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Introduction

Kaposi's sarcoma (KS) is a cancer in which abnormal cells are found under the skin or mucous membranes that line the mouth, nose, and anus. It causes red or purple lesions to form, and can spread to other body organs such as the lungs, liver, or intestines. In addition to the sometimes-severe external disfigurements, KS can lead some of these internal organs to fail and has also been associated with an increased risk for other cancers.

In the earliest stages of the US AIDS epidemic, the purple lesions of Kaposi's Sarcoma (KS) became symbolic of the deadly transformations wrought by this mysterious new plague. Suddenly, a rare skin disease, previously seen only in a very limited number of Eastern European, Jewish, and African men, was showing up in gay men all over the United States. At a time when AIDS-related stigmatization was at its peak, the visible KS lesions forced many to either hide from public view or risk identification as a person with AIDS. For a community that places a heavy emphasis on body image, KS became one of the most personally devastating symptoms of AIDS among gay men. It was the "pox" of this new plague.

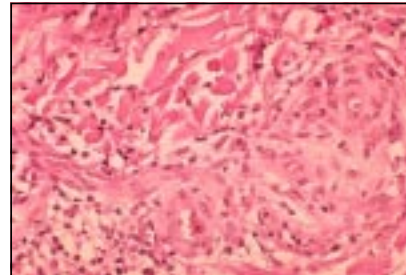


Figure 0: Early skin lesion of Kaposi's sarcoma (biopsy)
(Source: CDC)

Finding the cause of KS

After nearly two decades of increased research on KS and AIDS, the exact biological mechanism by which an associated human herpesvirus (HHV-8) causes KS is still not yet fully understood. There is, however, growing scientific consensus that KS is caused—at least in part—by HHV-8, first discovered in 1994. So strong is the association that HHV-8 is very often referred to as KSHV (KS-associated herpesvirus).

There is broad consensus in the scientific community that KSHV and KS are closely associated. Repeated analyses have demonstrated that certain genetic sequences unique to

KSHV are found with virtually every KS tumor. Put simply, you don't find KS without finding KSHV, though you can find KSHV in those who do not have KS.

This association was strengthened by improvements in testing methods for antibodies to KSHV. Initially, scientists faced many challenges in accurately assessing the prevalence of KSHV. One of the initial difficulties was isolating KSHV antibodies from antibodies for other similar viruses like Epstein-Barr Virus (EBV).

Another significant challenge was identifying an antigen that was clearly and uniquely related to KSHV. Various studies were published in 1996 and 1997 using different methodologies for identifying KSHV and measuring its prevalence in large groups. One series of studies looked at the presence of KSHV DNA in semen of different at-risk populations and found it in zero to 90% of samples—a range that offered little helpful information and highlighted instead the challenges of using highly sensitive laboratory technologies for wide-scale prevalence studies.

Other scientists, including several teams at UCSF, tried a different approach. Using a specific cell line known to harbor KSHV, they established methods for detecting KSHV-related antibodies in serum samples.

One team at UCSF identified a new assay using this cell line to grow KSHV-related antigens highly associated with the presence of KS. They found that all samples from persons with African KS and 96% from Americans with AIDS-associated KS were seropositive for this antigen. This was a remarkably strong correlation and represented a watershed in the understanding of KSHV. Because they also found no correlation between these KSHV antibodies and those detected for other similar viruses like EBV, these scientists now had an accurate and unique marker for KSHV infection that was relatively easy to detect in serum samples.

Other researchers studying the prevalence of KSHV built on the work of their colleagues using a similar serum testing method. Their test identifies the presence

of KSHV antibodies more closely associated with long-term infection (called LANA for latency-associated nuclear antigens). These antibodies are found in more than 80% of samples taken from persons with KS, but only 1-2% of HIV-negative blood donors (that more closely reflect the general population). Thus this test identifies an antibody that may be more closely associated with risk for the development of KS and not simply infection with KSHV.

Using this new serum testing method for antibodies to LANA, this team of scientists set out to determine anti-LANA prevalence among different

population groups. As expected, because these antibodies are more closely tied to disease risk, they found lower levels among groups not usually at risk for KS. Among HIV-negative blood donors (used to reflect prevalence in the general public), they found only 1-2% were positive by this new test. Among gay and bisexual men living with HIV, the team found 30% were positive. By contrast, only 2-4% of HIV-positive women and blood product recipients were positive for the antibodies to LANA. Because this mirrored the prevalence pattern of KS, scientists concluded that the distribution of KSHV infection by this test for antibodies mirrored the distribution of KS in developed countries. These data also demonstrates that KSHV, unlike many of the other forms of human herpesvirus, is not widely present in the general population but instead is limited to a rather small proportion.

KSHV (HHV-8) as a sexually transmitted infection

Another important conclusion from this and earlier studies was that KSHV, at least in Western and northern European countries, is largely a sexually transmitted infection. Among those living with HIV, the rates of response to the KSHV antibody tests—and ultimately the prevalence of KS itself—were consistently higher for gay men than those for blood product recipients. KS appears only rarely in HIV-negative gay men, so for Western KS, HIV disease clearly plays an important role.

Yet there had to be more to the explanation. Because the prevalence of KSHV (measured by the prevalence of antibodies) is much higher in gay men than in other groups with HIV disease, some additional factor must be involved. Scientists theorized the variation in prevalence was related to some sexual behavior in gay men that was transmitting the virus more frequently.

To test this hypothesis, UCSF researchers applied the test for antibodies to LANA to serum samples from participants in the San Francisco Men's Health Study. They looked at 400 HIV-positive and 400 HIV-negative men, testing for the prevalence of these antibodies and the time to development of KS. The researchers' findings strongly supported the hypothesis of a transmission mode for KSHV that put gay and bisexual men at increased risk of infection. Of the 593 gay and bisexual men who had been sexually active within the past five years, they found that 38% were positive for the antibodies to LANA. For the 195 that reported exclusively heterosexual activity, not a single one was positive.

In addition, the researchers confirmed the strong correlation between testing positive for the antibodies to LANA and the risk of KS. For those that were both HIV and KSHV positive at the start of the study, the probability of developing KS within 10 years was 50%. They also found that for sexually active gay and bisexual men, the likelihood of infection with KSHV correlated to the number of sexual partners.

Together, these studies strongly support the conclusion that KSHV is a cause of KS and is sexually transmitted. But is it the only cause? That question remains unanswered. Researchers were able to rule out a causative role for a second sexually transmitted agent. Attention turned instead to isolating the specific sexually transmission route that explains the significantly higher prevalence of KSHV and KS among HIV-positive gay and bisexual men.

To that end, UCSF researchers went back to the San Francisco Men's Health Study.

Table 1
Prevalence of Anti-LANA Antibodies

Men's Study ¹	
Gay and bisexual	38%
Heterosexual (exclusively)	0%
Women's Study ²	
HIV-positive or at high risk	3%
HIV-positive	4%
HIV-negative	1%
Other populations ³	
HIV-negative blood donors	1%
HIV-positive heterosexual hemophiliacs	2%
HIV-negative blood donors with syphilis	8%
HIV-negative, gay & bisexual blood donors	13%
HIV-positive, gay & bisexual blood donors	35%

¹Martin J, Ganem D, Osmond D, Page-Shafer K, Macrae D, Kedes D (1998)

²Kedes D, Ganem D, Ameli N, Bacchetti P, Greenblatt R (1997)

³Kedes D, Operskalski E, Busch M, Kohn R, Flood J, Ganem D (1996)

This time, they looked at the relationship between KSHV infection and specific sexual activities. Their sample included 26 HIV-positive and 53 HIV-negative men, about half of whom were at increased risk of sexually transmitted infections (reporting unsafe sex with more than one partner).

The researchers found that infection with KSHV was significantly associated with multiple homosexual contacts, and particularly with either receptive anal or oral intercourse with two or more partners. Significantly, all six subjects who reported neither receptive oral or anal intercourse within the previous year were KSHV-negative. The scientists concluded that homosexual exposure to seminal fluid via either the oral or anal route is highly associated with KSHV infection.

Yet further studies of various body fluids of persons with KS have found high levels of KSHV in saliva and at much lower levels in cervical and vaginal fluids and semen. UCSF researchers have confirmed the presence of KSHV in saliva and nasal secretions and are conducting further studies to determine whether the amounts found are infectious.

Non-sexual transmission

The non-sexual transmission of KSHV in western countries is rare, but KSHV (HHV-8) infection and KS do occur in children, in exclusively heterosexually active adults, and in immunosuppressed transplant recipients. Scientists have also identified the presence of infectious KSHV in at least one North American blood donor who did not fall into any of the known risk groups (gay or bisexually active, history of sexual transmitted diseases, multiple partners, etc.). Yet there is little evidence that blood donations, perinatal transmission, or heterosexual contact present risk for KSHV infection in western countries.

For non-Western KS, mother-to-child transmission of KSHV is a likely transmission route. Whereas KS in the west is almost always linked to sex between men, KS in Africa has been seen in children even before the advent of AIDS. Researchers in South African tested stored serum samples from 107 healthy mothers and 111 of their children for the presence of KSHV. They found that 16% of the mothers were KSHV-positive, as were 42% of their children. In contrast, only 1 of the 93 children with KSHV-

negative mothers was infected with KSHV (and this child was 14, suggesting the possibility of sexual transmission). They concluded that the mother-to-child transmission rate in this sample was 30% or greater. Further studies have been called for to better understand the risk and route of mother-to-child transmission of KSHV, and its implication for development of KS.

Work yet to be done

While impressive gains have been made in understanding the prevalence of KSHV in different populations and the likely risk behaviors that help it spread, many questions remain unanswered. Most scientists working in this field agree that (1) KSHV is a central player in the development of KS; and (2) that KSHV cannot by itself cause KS, but requires additional cofactors.

For western KS, these cofactors are immune deficiency; typically this is HIV-related, but in rare cases the forced immunosuppression required for organ transplantation can be a cofactor. Scientists also do not know why some people living with both HIV and KSHV infections do not develop KS.

For the HIV-negative African and Mediterranean KS, scientists have yet to discover the cofactors. Interestingly, some scientists seeking to understand the incidence pattern of KS among African children (which shows increasing prevalence with age) have suggested a possible transmission route. In many poor areas, mothers sometimes pre-chew food for young children. Since studies have shown high concentrations of KSHV in saliva, these scientists have postulated that the mothers may be unknowingly passing along the KSHV infection to their children with the chewed-up food. Research will be needed to confirm this theory.

In addition, study samples have not been adequately diverse to assess differences in prevalence by race, nor have they been able to fully explain differences by age, gender or mode of HIV transmission.

Finally, scientists will need do further study the differences in prevalence and disease progression by geographic area. Scientists have reported significant variations among those in developed and developing countries, and among North American, Caribbean, South American, and African populations but have yet to explain them.

KSHV and Antiretroviral Therapy

With the increased use of antiretroviral therapy (ART) to treat HIV, clinicians have seen up to a 70% decline in the incidence of KS. Earlier studies had shown some efficacy of certain drugs (especially gancyclovir and foscarnet) in treating KS, but much of that research has stopped because ART seems to significantly prevent this disease. As for those that may be unable to continue ART or for whom the benefits diminish, the future of Western KS remains uncertain.

Conclusion

While some of the outstanding questions regarding Western KS remain unanswered, much has been learned about the role of KSHV in the development of KS. Working together with its colleagues from around the world—including the many study volunteers who make all this research possible—UCSF will continue to strive for ways to prevent, treat, and cure Kaposi's sarcoma. Additional research to understand non-Western KS is needed to help identify more effective prevention and treatment strategies. While the problem may, at least for now, be reduced in the western nations, KS remains a global threat worthy of continued vigilance.

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Materials Available

For further information on KS:

- CancerNet, a service of the National Cancer Institute at the National Institutes of Health: <http://cancer.net.nci.nih.gov/>
- Project Inform offers helpful information through its national treatment hotline (800-822-7422) or on its web site: <http://www.projectinform.org>
- HIVInsite, a web site sponsored by UCSF: <http://hivinsite.ucsf.edu>
- The Kaposi's Sarcoma Resource Center, sponsored by the American Cancer Society, has a good deal of information about treatment of KS: <http://www.cancer.org>

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