Kaposi's sarcoma in HIV infected women in Germany: more evidence for sexual transmission. A Report of 10 cases and review of the literature

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Abstract

***Objective*—To assess the natural history of Kaposi's sarcoma (KS) in HIV-positive women living in Germany.**

***Methods*—All physicians reporting the diagnosis of KS in a female patient were contacted and asked for detailed information.**

***Design*—Descriptive study of clinical, epidemiological and immunological data of ten women with biopsy-proven KS living in Germany were evaluated. The results are compared with those of other previously published studies of women with KS from Italy, France and the USA.**

***Setting*—Five centres in Germany.**

***Results*—Of 765 German women with AIDS, only 10 (1·3%) were reported to suffer from Kaposi's sarcoma (KS) compared with 1771 of 8128 men (21·8%). Mean age in these women was 39·7 years. KS was the first AIDS defining event in nine women and the reason for HIV-testing in three. The mean CD4 count was 215/μl. Two patients were of African origin, had only recently come to Germany and were most likely to have acquired their HIV-infection in Africa. Three patients were iv-drug users (IVDU). Two of these (and most likely all three) had worked as prostitutes. Of five women who had contracted HIV via heterosexual contacts, one worked as a prostitute and the other four were married to or were living together with a bisexual HIV-positive man. All four male partners have also developed KS. The course of the disease seems to be particularly aggressive in female patients with eight of 10 women presenting with or progressing to widely disseminated disease with extensive involvement of internal organs. In this cohort survival was longer in females who acquired their HIV infection heterosexually compared to IVDU and was strongly correlated with higher CD4-counts at diagnosis.**

***Conclusion*—KS seems to run a particularly aggressive course in women. Our data are consistent with a sexually transmittable aetiological agent of KS. Prostitution, an issue yet to be addressed by other authors reporting series of women with KS, was reported in four of our patients. Further studies are needed to clarify the significance of this finding.**

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Keywords: Kaposi's sarcoma, neoplasm, female, prostitution, women, HIV, AIDS

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Introduction

In 1872, the Hungarian dermatologist Moritz Kaposi first described a vascular tumour that he had diagnosed in three of his patients.[1] He originally named this tumour "idiopathic multiple pigmented sarcoma". This tumour which is currently referred to as Kaposi's sarcoma (KS) first gained broad public attention when thousands of HIV infected patients were diagnosed as suffering from this tumour.[2 3] The diagnosis of KS in an HIV infected patient is AIDS-defining according to the classification of the Center for Disease Control (CDC). Between 1981 and 1990 more than 18,000 patients in the US alone were diagnosed as having KS, making this tumour second only to *Pneumocystis carinii* pneumonia (PcP), the most prevalent AIDS defining condition.[2] Despite the magnitude of the problem some characteristic features of HIV-related KS are still poorly understood. Most controversial is the fact that, whereas all other AIDS-defining conditions are more or less evenly distributed between the different risk groups, KS almost exclusively affects men who have sex with men. The risk of acquiring KS is much lower for all other risk groups and is especially low for female patients.[3–8] Accordingly the number of women with KS is very small, but this group displays some unique and important epidemiological features. Detailed analysis of these patients and their sex partners with assessment of potential infectious and environmental cofactors may prove helpful in tracing a hypothetical sexually transmitted aetiological agent of KS. Unfortunately, available reports of women with KS are rare and often incomplete, especially with regard to analysis of their sexual partners. In our study we have analysed the data of all female AIDS patients in Germany diagnosed as suffering from KS and have compared our results with those obtained in other countries.

Material and methods

Similar to the AIDS-surveillance system of the CDC in the USA, the first AIDS defining condition and death of German HIV infected patients are reported to the AIDS Centre of the Federal Health Office (BGA) in Berlin. Cases are reported voluntarily using an anonymous code. By September 1992 a total

of 8893 AIDS cases had been reported to the BGA, 8128 of which were males and 765 were females. Of the 1782 cases of KS recorded, 1771 were reported to have occurred in male and only eleven in female patients. All physicians reporting the diagnosis of KS in a female patient were contacted and asked for detailed information.

Three patients had to be excluded from analysis: one patient was in fact male and had only mistakenly been reported as being female. Two other female patients were incorrectly given a presumptive diagnosis of KS after the initial examination, which was later excluded by biopsy. Two further patients, who had not yet been reported to the BGA at the time of the initial inquiry, were also included making a total of 10 women with biopsy confirmed KS.

Results

The average age at the time of diagnosis of KS was 39·7 years (range 30 to 64). KS was the first AIDS-defining illness in nine patients. Only one patient (case 4) had experienced AIDS-defining opportunistic infections (*Pneumocystis carinii* pneumonia, cerebral toxoplasmosis) prior to the onset of KS. In one further patient (case 10) concurrent KS, PcP and oesophageal candidiasis were diagnosed upon initial presentation. In two patients (cases 3 and 8) oral candidiasis (CDC IVC2) had been noted prior to the diagnosis of KS. All other patients had been asymptomatic. In three women, KS was the reason for HIV testing. Six patients were born in Germany. One patient was born in Hungary and one in Korea, but both had lived in Germany since childhood. Two patients (cases 9 and 10) were of African origin and had come to Germany only four and 24 months prior to the diagnosis of KS. They most likely acquired their HIV-infection in Africa. All patients, including the two African patients, tested positive only for HIV-1; repeat tests for HIV-2 were negative. Mean CD4-count at the time of diagnosis was 215 cells/μl (range 5 to 682). The CD4 count was below 200 in 7/10 and below 100 in 4/10. The patient (case 2) who presented with the most extensive mucocutaneous involvement (more than 200 lesions at initial presentation) had the highest helper-cell-count (682/1) of the whole cohort. p24-Antigen was determined in six patients only and was positive in two.

In eight of nine patients who were tested for prior exposure to CMV, serological evidence of previous infection was detected. One of four patients had detectable IgG-titres for syphilis, 4/6 for EBV, 6/9 for hepatitis B and 5/9 for toxoplasmosis.

Aside from the African patients (cases 9 and 10), five other patients (cases 4–8) were believed to have acquired their HIV–infection through heterosexual contact. One woman worked as a prostitute, the other four were married to or were living together with a bisexual HIV-positive man. Three of these four men had developed KS prior to the onset of KS in their female partner. The fourth man has only recently developed KS himself, seven years after his wife was first diagnosed with the tumour. None of the four men was known to use recreational drugs. Because all four men have died in the meantime we were unable to obtain further information about their sexual practices and travel history. Patients 6, 7 and 8 were available for further questioning. All three denied use of recreational drugs including marijuana and nitrate inhalants or unprotected receptive anal intercourse. All three had practised unprotected receptive and active oral intercourse.

The three other women (cases 1–3) were known to be or to have been iv-drug users. Two stated that they had worked as prostitutes. One woman had worked close to army camps and reported numerous sexual contacts with American soldiers. There is no documented information as to whether the third iv-drug user had also worked as a prostitute. The attending physicians, however, reported her as being known in the prostitution community. Upon diagnosis two patients, including one of the African patients, presented with KS confined to one lymph node. In both patients the lymph node was biopsied to rule out lymphoma or tuberculosis. After histology confirmed the diagnosis of KS, thorough inspection of the skin and the visible mucous membranes failed to reveal further lesions. The African patient (case 10) died 11 months after the initial diagnosis of KS from recurrence of *Pneumocystis carinii* pneumonia without clinical evidence of KS progression. In the other patient (case 5), rapid dissemination was observed more than a year after the initial diagnosis.

Two patients already had advanced disease upon initial presentation. One woman (case 2) had more than 200 cutaneous lesions and extensive visceral involvement affecting the mucous membranes of her throat, lung and gastrointestinal tract. Despite intensive treatment with α-interferon and chemotherapy the patient died fourteen months later from progressive pulmonary disease. The other patient (case 9), a woman from Uganda, also presented with more than one hundred lesions. Extensive involvement of the oral cavity and the gastrointestinal tract were noted. She received palliative laser-therapy for a disabling oral lesion and was lost to follow-up shortly afterwards.

The six remaining patients presented with less than ten cutaneous KS lesions and no evidence of involvement of the mucous membranes. Of these six patients only one (case 6) has not shown progression. In all the other five, progressive disease with dissemination involving the lung and gastrointestinal tract was documented.

Six patients died after a mean follow-up of 16·7 months (range 7 to 43) following their initial diagnosis of KS. One patient died of recurrent *Pneumocystis carinii* pneumonia and one died at home with the cause of death not reported. In the remaining patients death was at least partly attributed to end-stage KS with

Table 1 Epidemiological, clinical and immunological findings in ten female patients with HIV-associated KS

Case number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Age at the time of KS diagnosis (years)	34·4	30·1	30·9	57·4	36·1	64·1	31·8	53·6	30·1	28·5
Time of HIV-positivity before KS in years	4·6	0	5·5	2·3	0	2·2	0·5	0·8	0	0
Country of birth	Germany	Germany	Germany	Germany	Italy	Germany	Hungary	Korea	Uganda	Angola
Manifestations of HIV-infection (months before or after KS diagnosis)	TBC + 1 NHL + 19	Thr + 5	Thr –1 bact. Pne +1	PcP –24 Thr –24 Toxo –8	TBC +42			Thr –5		PcP 0 TBC 0 PcP +11
Riskgroup										
iv-drug use	X	X	X							
+ prostitution	(yes)?	yes	yes							
heterosexual				X	X	X	X	X	X	X
+ prostitution				no	no	no	yes	no	?	no
Partner HIV-pos				yes	yes	yes	?	yes	?	?
Partner's mode of transmission				bisexual	bisexual	bisexual	?	bisexual	?	?
Partner with KS				yes	yes	yes	?	yes	?	?
CD4-cell count	163	682	10	5	313	180	600	120	25	60
p24-Antigen	neg	?	neg	?	pos	pos	neg	?	?	neg
Number of KS (initially)	< 10	> 100	10	<10	1	4	4	2	> 100	1
Therapy	AZT α-IFN CTX Rad	CTX Rad	AZT CTX	AZT Rad	AZT CTX Rad	AZT α-IFN	AZT α-IFN Rad	AZT CTX Rad	Laser	AZT
Results of therapy	PR	PD	PD	PD	PR	CR	PD	PR	—	—
Course of disease	Cutan. & viscer. Dissem.	Progress	Lost to follow-up	Cutan. & viscer. Dissem.	Cutan. & viscer. Dissem.	Remission	Cutan. & viscer. Dissem.	Cutan. & viscer. Dissem.	Lost to follow-up	Stable
CMV IgG antibody status	pos	pos	pos	pos	pos	pos	net	pos	unknown	pos
EBV IgG antibody status	pos	unknown	pos	unknown	neg	unknown	neg	unknown	unknown	pos
Syph. IgG antibody status	pos	pos	neg	neg	neg	neg	unknown	neg	neg	neg
Toxo. IgG antibody status	pos	pos	neg	pos	neg	pos	unknown	pos	neg	pos
Hep. B IgG antibody status	pos	pos	pos	pos	neg	neg	unknown	neg	pos	neg
Hep. C IgG antibody status	unknown	unknown	unknown	unknown	unknown	neg	unknown	neg	neg	neg
Death after KS (months)	19	14	7	6	43					11
Cause of death	NHL, KS, CMV	KS	?	KS	TBC, KS					PcP
Alive after KS (months)						9	34	13	1 (lost)	

KS = Kaposi's sarcoma; PD = Progressive disease; PR = Partial response; CR = Complete response; NHL = non Hodgkin's lymphoma; CMV = Cytomegalovirus; EBV = Ebstein-Barr Virus; Syph = Syphilis; Hep = Hepatitis; AZT = Zidovudine; CTX = chemotherapy; Rad. = local radiation therapy; α IFN = α-Interferon; TBC = tuberculosis; Thr = oral candidiasis; Toxo = cerebral toxoplasmosis; PcP = *Pneumocytis carinii* pneumonia; bact. = bacterial; pne = pneumonia.

extensive gastrointestinal and pulmonary involvement. Excluding the patient lost to follow-up, three patients are still alive in July 1992 and it has been 9, 13 and 34 months respectively since KS was first diagnosed. All three patients had initial CD4-counts greater than 100/μl (180, 120 and 600/μl).

Survival seemed to be longer for patients who had acquired their HIV infection heterosexually compared with IVDU. This is probably due to better compliance and more consequent use of antiretroviral and antineoplastic therapy, which may have improved survival in some cases. Only one patient, however, experienced complete remission with zidovudine and α-interferon treatment. Three patients showed partial and temporary remission with therapy. In four patients disease progression was basically unaffected by therapy. Longer survival was strongly correlated with higher CD4 counts at diagnosis. Epidemiological, clinical and immunological data of all patients are summarised in table 1.

Discussion

By September 1992 KS was diagnosed in 1771 of 8,128 men (21·8%) but only in 10 of 765 women (1·3%) with AIDS reported to the BGA. In the USA KS was diagnosed in 17,918 of 114,379 men (15·7%) with AIDS reported to the CDC by April 1990. During the same period 241 of 11,746 women (2·1%) were diagnosed as suffering from KS. The percentage of women with KS was similar for IVDU (2·0%), heterosexuals (2·1%) and transfusion recipients (2·7%).[2]

Three detailed reports of women with HIV associated KS from the USA,[6] France[7] and Italy[8] have reported data that in some aspects differ substantially from the epidemiological features that we observed in our patients. The American study[6] reported details on five black, one Hispanic and one Haitian woman with KS (age range 23 to 34 years). All but the Haitian patient were iv-drug users. All seven presented with pulmonary involvement and median survival was less than 4 months (range 1 to 6 months). Of 12 French women with KS, nine patients were reported to have acquired HIV infection through sexual contact with HIV-positive men; two of these women also were IVDU. The other three had transfusion-associated AIDS. Mean age was 39 years (range 21 to 81) and mean CD4-count was 116/μl (range 12 to 377). In only three patients could details about their sexual partners be obtained. None of the male partners were bisexual or had KS.[7] Among 23 Italian women with KS, the mode of transmission of HIV was IVDU in 16, heterosexual contacts in six and unknown in one. Four of six heterosexually infected women were partners of HIV-positive heterosexual men (whose mode of transmission was unknown), and the other two were partners of heterosexual IVDU. None of the 23 women reported contact with HIV-positive bisexual men.[8]

In general women with KS in Germany were slightly older and had higher CD4

Table 2 Demographic patient characteristics in different cohorts of women with HIV associated KS

Reference	*11*	*12*	*13*	*this report*
Country	USA	France	Italy	Germany
N	7	12	23	10
Age mean (years)	I.n.a.	39	29·7	39·7
Range	23–34	21–81	20–56	30–64
CD4 mean	I.n.a.	116	188	215
Range	I.n.a.	12–377	4–568	5–682

I.n.a. = Information not available.

counts at diagnosis than the patients in the other studies (table 2).

One hundred per cent of the American and 70% of the French women died within a year of KS diagnosis. If one excludes the woman who was lost to follow-up one month after initial presentation, only three of the remaining nine women (33%) from our cohort have died within the first 12 months following diagnosis. We noted, however, the same unusually aggressive course of KS in women that has been reported before, with eight of ten patients presenting with or progressing to widely disseminated disease.

Details about sexual partners were available for 3 of 12 French and all 23 Italian women with KS. Surprisingly none of these partners were bisexual or had KS. This was substantially different in our cohort: of four patients in whom details about their sexual partners were obtained, all reported sexual contact to bisexual men, all of whom had already been diagnosed with KS prior to the manifestation in their female partners or in one case developed KS seven years afterwards. Our results are consonant with data that were reported by Beral *et al.*[3] Among 2146 female AIDS patients of whom details about their sexual partners were available, KS was more common in women who reported to have had sex with bisexual men (9 of 303 = 3·0% of heterosexuals and 3 of 74 = 4·1% of IVDU) than in those who reported sex with male IVDU (9 of 1238 = 0·7% of heterosexuals and 6 of 531 = 1·1% of IVDU). The authors concluded that these results are highly consistent with a sexually transmittable aetiologic agent of KS.

This hypothesis is supported by the fact that all four bisexual partners that had transmitted HIV to their female partner who eventually developed KS suffered from the tumour themselves. The theory of a sexually transmittable agent becomes even more appealing when one considers that two (and possibly all three) of the drug users plus the only heterosexually infected patient (case 7) who did not report sexual contact with bisexual men and was not of African origin were known to have worked as prostitutes. Because none of the other published studies has ever addressed this issue, the significance of this finding remains unclear.

Results of large epidemiological studies also favour an infectious agent which is most likely transmitted sexually as the most probable aetiology of KS.[2 3 9] There are so far no sufficient data to indicate which pathogen could possibly be responsible for the development of KS, although many different infectious agents have already been implicated to induce KS formations. Cytomegalovirus (CMV) DNA and RNA have been isolated from KS tissue.[10] Molecular studies, however, were unable to confirm a direct relationship between CMV and KS.[11] HIV itself has also been implicated as the responsible pathogen. In 1988 Vogel and his group[12] demonstrated that injection of the tat-gene, a regulatory gene isolated from the genome of HIV, induced KS-like tumours in mice. Up to now all attempts to isolate HIV fragments from KS tissue have not been successful.[11 13]

The isolation of "retrovirus-like-particles" from KS from 5 of 12 HIV seronegative men[14] raised speculation about the possible aetiological role of a currently unidentified novel retrovirus.

Huang used molecular methods to trace different infectious agents in KS and found fragments of HPV 16 in 11 of 69 samples.[15] The significance of this finding is unclear, because fragments of human papilloma viruses can also be found in normal skin.[16] Two groups of workers[18 17] have isolated novel mycoplasma species from KS of HIV-seropositive and seronegative patients. The significance of these results, however, has not yet been validated in larger series of patients.

So far there are no data revealing preferential infection of males with any of the above mentioned pathogens. Accordingly, none of the studies mentioned can provide a plausible explanation for a gender difference in the susceptibility to KS.

Several cytokines and growth hormones have been found to regulate growth and development of KS.[19–22] The possibility of gender variation in any of these substances as an explanation for the observed different incidence of KS in men and women has not yet been investigated and should be evaluated in further studies.

For the future we would like to encourage other authors to report further cases of HIV associated KS in female patients. A thorough investigation including a detailed history of the sexual behaviour of these patients and their respective partners might contribute to the identification of the hypothetical long sought after aetiological agent of KS.

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1 Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. Archiv für Dermatologie und Syphilis 1872;4:265–72. English translation: Classics in oncology: Idiopathic multiple pigmented sarcoma. *Cancer Journal for Clinicians* 1982;**32**:342–47.
2 Haverkos HW, Drotman DP, Morgan WM: Kaposi's sarcoma in patients with AIDS: sex, transmission mode, and race. *Biomed Pharmacother* 1990;**44**:461–6.
3 Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexual transmitted infection? *Lancet* 1990;**335**:123–8.
4 Bary M, Vittecoq D, Liotier D, Galamy G. Heterosexual transmission of the aetiological agent of Kaposi's sarcoma. *Lancet* 1991;**336**:234.
5 Janier M, Caumes E, Miclea JM, Morel P. Kaposi's sarcoma in an HIV-infected heterosexual couple: an argument for sexual transmission of Kaposi's sarcoma. *Presse Med* 1990;**19**:1723.

6 Cheung TW, Siegal F. Kaposi's sarcoma (KS) in women with acquired immunodeficiency syndrome (AIDS). *Int Conf AIDS* 5; Stockholm 1989 (abstract no. M.B.P. 297).
7 Lassoued K, Clauvel JP, Fegueux S, Matheron S, Gorin I, Oksenhaendler E. AIDS-associated Kaposi's sarcoma in female patients. *AIDS* 1991;5:877–80.
8 Benedetti P, Greco D, Figoli F, Tirelli U. Epidemic Kaposi's sarcoma in female AIDS-patients—a report of 23 Italian cases. *AIDS* 1991;5:466–7.
9 Wahmann A, Melnik SL, Rahme FS, Potter JD. The epidemiology of classic, African, and immunosuppressed Kaposi's sarcoma. *Epidemiol Revs* 1991;**13**:178–99.
10 Giraldo G, Beth E, Huang ES. Kaposi's sarcoma and its relationship to cytomegalovirus (CMV). III. CMV DNA and CMV early antigens in Kaposi's sarcoma. *Int J Cancer* 1980;**26**:23–6.
11 Jahan N. Analysis of human Kaposi's sarcoma biopsies and cloned cell lines for cytomegalovirus, HIV 1 and other selected DNA virus sequences. *AIDS Res Hum Retroviruses* 1989;**5**:225-30.
12 Vogel J, Hinrichs SH, Reynolds KR, *et al.* The HIV tat gene induces dermal lesions resembling Kaposi's sarcoma in transgenic mice. *Nature* 1988;**335**:606–11.
13 Delli Bovi P, Donti E, Knowles DM, *et al.* Presence of chromosomal abnormalities and lack of AIDS retrovirus DNA sequences in AIDS-associated Kaposi's sarcoma. *Cancer Res* 1986;**46**:6333–8.
14 Rappensberger K, Tschachler E, Zonzits E, *et al.* Endemic Kaposi's sarcoma in human immunodeficiency virus type 1-seronegative persons: demonstration of retrovirus-like particles in cutaneous lesions. *J Invest Dermatol* 1990;**95**:371–81.
15 Huang OH, Li JJ, Rush MG, *et al.* HPV-16 related DNA sequences in Kaposi's sarcoma. *Lancet* 1992;**339**: 515–8.
16 Boyd JF. Human papillomavirus type 16 and Kaposi's sarcoma. *Lancet* 1992;**339**:938–9.
17 Lo SC, Shih JWK, Newton PB III, *et al.* Virus-like infectious agent (VLIA) is a novel pathogenic mycoplasma: *Mycoplasma incognitus*. *Am J Trop Med Hyg* 1989;**41**: 586–600.
18 Marquart KH, Engst R, Oehlschlaegel G. An 8-year history of Kaposi's sarcoma in an HIV-negative bisexual man. *AIDS* 1991;5:346–8.
19 Nair BC, De Vico AL, Nakamura S, *et al.* Identification of major growth factors for AIDS-Kaposi's sarcoma cells as Oncostatin M. *Science* 1992;**225**:1430–2.
20 Nakamura S, Salahuddin SZ, Biberfeld P, *et al.* Kaposi's sarcoma cells: long term culture with growth factor from retrovirus-infected CD4 + T cells. *Science* 1988;**242**: 426-30.
21 Plettenberg A. Neue Erkenntnisse zur Ätiopathogenese des Kaposi-Sarkoms-Möglichkeiten der systemischen Therapie. In: Jäger H (ed.) *AIDS: Eine Krankheit Wird Behandelbar*. Materialien zur HIV-Erkrankung im 2. Jahrzehnt. Ecomed Verlag München, AIDS Monographien, Vol. 3. 1993:119–122.
22 Roth WK, Werner S, Schirren CG, *et al.* Depletion of PDGF from serum inhibits growth of AIDS related and sporadic Kaposi's sarcoma cells in culture. *Oncogene* 1989;4:483–7.