further cases of muscular sarcomas will be necessary to understand better the relation between HIV and these rare neoplasms and to improve their management.

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