AIDS-Associated Kaposi's Sarcoma: A Rare Entity at Maharaj Nakorn Chiang Mai Hospital

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Kaposi's sarcoma (KS) is well know for its occurrence in immuno-suppressed patients and, particularly in patients with AIDS. In Asia, KS was rarely reported before the spread of AIDS[1]. Since the advent of the AIDS epidemic, however, the incidence rate of KS has significantly increased in several areas[2-4]. A few cases of AIDS-associated KS have been reported from Asian countries[5,6]. As Chiang Mai and its adjacent provinces, now the high prevalent area of HIV infection in Thailand, we studied the occurrence of KS and its associated factors at the Maharaj Nakorn Chiang Mai Hospital, the major referral center in the Northern Thailand.

MATERIALS AND METHODS

A retrospective study was performed on cases registered as Kaposi's sarcoma in the surgical pathology files of the Maharaj Nakorn Chiang Mai Hospital during September 1990 and March 1996. No case of KS was

SUMMARY Kaposi's sarcoma (KS) is rare in Asian countries. Since the AIDS epidemic, KS has become the most common AIDS-related cancer reported in the international literature. Up to March 1996, 4 cases of AIDS-associated KS were histologically documented at the registry at the Maharaj Nakorn Chiang Mai Unversity Hospital, comprising 2 adult and 2 pediatric male patients. Routes of HIV exposure included intravenous injection and heterosexual contact in adult cases, and perinatal transmission and blood transfusion in the pediatric ones. KS was present as an AIDS diagnostic condition in one of the adults and in both children. In our institution, KS was second in frequency to malignant lymphoma among AIDS patients. Predomination of non-homosexual transmission of HIV infection in this region was probably a factor associated with the rarity of AIDS-associated KS.

diagnosed before this period. The available clinical data and the histo-pathologic material were reviewed. The histopathologic material included hematoxylin and eosin-stained of formalin fixed, paraffin-embedded tissue. Special stains included histochemical stains (periodic acid Schiff with and without diastase predigestion) and immunohistochemical studies. The expression of factor VIII-related antigen (a marker for endothelial cells) and vimentin (a marker for cells of mesenchymal origin) were determined on deparaffinized tissue sections using an avidin-biotin immunoperoxidase technique. Seven cases diagnosed as KS were retrieved, but three of them were excluded on reviewing. These deleted cases comprised a non HIV-positive KS case and two cases of

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other vascular tumors including angiosarcoma and hemangioendothelioma. Thus, 4 cases of AIDS-associated KS were included in the study. All patients had positive serology for HIV (ELISA technique and particle agglutination test). AIDS was defined by Thai AIDS criteria which includes disseminated *Penicillium marneffei* infection.[7]

RESULTS

Patients

The four AIDS-associated KS patients were all males, 2 adults and 2 children, one of which was previously reported (patient 3).[8] The clinical data are shown in Table 1. Risk factors for HIV infection were intravenous drug injection (patient 1), heterosexual contact (patient 2), perinatal transmission (patient 3) and blood transfusion (patient 4). Concerning patient 3, both of his parents were HIV-positive and his father had a history of heterosexual contacts with many partners. Patient 3 also had received several blood tranfusions since 2 years of age in other hospital, so documented evidence to confirm whether or not the blood transfused was HIV-positive was not available. Thus, we prefer perinatal tranmission to blood tranfusion as a route of HIV infection in the patient. KS was the initial presentation of AIDS with or without coexistent infection in patients 2,3 and 4. Presenting lesions of skin or mucous membrane were observed in all cases. The lesions were invariably multiple. Visceral involvement was documented in patient 4 at presentation. Patient 3 had also pulmonary lesions at his death, ten months

Table 1. Clinical data of AIDS-associated KS patients

Patient No.	1	2	3	4
Demographic area	Chiang Mai	Chiang Rai	Chiaing Mai	Mae Hong Son
Sex, Age (years)	Male, 30	Male, 31	Male, 3	Male, 14
Sexual behavior	heterosexual	heterosexual	-	-
Risk of HIV exposure	intraven. injection	heterosex. contact KS	perinatal infection KS	blood transfusion KS
AIDS diagnostic condition	cerebral Toxo. candida septicemia			
Sites of KS at presentation				
- skin	lower extremities	chest. upper ext	chin.up. &low.ext.	-
- mucous membrane ($/mm^3$)	-	hard palate	-	hard palate
- lymph node	-	-	cervical	-
- visceral organ(s)	-	-	-	lungs
Times from AIDS to death/last follow up	41 Months#	5 Months	10 Months	2 Weeks
Cause of death	-	disseminated Cr.	pneumonia	meningitis+
Lymphocyte count at KS dx ($/mm^3$)	950	400	5,200	1,850
- CD4+ cell count ($/mm^3$)	-	-	490	90
- CD4+/CD8+ cell ratio	-	-	0.1	0.1
Specific treatment of HIV/KS	-	Azidothymidine	Vincristine	-
Other serological investigation(s)	Anti-HBsAg+	VDRL- Widal test-	anti CMV IgM- -	anti CMV IgM- Toxo. titer-
Prior or coexistent illness	SBE	nocardiosis **	anemia, pneumonia	malaria,meningitis †

**Toxo** : Toxoplasmosis; KS:Kaposi's sarcoma; Cr : Cryptococcosis; SBE: Subacute bacterial endocarditis

Regression of KS after 8 months of diagnosis; ** Pulmonary & hepatic nocardiosis ; † Chronic meningitis of unidentified cause.

following KS diagnosis when he was readmitted due to recurrent cerebral toxoplasmosis. The lesions regressed after 8 months with his recovery from the illness. He was monitored 41 months after diagnosis of AIDS and had no evidence of serious illness in the last follow up (CD4+ cell count 380/mm,^{3} CD4 to CD8+ cell ratio 0.8)

History of regular smoking was present in both adult patients. Heroin and marijuana were also used by patient 1. No relevent specific infection other than HIV was associated with occurrence of KS. Data of CD4 and CD8+ cell counts were not available in patients 1 and 2 due to limited laboratory facilities at the time of diagnosis.

Histopathologic findings

The biopsy specimens were obtained from the skin (patients 1,2, and 3), from the lymph node (patient 3), and from the lungs (patients 3 and 4) The histopathologic spectrum of KS ranged from early patch lesion characterized by discrete islands of proliferating miniature vascular spaces and jagged endothelium-lined channels dissecting the dermal collagen in the skin biopsy of patient 1(Fig.1) to nodule formation of proliferated uniform spindle cells with slit-like spaces containing red blood cells, found in patients 2,3 and 4 (Figs. 2,3 and 4). Small round PAS-positive diastase-resistant hyaline globules, whose presence is a characteristic feature of KS, were seen both intracellularly and extracellularly in all lesions. Deposition of hemosiderin
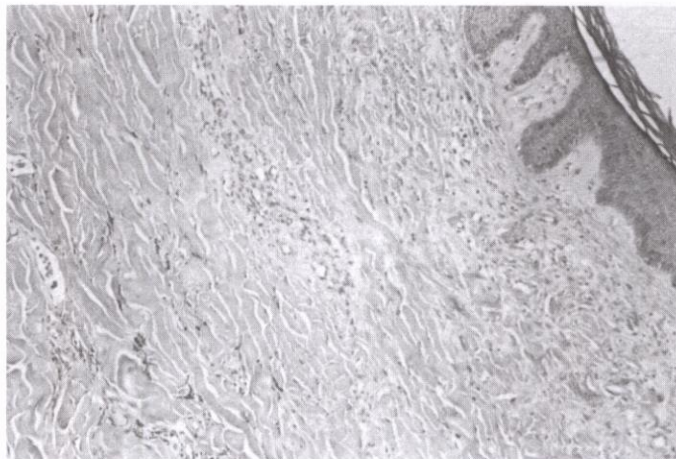

Fig. 1 Skin biopsy of patient 1 revealing early lesion of Kaposi's sarcoma characterized by proliferation of miniature vessels and jagged endothelial channels dissecting the dermal collagen (H&E, x 100)
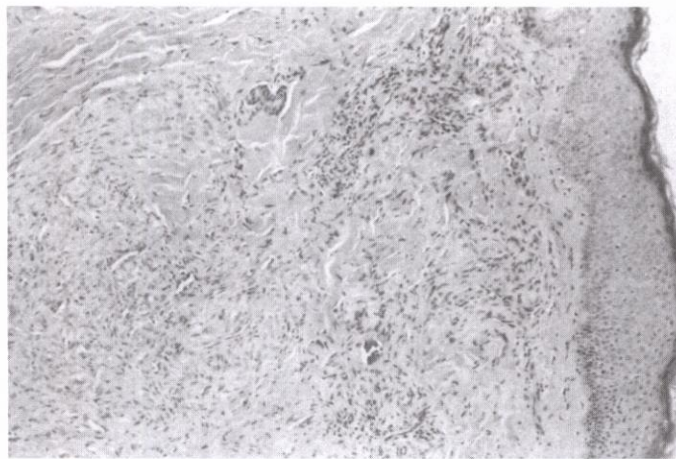

Fig. 2 Skin biopsy of patient 2 demonstrating a vague nodule of uniform bland spindle cells with vascular slit formation (H&E, x 100)

was evident in patient 1. Mitotic figures were occasionally observed but were frequent in some spindle cell areas (up to 10/10 HPF in case 4). The immunopathologic findings revealed strong reactivity for factor VIII-related antigen in the areas of better-formed vascular element, whereas the spindle cell component demonstrated mild to absent immunostaining. Reactivity for vimentin was demonstrated in almost all spindle cell components including vascular elements.
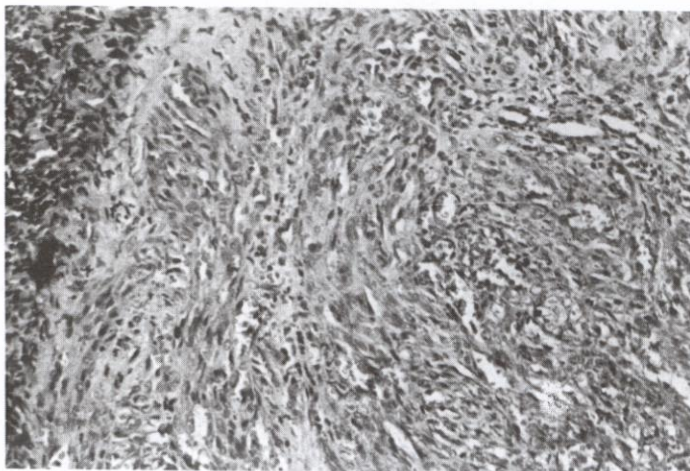
Fig. 3 Kaposi's sarcoma in the lymph node biopsy of patient 3 illustrating interlacing bundles of uniform spindle cells with numerous vascular slits containing erythrocytes (H&E, x 200)
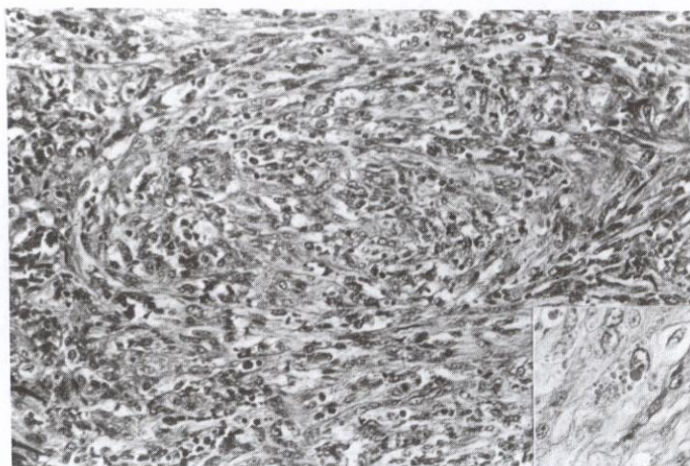
Fig. 4. Kaposi's sarcoma in the lung necropsy of patient 4 (H&E, x 200). Inset, a tumor cell containing intracellular small round hyaline globules (H&E, x 400)

DISCUSSION

KS has been described for over one hundred years. In addition to the well recognized classic form, the African form, and immunosuppressed KS, AIDS-associated KS has become a distinctive entity.[1] KS may be the initial presentation of AIDS (early KS) or develop subsequent to other AIDS diagnostic conditions (later KS).[9] Skin manifestations are more commonly observed in the early KS group.

Before the AIDS epidemic, KS had variable geographic and racial distribution.[3] Classic KS was prevalent in the Mediteranean or the southen European countries, in particular Greece and Italy, while KS was rarely reported in South America, Australia, and Asia.[1] No case of KS was reported in our hospital registry prior to the spread of HIV. Incidence rates of KS rose remarkably with the AIDS epidemic.[2-4] KS is well known for being the most common AIDS-associated malignant neoplasm.[10,11] Malignant lymphoma, the second most common AIDS-associated cancer after KS in the Western literature,[10] outnumbered KS in AIDS patients in our hospital.[12]

The histopathologic features confirmed the presence of KS lesions. Variable immunostaining for Factor VIII-related antigen was undertaken, although controversial, as is the histogenesis of KS.[5,13] The spindle component in KS displays immunophenotypes of endothelial cells, pericytes, bone marrow progenitor cells, and dendrocytes.[11] The true nature of a KS tumor cell remains to be confirmed.

Adult patient 1 presented cutaneous KS lesions subsequent to AIDS diagnosis. The initial site of KS lesions in the skin of the lower extremities in this patient was associated with longer survival than the other sites.[14] He had spontaneous regression of the lesion with recovery of the clinical condition. At the last follow-up, his CD4+ cell count had not severely

decreased. By comparison, adult patient 2 had a greater extent of KS involvement with generalized muco-cutaneous lesions at presentation. He had a much lower lymphocyte count with a complicated opportunistic infection and had remarkably short-ened survival.

Between the two pediatric cases, patient 3, who presented with cutane-ous and lymph node lesions and received Vincristine therapy, had much longer survival than patient 4 who had initial visceral lesions. Although patient 3 had higher lym-phocyte and CD4+ cell levels than patient 4, significance of these values in correlation with survival may not be readily interpreted due to age difference between both patients. Infection was the final factor that led to the death of the patients. CD4+ cell level less than $200/mm^3$ and systemic illness were postulated to be predic-tive of shortened survival, rather than anatomical extent of lesions in patients with AIDS-associated KS.[15] CD4+ cell levels were inversely related to the progression of KS.[9] Regression of KS in patient 1 was not unexpected with his improved condition and also suggest that there are different suscep-tibility thresholds among the AIDS patients who are destined to develop KS.[9] This may explain the different timing of presentation as early or later KS different degree of immunosup-pression.

In general, AIDS-associated KS primarily has affected male patients, the majority of whom are homosexual men.[4] Analytic epidemiologic studies of AIDS-associated KS were based on the homosexual or bisexual populations.[9,16] AIDS patients who acquired HIV infection by hetero-sexual contact had almost the same or slightly increased risk for KS compared to other parenteral routes of transmission.[4,17,18] The routes of HIV exposure in our patients were uncommon to developing of KS, particularly perinatal transmission.[4]

The pathogenesis of KS is not well understood. Immunogenetic factors determined by the major histocompatibility complex may influence evolution of KS in HIV-infected patients.[19] Nitrite or "popper", a recreational drug, was once thought to play a role and may have induced KS by direct contact of its vapor with the skin and mucous menbrane.[20] The recent decrease of KS incidence has paralleled the decrease of nitrite use.[1] Intravenous drug use apparently has no association over time with devel-opment of KS in HIV-infeeted asymptomatic homosexuals.[1] The association between use of recreational drugs or types of sexual activity and KS was probably non-specific and related to a broader pattern of behav-ior with multiple activities.[16]

Among infections that have been implicated as the causative agent in KS, cytomegalovirus (CMV) and HIV are of particularly interest, although the role of CMV in KS is controver-sial.[1] HIV, its tat gene or oncostatin-M, a cytokine secreted by chronically HIV-1 infected T-cells, may have a role in KS development[21-23] Occur-rence of KS in HIV-seronegative homosexual patients may, however, make this suggestion moot.[24] An angiogenic cytokine produced by retrovirus-infected T-cells, named scatter factor, suggested a possible role of retroviruses other than HIV as a cause of KS.[25]

Human papilloma virus, herpes virus, hepatitis A virus, hepatitis B virus, and Epstein-Barr virus have been considered as KS causative agents.[1,26] These infectious agents are common in this region. Increased risk of KS in HIV-infected patients in association with sexually-transmitted infections is consistent with the postulation that KS may be caused by an infectious agent which is sexually transmissible in addition to HIV.[4,18] A newly identified herpes virus, termed KS-associated herpes-virus, or human herpesvirus 8 (HHV 8) showed strong evidence as a KS agent.[27]

Recent decline of KS has been attributed to adoption of safer sexual practices.[17,18] Sexual transmission alone can not explain the occurrence of AIDS-associated KS in pediatric patients. KS agent may be coinfected with HIV and it is probably prevalent only in certain populations or in some geographic areas.[4]

KS is rare in our hospital. The four cases of AIDS-associated KS have been histologically documented among adult and pediatric AIDS patients during the time of this study. The great majority of AIDS patients in our hospital acquire HIV infection by either heterosexual contact or intravenous drug injection, routes usually not associated with the devel-opment of KS which has been largely confined to homosexual or bisexual

patients in the Western studies.[4] HIV transmission through heterosexual contact or drug injection may also account for the relative absence of AIDS-associated KS cases in our population when compared to populations in Western reports. Differences in genetic and environmental factors can not also be excluded. Some degree of diagnostic biases in case detection may exist; however, we think that this can not totally explain the distinct rarity of KS in this prevalent area of HIV infection.

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