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# Kaposi's Sarcoma: Clinico-pathological Analysis of Human Immunodeficiency Virus (HIV) and Non-HIV Associated Cases

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**Kaposi's sarcoma (KS) is a angioformative lesion that classically occurs in elderly Eastern European and Mediterranean males but is also common in immunosuppressed individuals particularly human immunodeficiency virus (HIV)-infected patients. This study investigates the clinical and histopathological features of 47 patients with Kaposi's sarcoma from a teaching hospital in Sydney, Australia, in which 44 cases had adequate clinical follow-up information over a 10-year period. Most of the lesions were of late stage (37/47 cases; 79%), consisting of 11 cases of plaque stage KS and 26 cases of nodular stage KS with only 10 cases of early or patch stage KS. The majority of the HIV-positive cases (23/33; 70%) and all of the HIV-negative (14/14; 100%) cases had late stage lesions (p=0.020; $X^2$-test). The histopathological features that were more common in the KS lesions of HIV-negative patients were lesional cell mitosis (p=0.0002), single cell necrosis (p=0.001), apoptosis (p=0.0001) and single cell anaplasia (p=0.0001). The KS lesions in HIV-positive patients tended to have dissecting blood vessels (14/33 cases; 42%) unlike those seen in HIV-negative patients (0/14 cases; 0%) (p=0.004). Most HIV-positive cases (30/33; 90%) were males (p=0.0068); and all these patients (33/33 cases; 100%) were <60 years old, in contrast to HIV-negative patients (1/11 cases; 9%) (p=0.0001). HIV status does not affect the occurrence of multiplicity of KS lesions. However, extracutaneous or visceral KS lesions were more likely to occur in HIV-positive patients (p=0.027). The number of cases of histologically proven KS cases has decreased markedly over the recent 5 year period of 1995-1999 (n=14), which was less than half of the number of the preceding 5 year period, 1990-1994 (n=33). In summary, there are distinct differences in the clinical and histopathological features of Kaposi's sarcoma lesions in HIV-positive and HIV-negative patients. Despite the recent discovery of the HHV8 virus as the initiating and promoting factor of most of the KS lesions, these differences indicated that there might be different mechanisms that occur in HIV-positive and HIV-negative patients in the development of this lesion.** (Pathology Oncology Research Vol 8, No 1, 31–35, 2002)

*Keywords:* Kaposi's sarcoma, human immunodeficiency virus, HIV, neoplasia, human herpesvirus 8, HHV8

### *Introduction*

Kaposi's sarcoma (KS) is a vascular proliferative lesion that classically occurs in elderly Eastern European and Mediterranean males.[1] However, since 1979, KS is found to be increasingly common in immunosuppressed individuals such as organ transplant recipients or patients infected with the human immunodeficiency virus (HIV).[2,3]

The tumor can be multicentric and involve internal viscera. Typically, initial clinical presentation is characterised by purplish to red cutaneous macules on the hands and feet and progress up the limbs forming nodules and culminating with visceral or mucosal involvement in some patients.[4] These patients often die from complications of their immunosuppression rather than from the KS lesions per se although some can succumb to the visceral complications with haemorrhage.

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Histologically, the lesion is characterised by spindle cell proliferation, usually in a directional streaming pattern, admixed with endothelial cells, fibroblasts and inflammatory cells. Although the lesion has been described to evolve through a sequence of morphologically distinct stages ranging from an early stage low grade lesion to an advanced stage high grade nodular lesion, accelerated forms with the appearance of the latter lesions are observed without having progressing from the early low-grade lesion.[5] Early KS lesions can be histologically confused with inflammatory dermatosis or angiodermatitis[6] whereas more advanced lesions can be mistaken for a pyogenic granuloma or bacillary angiomatosis.[7]

This study investigates the incidence, clinical and histopathological features of patients with Kaposi's sarcoma at a major teaching hospital in Sydney, Australia, over the 10-year period 1990-1999.

## *Materials and Methods*

The study material consisted of paraffin-embedded, archival tissues of surgical resection and biopsy specimens from patients with Kaposi's sarcoma (n=47). However, adequate clinical details and follow-up information were available only in 44 of the patients. Routine histological sections were prepared using standard staining methods with haematoxylin and eosin.

The patch stage lesion is considered to be the early stage KS whereas the plaque stage lesion is said to be the developed KS lesion. In the current study, the patch stage is considered as the early stage KS lesion whereas plaque and nodular KS lesions are grouped as developed or late stage lesions. The histological sections of each of the KS lesions were examined for a range of pathological features as listed in *Table 1*. The clinical histories were obtained from the Medical Records Department of the Central Sydney Area Health Service. Ethics approval was obtained from the Ethics Review Committee of the Central Sydney Area Health Service, Protocol No. X00-0041. The HIV status of 44 patients was obtained and documented.

*Table 1.* **Histological subtypes of KS and relationship to pathological features.**

| | *HIV Status* | | *Chi-square* | *p-value* |
|---|---|---|---|---|
| | *Positive* | *Negative* | | |
| *Histological stage* | | | | |
| Early | 10 (30%) | 0 (0%) | | |
| Late | 23 (70%) | 14 (100%) | 5.39 | 0.020 |
| *Plasma cells* | | | | |
| Present | 15 (45%) | 8 (57%) | | |
| Absent | 18 (55%) | 6 (43%) | 0.54 | 0.460 |
| *Dissecting vessels* | | | | |
| Present | 14 (42%) | 0 (0%) | | |
| Absent | 19 (58%) | 14 (100%) | 8.46 | 0.004 |
| *Protruberant vessels* | | | | |
| Present | 2 (6%) | 0 (0%) | | |
| Absent | 31 (94%) | 14 (100%) | 0.89 | 0.347 |
| *Hyaline globules* | | | | |
| Present | 25 (76%) | 13 (93%) | | |
| Absent | 8 (24%) | 1 (7%) | 1.86 | 0.173 |
| *Red cell extravasation* | | | | |
| Present | 33 (100%) | 14 (100%) | | |
| Absent | 0 (0%) | 0 (0%) | NA | NS |
| *Haemosiderin* | | | | |
| Present | 31 (94%) | 14 (100%) | | |
| Absent | 2 (6%) | 0 (0%) | 0.89 | 0.347 |
| *Mitosis* | | | | |
| Present | 11 (33%) | 13 (93%) | | |
| Absent | 22 (67%) | 1 (7%) | 13.94 | 0.0002 |
| *Single cell necrosis* | | | | |
| Present | 11 (33%) | 12 (86%) | | |
| Absent | 22 (67%) | 2 (14%) | 10.79 | 0.001 |
| *Apoptosis* | | | | |
| Present | 13 (39%) | 14 (100%) | | |
| Absent | 20 (61%) | 0 (0%) | 14.77 | 0.0001 |
| *Single cell anaplasia* | | | | |
| Present | 1 (6%) | 8 (57%) | | |
| Absent | 32 (97%) | 6 (43%) | 18.59 | 0.0001 |

### *Statistical analysis*

The significance of the histopathological features in relation to the HIV status of patients was statistically analysed. Categorical variables were analysed with the chi-squared ($X^2$) contingency test. Only p values of less than 0.05 were considered significant.

***Results***

*Histopathology and classification of KS lesions at different stages of development*

In the current study, there are a total of 47 cases of KS consisting of 10 (21%) cases of early or patch stage KS, 11 (24%) cases of plaque stage KS and 26 (55%) cases of nodular stage KS. Patch stage KS lesions are characterised by a poorly circumscribed collection of thin-walled vessels with some surrounding spindle cells dissecting into the stromal connective tissue associated with extravasation of erythrocytes, some lymphoplasmacytic inflammatory cells and oedema. Plaque stage KS lesions show similar features to those of patch stage KS but with more prominent number of spindle cells. The nodular KS lesion is featured by a circumscribed collection of spindle cell fascicles with some intervening thin-walled vessels, extravasation of red blood cells, haemosiderin collections and spindle cells with intracytoplasmic, PAS positive and diastase-resistant globules. In this study, plaque and nodular lesions are considered as late stage lesions.

*HIV status and histopathological features in Kaposi's sarcoma*

The patients with known HIV-positive status showed a relatively uniform range in the recognised specific histological types of KS. Of the 33 cases of HIV-positive cases, the majority (23/33; 70%) of cases were late stage KS but all of the HIV-negative (14/14; 100%) cases also had late stage lesions ($X^2$=5.39, p=0.020; $X^2$-test) (*Table 1*). Of the various histopathological features examined, the presence of lesional cell mitosis ($X^2$=13.94, p=0.0002; $X^2$-test), single cell necrosis ($X^2$=10.79, p=0.001; $X^2$-test), apoptosis ($X^2$=14.77, p=0.0001; $X^2$-test) and single anaplasia ($X^2$=18.59, p=0.0001; $X^2$-test) were more likely to be found in the KS lesions of HIV-negative patients than in HIV-positive patients *(Table 2).* However, KS lesions in HIV-positive patients tended to have dissecting blood vessels (14/33 cases; 42%) unlike those seen in HIV-negative patients (0/14 cases; 0%) ($X^2$=8.46, p=0.004; $X^2$-test).

There was no significant difference in the presence of plasma cells, newly formed blood vessels protruding into vascular lumens ("protuberant vessel", which are the promontory sign of early KS), hyaline globules, red cell extravasation and haemosiderin in the lesions between HIV-positive and HIV-negative patients (*Table 1*).

*HIV status and relationship to clinical features in patients with KS*

Of the 47 cases studied, 44 had adequate clinical follow-up information. There were 33 HIV-positive cases in which the majority (30/33; 90%) was males (*Table 2*). This was in contrast with the HIV-negative cases with almost equal distribution between males (6/11; 55%) and females (5/11; 45%) ($X^2$=7.33, p=0.0068; $X^2$-test).

All of the HIV-positive patients (33/33 cases; 100%) were <60 years old, with a median age of 35 years (range: 24-54 years). This contrasted significantly with HIV-negative patients, in which the majority (10/11 cases; 91%) were 60 years of age ($X^2$=38.8, p=0.0001; $X^2$-test), with a median age of 70.5 years (range: 60-86). Of the 44 cases with adequate follow-up in the study group, 12 (36%) had multiple lesions. However, there was no significant difference between the HIV-positive and HIV-negative groups in the occurrence of multiplicity of KS lesions. In addition, neither group of patients was more likely to develop recurrence of the KS lesions. The majority of the cases were cutaneous KS (33/44; 75%). However, HIV-positive patients were more likely than HIV-negative patients to have extracutaneous or visceral KS lesions ($X^2$=4.89, p=0.027; $X^2$-test).

*Table 2.* **Histological subtypes of KS and relationship to clinical features.**

| *Parameter* | *HIV Status* | | *Chi-square* | *p-value* |
|---|---|---|---|---|
| | *Positive* | *Negative* | | |
| *Sex* | | | | |
| Male | 30 (90%) | 6 (55%) | | |
| Female | 3 (10%) | 5 (45%) | 7.33 | 0.0068 |
| *Age* | | | | |
| <60 | 33 (100%) | 1 (9%) | | |
| ≥60 | 0 (0%) | 10 (91%) | 38.8 | 0.0001 |
| *Multiplicity of lesions* | | | | |
| Single | 21 (64%) | 7 (64%) | | |
| Multiple | 12 (36%) | 4 (36%) | *** | 0.717 |
| *Recurrence* | | | | |
| Absent | 28 (85%) | 7 (64%) | | |
| Present | 5 (15%) | 4 (36%) | 2.28 | 0.13 |
| *Site* | | | | |
| Cutaneous | 22 (67%) | 11 (100%) | | |
| Visceral / extra-cutaneous | 11 (33%) | 0 (0%) | 4.89 | 0.027 |

***: cannot be estimated

*Incidence of histologically proven KS cases over the 10 year period 1990-1999*

Although a number of clinically documented KS cases were not biopsied, the incidence of histologically proven KS cases has decreased markedly over this period. The number of cases over the 5 year period 1990-1994 was 33 whereas that over the 5 year period of 1995-1999 was 14, which was less than half of the number of the preceding 5 year period.

## *Discussion*

Classical Kaposi's sarcoma is uncommon and is seen more commonly in males of more than 60 years old and of Mediterranean or Ashkenazic Jewish origin.[8] The increased risk of developing Kaposi's sarcoma in immunosuppressed patients receiving immunosuppressive therapy for transplants or those who have haematological malignancies, is well-documented.[9-14] However, it is well known that Kaposi's sarcoma is frequently seen in patients with acquired immunodeficiency syndrome (AIDS).[15,16]

Although it was previously reported that the histopathological features seen in the KS lesions in HIV-positive and HIV-negative patients were similar in each stage of development, the lesions in HIV-positive patients differed from those of HIV-negative patients in relation to the rapid progression of the lesions to more advanced stage lesions.[2,16]

In the present study, we found that in the combined cohort of HIV and non-HIV patients, the majority of the lesions (37/47; 79%) were of developed or late stage lesions. In the HIV-positive group of patients, although the majority of the KS lesions were of developed or late stage, early stage lesions were more common in this group than in the HIV-negative group of patients. Because there were more early stage KS in HIV-positive cases than in the HIV-negative patients, the lesions in the former group were more likely to have dissecting vessels. These findings were consistent with those found by others.[17,18] In contrast, the current study showed that the KS lesions in HIV-negative cases were exclusively of developed or late stage and not surprisingly the presence of lesional cell mitosis, single cell necrosis, apoptosis and single cell anaplasia were found to occur significantly more frequently than in the KS lesions of HIV-positive patients.

There was no significant difference in the presence of plasma cells, protuberant blood vessels, hyaline globules, red cell extravasation and haemosiderin in the lesions between HIV-positive and HIV-negative patients. It was of interest to note that plasma cells were found in a minority of the early KS lesions in this study despite its reported usefulness as a clue to its diagnosis.[5] However, previous studies made by others also found that the plasma cells was a minor finding in early HIV-associated KS lesions.[2,17]

In the evaluation of the HIV status and the various clinical parameters, it was found that there were significant differences in the age and sex of the patients between HIV-positive and HIV-negative patients, a result that is expected due to the clinical and epidemiological influence of HIV infection. Of interest, it was also found that patients who were HIV-positive were far more likely to develop extracutaneous or visceral KS lesions in this study. In contrast, previous studies had documented visceral involvement by KS in classical KS,[19,20] although those studies were made before the discovery of AIDS and the presence of HIV infection in those patients could not be completely excluded.

The recent discovery of the human herpesvirus 8 (HHV8) as the initiating factor for the development of Kaposi's[4] has provided important insight into the pathologenesis of this tumor in both HIV-positive and HIV-negative patients. High HHV8 infection rate is found in central and southern Africa with intermediate infection rates in Mediterranean and eastern European countries and low rates in Asia, North America and northern Europe.[21,22] Homosexual and bisexual men have a higher risk of HHV8 infection in Western societies and the virus appears to be spread by sexual transmission, although there is evidence that other routes of transmission may be important.[21,23,24,25] It appears that HHV8 initiates and promotes the development of KS lesions through the viral interleukin-6 (vIL-6) a cyclin and vascular endothelial growth factor (VEGF) that it produces.[21] In HIV-infected cases, the Tat protein of HIV virus induces various cytokines that synergistically interact with the products of HHV8 that may account for the development and progression of KS.[26,27] It is interesting to note that the HHV8 virus is found in over 95 percent of all KS lesions in various studies[4,21] and it would be expected that the pathological features of these lesions should be similar in both HIV-positive and HIV-negative patients. It is obvious that this is not the case in the current study and in those of others.[2,15,16,28] This suggests that the evolution and progression of KS in HIV-positive and HIV-negative patients may require different cofactors and may well follow different mechanisms, which are currently the subject of further studies.

In summary, there are distinct differences in the clinical and histopathological features of Kaposi's sarcoma lesions in HIV-positive and HIV-negative patients found in this study. Despite the recent discovery of the HHV8 virus as the initiating and promoting factor of most of the KS lesions, these differences highlighted the probable important mechanisms that are different in the presence or absence of HIV infection.

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