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Original Article

Kaposi's sarcoma in patients with human immunodeficiency virus infection in Taiwan

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Background and purpose: Kaposi's sarcoma (KS) continues to occur in patients with human immunodeficiency virus (HIV) infection in the era of highly active antiretroviral therapy (HAART), and remains the most common HIV-associated malignancy. This retrospective study was conducted to describe the change in incidence and characteristics of HIV-associated KS in Taiwan.

Methods: The medical records of patients with HIV infection who received a diagnosis of KS at the National Taiwan University Hospital between June 1994 and March 2008 were reviewed.

Results: During the 14-year study period, 62 HIV-infected patients were diagnosed with KS, which included 40 definite diagnoses (64.5%) by pathology and 22 probable diagnoses (35.5%) ascertained by characteristic lesions, compatible clinical manifestations, and response to treatment. Most of the patients were men who have sex with men (MSM; n = 53; 85.5%). At the time of diagnosis of KS, the median CD4 count was 20 cells/μL (range, 1-371 cells/μL). A considerable decline in the incidence of KS in HIV-infected patients since the introduction of HAART was demonstrated; in the pre-HAART era, 18 of 175 patients (10.3%; 95% confidence interval [CI], 6.53-15.75) developed KS, compared with 44 of 1615 patients in the HAART era (2.7%; 95% CI, 2.03-3.65) [$p < 0.0001$]. The prognosis of HIV-infected patients with KS has improved since the introduction of HAART, as the mortality rate has declined from 77.8% in the pre-HAART era to 34.1% in the HAART era ($p = 0.002$).

Conclusions: The incidence of KS in HIV-infected patients and the mortality rate of these patients significantly declined in the HAART era, although KS continued to occur in patients with advanced HIV infection.

Key words: Acquired immunodeficiency syndrome; HIV; Sarcoma, Kaposi; Taiwan

Introduction

Kaposi's sarcoma (KS) was first described in the medical literature by Moritz Kaposi, who was originally known as Moritz Kohn and adopted the name of his birthplace, Kaposivar, on the Kapos River in 1872 [1]. 109 years after Kaposi's description, Hymes et al [2] and Friedman-Kien et al [3] reported this previously rare malignancy that presented in an unusually aggressive form in 8 young homosexual men in the United States in the early 1980s. The sudden increase in incidence of KS heralded the onset of the acquired immunodeficiency syndrome (AIDS) epidemic. In 1982, the United States Centers for Disease Control and Prevention defined KS and primary central nervous system (CNS) lymphoma as AIDS-defining malignancies [4]. Subsequent revision of AIDS-defining illnesses in 1987 [5] and 1992 [6] resulted in the addition of non-Hodgkin's lymphoma not restricted to CNS and invasive cervical cancer, respectively.

In 1994, a novel virus was discovered in all types of KS, whether or not the KS was related to human immunodeficiency virus (HIV). The new virus was termed human herpesvirus 8 (HHV8), and was also known as KS-associated herpes virus [7]. This discovery led to greater understanding of the role of viral oncogenesis in the pathogenesis of this mesenchymal tumor [8-10].

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Although the introduction of highly active antiretroviral therapy (HAART) in 1996 has led to a dramatic decrease in HIV-associated morbidity and mortality, AIDS-defining illnesses still occur because of unawareness of HIV serostatus, delay in seeking HIV care, or poor compliance with therapies among patients with HIV infection [11-13]. Among the AIDS-defining malignancies, KS remains the most common in HIV-infected patients. To the authors' knowledge, few studies have reported the epidemiology and characteristics of KS in HIV-infected patients in Taiwan. The aim of this study was to describe the incidence and clinical characteristics of KS in patients with HIV infection at a medical center in Taiwan.

Methods

Study population

From June 1994 to March 2008, an ongoing open observational cohort study at the National Taiwan University Hospital, Taipei, Taiwan, has enrolled 1790 consecutive non-hemophiliac HIV-infected patients aged 15 years or older [14]. In this retrospective study, the medical records of all patients with KS were retrieved for analysis. A computerized case report form was used to record patients' demographics, risk factors for HIV infection, CD4 and CD8 lymphocyte counts, plasma HIV RNA load, HIV-related opportunistic illnesses, antiretroviral therapy, and outcome.

Diagnostic investigations

During the 14-year study period, stepwise investigations were performed as routine clinical care practices to identify the etiology of any presenting symptoms and signs [14]. For patients who presented with mucocutaneous lesions or lymphadenopathy, biopsy would be performed if necessary. For visceral lesions for which the etiology remained unknown after non-invasive diagnostic tests, sonography, computed tomography (CT), or endoscopy-guided aspiration and biopsy were performed for all lesions that were accessible to aspiration and biopsy. Histopathologic examinations, microbiological cultures, including cultures for bacteria, fungi, mycobacteria, and viruses, were performed, especially for febrile patients.

Definitions

KS was defined as definite if the lesions were diagnosed by pathology. Probable KS was defined as those lesions with a characteristic appearance plus compatible clinical findings and responsive to antiretroviral therapy alone or in combination with specific therapy for KS, including local therapy or systemic chemotherapy.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences for Windows (Version 12.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared by chi-squared analysis or Fisher's exact test. Non-categorical variables were compared by Mann-Whitney *U* test. All comparisons were 2-tailed and a p value of <0.05 was considered significant.

Results

Malignancy was identified in 128 of 1790 patients (7.2%) with HIV infection. KS was the most common malignancy, and 62 patient (48.4%) were diagnosed with KS; the second and third most prevalent malignancies were lymphoma (n = 34; 26.6%) and cervical neoplasm (n = 8; 6.3%), respectively. The median CD4 count at baseline was 130 cells/μL and 58.8% of the patients had a baseline CD4 count <200 cells/μL.

The demographics and clinical characteristics of the 62 patients with KS are shown in Table 1. Most of the patients were men who have sex with men (MSM; n = 53; 85.5%), followed by heterosexuals (n = 9; 14.5%). No patients who were injection drug users were diagnosed with KS. The median CD4 and CD8 counts and plasma HIV RNA load at enrolment were 26 cells/μL (range, 1-371 cells/μL), 476 cells/μL (range, 102-1744 cells/μL), and 5.32 $\log_{10}$ copies/mL (range, 2.60-5.88 $\log_{10}$ copies/mL), respectively (Table 1). Forty patients (64.5%) had definite KS and 22 (35.5%) had probable KS. The median age was 35 years (range, 21-83 years) at the time of diagnosis of KS. Fifty two patients (83.9%) had KS as an initial presenting disease of HIV infection. Fifty nine patients (95.2%) had the criteria for a diagnosis of AIDS [6], and 55 (88.7%) had other concurrent opportunistic infections. In addition to KS, other malignancy was identified in 4 patients (6.5%). These four patients developed non-Hodgkin's lymphoma after the initial diagnosis of KS and they all died subsequently due to progression of AIDS-defining illnesses.

Forty two patients (67.7%) were naive to antiretroviral therapy and most of the KS (n = 51; 82.3%) occurred in patients with CD4 counts <100 cells/μL. At the time of diagnosis of KS, the median CD4 count

Table 1. Characteristics of patients with human immunodeficiency virus with Kaposi's sarcoma.

Characteristic	No. (%)
Patients	62
Men	59 (95.2)
HIV risk factors	
Homosexual or bisexual	53 (85.5)
Heterosexual	9 (14.5)
Injection drug use	0
Laboratory data at enrolment	
CD4 (cells/μL) [median (range)]	26 (0-371)
CD8 (cells/μL) [median (range)]	476 (102-1744)
Plasma HIV RNA load (log_{10}/mL) [median (range)]	5.32 (2.60-5.88)
Diagnosis of Kaposi's sarcoma	62
Definite	40 (64.5)
Probable	22 (35.5)
Concurrent opportunistic infection	55 (88.7)
Concurrent malignancy	4 (6.5)
Age (years) [median (range)]	35 (21-83)
Pre-HAART era (n = 175)	18 (10.3)
Post-HAART era (n = 1615)	44 (2.7)
Naïve to ART	42 (67.7)
AIDS	59 (95.2)
CD4 (cells/μL) [median (range)]	20 (1-371)
Plasma HIV RNA load (log_{10}/mL) [median (range)]	5.28 (1.69-6.02)
CD4 count (cells/μL)	
<100	51 (82.3)
100-200	3 (4.8)
200-350	4 (6.5)
>350	1 (1.6)
Unknown	3 (4.8)
Death	29 (46.8)

Abbreviations: HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; ART = antiretroviral therapy; AIDS = acquired immunodefiency syndrome.

and plasma HIV RNA load were 20 cells/μL (range, 1-371 cells/μL) and 5.28 log_{10} copies/mL (range, 1.69-6.02 log_{10} copies/mL), respectively (Table 1).

The incidence of KS and other clinical data at the time of diagnosis of KS are shown in Table 2. After the introduction of HAART, a significant decline in the incidence of KS in HIV-infected patients was demonstrated; in the pre-HAART era, 18 of 175 patients (10.3%; 95% confidence interval [CI], 6.53-15.75) developed KS, compared with 44 of 1615 patients (2.7%; 95% CI, 2.03-3.65) in the HAART era ($p < 0.0001$). In both pre-HAART and HAART eras, most of the HIV-infected patients had late-stage HIV infection, with low CD4 counts, and development of AIDS and concurrent opportunistic infections, when diagnosed with KS. More patients with HIV infection were naïve to antiretroviral therapy in the HAART era (n = 34; 77.3%) than in the pre-HAART era (n = 8; 44.4%) [$p = 0.012$]. The mortality rate declined from 77.8% in the pre-HAART era to 34.1% in the HAART era ($p = 0.002$). Of the 4 patients who survived the pre-HAART era, 1 was diagnosed with KS in 1993 and 3 in 1997, and all of them received HAART.

The sites of involvement of KS and treatment modalities for KS are shown in Table 3. In both the pre-HAART and HAART eras, cutaneous lesions were most prevalent (pre-HAART era, 88.9%; HAART era, 70.5%), followed by the oral mucosa (pre-HAART era, 38.9%; HAART era, 45.5%) and lymph nodes (pre-HAART era, 27.8%; HAART era, 20.5%). The lungs and gastrointestinal tract were the 2 most common visceral organs involved and some patients had more than 2 sites of involvement at the time of initial diagnosis or during the course of illness, especially in the pre-HAART era (pre-HAART era, 66.7%; HAART era, 45.5%) [Table 3].

The most frequently used treatments were chemotherapy with antiretroviral therapy (pre-HAART era, 61.1%; HAART era, 38.6%), antiretroviral therapy alone (pre-HAART era, 33.3%; HAART era, 36.4%), or local therapy (pre-HAART era, 16.7%; HAART era, 27.3%). The chemotherapy regimen for KS in HIV-infected patients evolved during these 2 periods from combination chemotherapy with adriamycin, bleomycin, and vinblastine in the pre-HAART era to monotherapy with liposomal doxorubicin in the HAART era. More than 2 treatment modalities were sometimes necessary for refractory disease, which was more common in the pre-HAART era than in the HAART era (pre-HAART era, 27.8%; HAART era, 9.1%) [Table 3].

Discussion

In this study of KS in patients with HIV infection in Taiwan, most patients had late-stage infection and acquired HIV infection through sexual transmission. Although not a common AIDS-defining illness (3.4%), KS was the most prevalent HIV-associated malignancy (48.4%). The incidence of KS in HIV-infected patients in this study is comparable to reports from Europe and the United States [11,15]. In the studies by Mocroft et al [15] and Kaplan et al [11], the crude incidences of KS among HIV-infected patients were 5.7% (560 of 9803 patients) and 3.9% (527 of 13,420 patients) in Europe and the United States, respectively.

Table 2. Characteristics at diagnosis of human immunodeficiency virus–associated Kaposi's sarcoma according to treatment era.

Characteristic	Pre-HAART era[a] No. (%)	HAART era[b] No. (%)	*p*
Patients	18	44	
Incidence of Kaposi's sarcoma (%)	10.3	2.7	<0.001
CD4 (cells/μL) [median (range)]	7 (1-303)	26 (0-371)	0.089
Plasma HIV RNA load (log_{10}/mL) [median (range)]	NA	5.32 (2.60-5.32)	
AIDS	18 (100)	41 (93.2)	0.550
Naïve to antiretroviral therapy	8 (44.4)	34 (77.3)	0.012
Kaposi's sarcoma as one of the presenting diseases	16 (88.9)	36 (81.8)	1.000
Concurrent opportunistic infection	17 (94.4)	38 (86.4)	0.263
Concurrent malignancy	2 (11.1)	2 (4.5)	0.573
Death	14 (77.8)	15 (34.1)	0.002

[a]June 1994 to March 1997.

[b]April 1997 to March 2008.

Abbreviations: HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; NA = not available; AIDS = acquired immunodeficiency syndrome.

Table 3. Clinical manifestations and treatment of human immunodeficiency virus–associated Kaposi's sarcoma according to treatment era.

Manifestation	Pre-HAART era[a] No. (%)	HAART era[b] No. (%)
Diagnosis	18	44
Definite	12 (66.7)	28 (63.6)
Probable	6 (33.3)	16 (36.4)
Sites of involvement		
Skin	16 (88.9)	31 (70.5)
Oral mucosa	7 (38.9)	20 (45.5)
Lymph node	5 (27.8)	9 (20.5)
Visceral organ	4	10
Lung	4 (22.2)	6
Gastrointestinal tract	-	4 (22.7)
More than 2 sites of involvement	12 (66.7)	20 (45.5)
Treatment		
Antiretroviral therapy	6 (33.3)	16 (36.4)
Chemotherapy	11 (61.1)	17 (38.6)
Local therapy	3	12
Radiotherapy	2	10
Cryotherapy	1 (16.7)	2 (27.3)
Excision	2 (11.1)	1 (2.3)
Other (interferon)	2 (11.1)	0
More than 2 treatment modalities	5 (27.8)	4 (9.1)

[a]June 1994 to March 1997.

[b]April 1997 to March 2008.

Abbreviation: HAART = highly active antiretroviral therapy.

When comparison of the incidence of KS in HIV-infected patients between the pre-HAART era and the HAART era was made, there was a significant decline in the incidence of KS after the introduction of HAART (10.3% vs. 2.7%; $p < 0.001$). However, KS continued to occur, especially in those with advanced HIV infection, despite the marked decline in incidence. These findings were also comparable with the data from previous studies, in which the incidence of most AIDS-defining illnesses, including KS, decreased significantly after HAART was introduced. Although the incidence has decreased, the spectrum of disease and the relative frequencies of opportunistic illnesses have not changed appreciably, and they continue to occur in HIV-infected patients with low CD4 lymphocyte counts [10-13,15-18].

Most of the HIV-infected patients diagnosed with KS were MSM (85.5%). No patients with HIV-associated KS were injection drug users. These findings are consistent with a previous observation that different opportunistic illnesses have different incidences by sex and risk of HIV exposure [11]. KS is most common among MSM. This may reflect the fact that the causative agent of KS, HHV8, is mainly transmitted through sexual contact in HIV-infected MSM, although other routes of transmission have also been suggested [19-21]. Among the 62 HIV-infected patients with KS in this study, only 2 patients had received examination for HHV8 infection. Therefore, the association between HHV8 infection and KS in HIV-infected patients in Taiwan needs further study.

As most of the patients in this study were at a late stage of HIV infection and met the criteria for AIDS at the diagnosis of KS in both the pre-HAART and HAART eras, the majority had concurrent opportunistic infections (n = 55; 88.7%). These infections further complicated the clinical course and treatment decisions, due to the difficulty of differential diagnosis, complex drug-drug interactions, adverse effects of treatment, pill burden, and cancellation or delay of systemic chemotherapy due to active infection. In addition, 4 patients initially diagnosed with HIV-associated KS developed non-Hodgkin's lymphoma, which resulted in death due to immunosuppression after chemotherapy for lymphoma and progression of opportunistic illness.

The most common sites of involvement of KS were skin, oral mucosa, and lymph nodes in both the pre-HAART and HAART eras. The lower extremities, face (particularly the tip of the nose), and genitalia were the most common sites for skin lesions, and the hard palate and gingiva were the most common sites in the oral mucosa. These manifestations are consistent with previous observations that cutaneous and oral mucosal lesions were the most prevalent sites of HIV-associated KS [10,22,23]. Lesions at these sites were more easily recognized and were attainable for diagnosis. However, visceral organ involvement of KS poses diagnostic challenges and may have been underestimated because of the sometimes non-specific appearance on imaging studies, non-specific or no symptoms, difficulty in obtaining pathologic diagnosis, and physicians' lack of awareness, especially in patients with no mucocutaneous involvement. Fourteen patients (22.6%) had KS involving the visceral organs (lung, 10; gastrointestinal tract, 4). Gastrointestinal involvement has been reported in 40% of patients at initial diagnosis and up to 80% at autopsy [24]. Pulmonary KS is also common and 15% of cases may occur in patients without evidence of mucocutaneous lesions [25]. More than half (51.6%) of the HIV-infected patients with KS in this study had more than 2 sites of involvement at the time of initial diagnosis of KS or that were subsequently identified due to progression of disease. Therefore, extracutaneous involvement of KS should always be investigated in HIV-infected patients with suspicious clinical manifestations.

Treatment for KS is continually evolving, especially chemotherapy regimens. In the pre-HAART era, combination chemotherapy with adriamycin, bleomycin, and vinblastine was the most commonly used regimen for advanced KS. However, patients can develop neutropenic fever and peripheral neuropathy. In the HAART era, liposomal doxorubicin has become the first-line chemotherapy for HIV-associated KS and most of the patients receiving liposomal doxorubicin in this study tolerated it well. Liposomal doxorubicin is one of the 5 United States Food and Drug Administration approved agents for the treatment of KS, the other treatments being alitretinon gel, liposomal daunorubicin, paclitaxel, and interferon-α [10,19,22]. Significantly higher response rates and lower toxicity rates have been found for liposomal doxorubicin compared with other agents [26-29].

In addition to chemotherapy, some patients with AIDS-associated KS respond well to HAART. Approximately one-third of patients in the pre-HAART era (33.3%) and HAART era (36.4%) were treated with antiretroviral therapy alone. The effects may be mediated by immune reconstruction following HAART that leads to better immune recognition and clearance of HHV8; better inhibition of KS invasion, especially via protease inhibitors; direct action on HIV, which is known to trigger KS; and direct antiviral potency against HHV8 [10,20]. These improvements in treatment for patients with KS also resulted in a decline in the mortality rate (pre-HAART era, 77.8%; HAART era, 34.1%; $p = 0.002$), although the deaths may or may not have been directly related to KS. In this study, the treatment modalities for KS were diverse and the number of patients in the study was small, which precluded assessment of the relationship between a specific treatment modality and outcome.

In conclusion, these findings suggest that the incidence of KS in HIV-infected patients significantly

declined since the introduction of HAART, although it continued to occur in patients with advanced HIV infection. The introduction of HAART and improvement of treatment modalities for KS have led to a better prognosis for HIV-infected patients with KS.

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