Kaposi’s Sarcoma in South Africa

Freddy Sitas, Robert Newton

Kaposi’s sarcoma was endemic in South Africa even before the advent of the human immunodeficiency virus (HIV). Between 1988 and 1996, the incidence of Kaposi’s sarcoma in South Africa has risen at least threefold and continues to increase as the HIV epidemic grows. Research from South Africa has shown that infection with human herpesvirus 8 (HHV8) is associated with Kaposi’s sarcoma but not with any other major cancer site or type. In addition, the risk of Kaposi’s sarcoma increases with increasing antibody titer to HHV8, but, for a given titer, the risk is greater in HIV-seropositive compared with HIV-seronegative individuals.

The age- and sex-standardized seroprevalence of HHV8 in black South African hospital patients was found to be slightly more than 30%; the seroprevalence of HHV8 increased with age and was similar in men and in women. The modes of transmission of HHV8 are yet to be fully elucidated. Limited evidence exists for sexual transmission in black South African adults, but mother-to-child and person-to-person transmission in childhood is also likely. Furthermore, the seroprevalence of HHV8 decreases with increasing levels of education and is lower in whites than in blacks, suggesting that factors associated with poverty may be important determinants of transmission. Future research should focus on risk factors for Kaposi’s sarcoma in HHV8-infected individuals, as well as on determinants of mode and transmission of HHV8. In addition, the elucidation of the effect of primary HHV8 infection in adults and in children. [J Natl Cancer Inst Monogr 2000;28:1–4]

Before the human immunodeficiency virus (HIV) epidemic, Kaposi’s sarcoma showed a greater geographic variation in incidence than almost any other cancer. It was as common in parts of sub-Saharan Africa, such as Uganda and eastern Zaire, as colon cancer is in the United States and Europe, representing up to 9% of all cancers in men (1–4). Narrow belts of relatively high incidence stretched westward across the former Zaire to the coast of Cameroon and southward down the Rift Valley into Malawi and parts of South Africa (Fig. 1) (4,5). Kaposi’s sarcoma was also endemic, although much rarer, in countries around the Mediterranean, particularly Italy, Greece, and the Middle East, but it was almost nonexistent elsewhere in the world, except in immigrants from those endemic countries (6–8). In all of these areas, Kaposi’s sarcoma was considerably more common in men than in women (4).

HIV AND KAPOSI’S SARCOMA

It was the appearance of aggressive forms of Kaposi’s sarcoma in the United States in the early 1980s that heralded the onset of the HIV epidemic in western countries. Although the incidence of Kaposi’s sarcoma has increased in populations at high risk of HIV in northern Europe and in the United States, it existed in the rest of these populations at such a low level before the onset of the epidemic that it still remains a relatively rare tumor (6,9). However, parts of Africa with a high prevalence of HIV and where Kaposi’s sarcoma was relatively common even before the era of acquired immunodeficiency syndrome (AIDS) have seen an explosion in the incidence of the disease. In the past 10–15 years, the incidence of Kaposi’s sarcoma has increased about 20-fold in Uganda and Zimbabwe, such that it is now the most common cancer in men and the second most common in women (10,11). Similarly, between 1988 and 1996, the incidence of Kaposi’s sarcoma has risen at least threefold in South Africa and continues to increase as the HIV epidemic grows (12). Data from the South African National Cancer Registry show that, between 1992 and 1996, the incidence rates of Kaposi’s sarcoma have doubled in men but have increased about sevenfold in women, such that the sex ratio of 7:1 in males versus females in 1988 has now declined to only 2:1 (12).

The epidemiology of HIV-associated Kaposi’s sarcoma varies around the world, reflecting to a certain extent the situation that existed in the era before AIDS. For example, in a South African study (13), the relative risk of Kaposi’s sarcoma in HIV-infected individuals, compared with HIV-uninfected individuals, was 62 (95% confidence interval [CI] = 20–194). Although this is similar to results from elsewhere in Africa (14,15), it is an order of magnitude lower than would be expected from studies in, for example, the United States (5). This result simply reflects the fact that Kaposi’s sarcoma is endemic in Africa with a relatively high proportion of HIV-uninfected cases; thus, the absolute risk of developing Kaposi’s sarcoma among those individuals who are co-infected with HIV and with human herpesvirus 8 (HHV8) is probably about the same as in the United States.

HHV8 AND KAPOSI’S SARCOMA

HHV8, a newly discovered human herpesvirus (16), has been consistently associated with Kaposi’s sarcoma and is now considered to be the principal cause of the disease (17). Genomic sequences of HHV8 are present in tumor cells of Kaposi’s sarcoma lesions in virtually all subjects (18), and its presence, detected by polymerase chain reaction or serology in peripheral blood, predicts the subsequent development of the tumor (19,20). Furthermore, HHV8 is not a ubiquitous virus but is most prevalent in groups or populations at highest risk of developing Kaposi’s sarcoma, such as HIV-infected homosexual men in the United States and African populations in whom the tumor has long been endemic (4,21,22).

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A recent case–control study (23) of black cancer patients from Johannesburg and Soweto, South Africa, found that infection with HHV8 was strongly associated with Kaposi’s sarcoma but not with any other major cancer site or type, including prostate cancer and multiple myeloma. In addition, the risk of Kaposi’s sarcoma increased with increasing antibody titer (as measured by the intensity of the fluorescent signal) to HHV8; however, for a given titer, the risk was much greater in HIV-seropositive subjects. HHV8 seroprevalence rates and antibody titers to HHV8 were not, however, markedly related to HIV infection among those without Kaposi’s sarcoma (Table 1). The highest fluorescent signal intensity for HHV8, corresponding to an antibody titer of 1 : 204 800, was associated with a 12-fold increase in risk of Kaposi’s sarcoma among HIV-seronegative subjects but with a more than 1600-fold increase in risk among HIV-seropositive subjects. HHV8 seroprevalence rates and antibody titers to HHV8 were not, however, markedly related to HIV infection among those without Kaposi’s sarcoma (Table 2).

Table 1. Relation of Kaposi’s sarcoma to fluorescent signal intensity (a measure of antibody titer) for HHV8, according to HIV serostatus

<table>
<thead>
<tr>
<th>Fluorescent signal intensity for HHV8 (and median titer)</th>
<th>No. with Kaposi’s sarcoma</th>
<th>No. without Kaposi’s sarcoma</th>
<th>Odds ratio† (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1-seronegative subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (&lt;1 : 100)</td>
<td>5</td>
<td>1990</td>
<td>1.0‡</td>
</tr>
<tr>
<td>Low (1 : 200)</td>
<td>2</td>
<td>665</td>
<td>1.5 (0.3–7.8)</td>
</tr>
<tr>
<td>Medium (1 : 51 200)</td>
<td>4</td>
<td>331</td>
<td>6.2 (1.6–24.2)</td>
</tr>
<tr>
<td>High (1 : 204 800)</td>
<td>2</td>
<td>131</td>
<td>12.0 (2.1–68.2)</td>
</tr>
<tr>
<td>Test for trend</td>
<td></td>
<td></td>
<td>$\chi^2 = 11.4; P = .0007$</td>
</tr>
<tr>
<td>HIV-1-seropositive subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (&lt;1 : 100)</td>
<td>5</td>
<td>105</td>
<td>10.8 (2.9–40.6)</td>
</tr>
<tr>
<td>Low (1 : 200)</td>
<td>2</td>
<td>31</td>
<td>48.1 (7.7–300)</td>
</tr>
<tr>
<td>Medium (1 : 51 200)</td>
<td>10</td>
<td>28</td>
<td>62.2 (18.0–214)</td>
</tr>
<tr>
<td>High (1 : 204 800)</td>
<td>21</td>
<td>8</td>
<td>1682 (390–7253)</td>
</tr>
<tr>
<td>Test for trend</td>
<td></td>
<td></td>
<td>$\chi^2 = 37.2; P &lt; .00001$</td>
</tr>
</tbody>
</table>

*HHV8 = human herpesvirus 8; HIV = human immunodeficiency virus.
†Adjusted for age, sex, and, where possible, education and number of sexual partners.
‡Comparison (referent) group.
Adapted from (23).

Table 2. Relation of HIV-1 serostatus to fluorescent signal intensity for HHV-8 in subjects without Kaposi’s sarcoma

<table>
<thead>
<tr>
<th>Fluorescent signal intensity for HHV8</th>
<th>HIV-1 seropositive</th>
<th>HIV-1 seronegative</th>
<th>Odds ratio† (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent (&lt;1 : 100)</td>
<td>105</td>
<td>1990</td>
<td>1.0‡</td>
</tr>
<tr>
<td>Low (1 : 200)</td>
<td>31</td>
<td>665</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>Medium (1 : 51 200)</td>
<td>28</td>
<td>331</td>
<td>2.0 (1.3–3.2)</td>
</tr>
<tr>
<td>High (1 : 204 800)</td>
<td>28</td>
<td>131</td>
<td>2.0 (0.9–4.4)</td>
</tr>
</tbody>
</table>

*HIV = human immunodeficiency virus; HHV8 = human herpesvirus 8.
†Odds ratio for HIV-1 seropositivity compared with HIV-1 seronegativity, adjusted for age, sex, education, and number of sexual partners.
‡Comparison (referent) group.
Adapted from (23).

The modes of transmission of HHV8 are yet to be fully elucidated. In the United States, sex between men may be an important route of transmission because this is the main behavioral risk factor for Kaposi’s sarcoma and indeed some evidence now exists that this is so (26). There is weak evidence of sexual transmission of HHV8 in the South African population, although the increase in risk with increasing number of sexual partners was not great (23). Furthermore, no difference was seen in the seroprevalence of HHV8 in those individuals with or without HIV infection. However, throughout sub-Saharan Africa, where Kaposi’s sarcoma was seen in children even before the advent of AIDS, other routes of transmission must also be occurring.

In three South African studies (23,27,28), the seroprevalence of HHV8 was relatively high compared with that in the United States and has been found to increase statistically significantly.
and steadily with age (from birth, through childhood, and into adult life) and to decrease with increasing level of education. In black hospital patients in Johannesburg and Soweto, the age- and sex-standardized seroprevalence of HHV8 was slightly more than 30%, compared with 20% in black blood donors and about 5% in white blood donors, and it did not vary by sex (23). In a rural South African (black) population, seroprevalence rates were even higher (27). These findings are echoed by those from elsewhere in Africa, where HHV8 seroprevalence is also high and has been found to increase with age, suggesting that the virus is not a newly introduced sexually transmitted infection in Africa, as it may be in the United States (29). Furthermore, the lower seroprevalence of HHV8 in whites than in blacks in South Africa and the decrease in seroprevalence with increasing education (23) might suggest that factors associated with poverty contribute to transmission of the virus.

The presence of anti-HHV8 antibodies in infants suggests that transmission of HHV8 from mother to child is likely (27). A study of South African mothers and their children found that about 30% of the children (<10 years old) of HHV8-seropositive mothers were themselves HHV8 seropositive, whereas none of the children of HHV8-seronegative mothers were themselves HHV8 seropositive (28). Furthermore, the proportion of children who were seropositive for HHV8 increased in relation to their mothers’ HHV8 antibody titer; although inconclusive, the data suggested that HHV8-seropositive mothers with high-titer infection may be about twice as likely to have HHV8-seropositive children as the mothers with low-titer infections (30). The steady increase in the prevalence of HHV8 infection throughout childhood suggests that transmission of the virus from person to person, via nonsexual routes, may also occur (27,29). A study in Uganda (29) showed that HHV8 seropositivity in children was strongly associated with the presence of antibodies to hepatitis B core antigen. Hepatitis B is known to be transmitted from person to person, and this may suggest a similar route for HHV8 (31).

**SUMMARY AND FUTURE RESEARCH**

Little doubt exists that HHV8 is responsible for most, if not all, cases of Kaposi’s sarcoma. However, many questions remain unanswered about the etiology of this tumor. Why, for example, is Kaposi’s sarcoma more common in men than in women in South Africa, when the prevalence of HHV8 is the same? The association between high anti-HHV8 antibody titers and risk of Kaposi’s sarcoma is clear, but it is not known if those antibody titers are persistently high, prior to the diagnosis of the tumor, nor is it known what the determinants of high antibody titer are. It is assumed that anti-HHV8 antibody titers reflect the viral load of HHV8, but little evidence exists for this assumption, and, for a given HHV8 titer, the exact mechanism by which HHV8 has such a dramatic impact on the risk of Kaposi’s sarcoma is not clear.

The association of HHV8 seropositivity with poor education and low social class in South Africa is in complete contrast to the risk factors for Kaposi’s sarcoma identified in studies from Uganda (32,33). The development of Kaposi’s sarcoma in HIV-seronegative and in HIV-seropositive individuals in Uganda is associated with markers of high social class, such as better education and wealth. Furthermore, despite the fact that HHV8 is very prevalent in Uganda, Kaposi’s sarcoma is a relatively uncommon manifestation of HIV disease, occurring in less than 7% of cases (10). The interpretation of these findings is difficult; however, if high social status protects an individual from early infection with HHV8, it could imply that the age at which infection occurs (or even the route of infection) affects the subsequent risk of Kaposi’s sarcoma. This hypothesis is reminiscent of the effect of infection in adult life with the Epstein-Barr virus (a closely related gamma herpesvirus) in relation to the risk of infectious mononucleosis.

Kaposi’s sarcoma is one outcome of infection with HHV8, both in HIV-seropositive and in HIV-seronegative adults and children. In children, it is possible that the tumor is a manifestation of primary infection with HHV8, although this is speculative; in adults, all of the available evidence suggests that Kaposi’s sarcoma occurs after primary infection (17). Almost no data are available on the clinical manifestations, if any, of primary infection with HHV8; therefore, there is no understanding of how important those manifestations might be in terms of morbidity. In a case report (34), transient angiolymphoid hyperplasia was found to occur as part of an HHV8 seroconversion syndrome in an HIV-infected adult. Nothing is known about the clinical manifestations of primary HHV8 infection in HIV-seropositive or HIV-seronegative children or in HIV-seronegative adults.

In South Africa, about a third of the children of HHV8-seropositive mothers are themselves HHV8 seropositive, but the determinants of transmission from an HHV8-seropositive mother to her child are unknown. Maternal anti-HHV8 antibody titers may be important and probably reflect the number of circulating HHV8-infected cells (i.e., the viral load), although this area needs clarification. The role of other factors, such as co-infection with HIV, maternal age at delivery, mode and place of delivery, and length of breast-feeding in relation to mother-to-child transmission of HHV8, remains to be investigated. It is not even known if HHV8 is present in breast milk, although it has been identified in saliva (35). Similarly, if person-to-person transmission occurs via nonsexual routes, other than from a mother to her child, little is known about the mechanism or possible outcomes of this transmission.

Incidence rates for Kaposi’s sarcoma in South Africa are rising rapidly, much as they did in Kampala at the beginning of the AIDS epidemic. Applying the age-specific incidence rate of Kaposi’s sarcoma, estimated from the Kampala Cancer Registry (10), to the South African black population would lead to an additional 8000 cases of Kaposi’s sarcoma in South Africa and an increase in the overall population lifetime risk (0–74 years) of developing a cancer from about 1 in 4 to 1 in 3.5 (12).

Finally, Kaposi’s sarcoma is being increasingly reported in HIV-seronegative homosexual men in New York and in HIV-seronegative children in Africa (36,37). If the recent spread of HIV in the South African population has also led to an increase in the spread of HHV8 infection, this spread may result in an increase in the incidence of Kaposi’s sarcoma even in people who are not infected with HIV.

**REFERENCES**

(4) Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical


NOTES

Presented at the International Symposium on HIV, Leukemia, and Opportunistic Cancers.

The South African Cancer Epidemiology Research Group is funded by the Medical Research Council of South Africa, the Cancer Association of South Africa, the South African Institute for Medical Research, the University of Witwatersrand, and the Imperial Cancer Research Fund (U.K.). The National Cancer Registry is also funded by the Department of Health. The U.K.-Cancer Epidemiology Unit is funded by the Imperial Cancer Research Fund (U.K.).