Perhaps the greatest advance in the area of AIDS-related malignancies has been the identification of human herpesvirus-8 (HHV-8), also known as Kaposi’s sarcoma-associat-ed herpesvirus (KSHV). Since its discovery by Drs. Yuan Chang and Patrick Moore and their colleagues almost eight years ago, KSHV has been identified in virtually all AIDS- and non-AIDS-related KS lesions. At the same time, several research teams have identified the virus in a subset of other less common pathologic conditions, including primary effusion lymphomas (PEL) and multicentric Castleman’s disease (MCD). While a definitive link exists between KSHV and these specific malignancies, the precise role that it plays in their development is just now coming into focus.

This article is based on a PRN lecture delivered by Dr. Chang in November, 2001. In essence, it is a more focused update of an extensive review that originally appeared in the December 1999 issue of The PRN Notebook discussing KSHV, KS, and MCD, which can be easily accessed through the PRN website (http://www.prn.org). Information related to the approved and experimental treatments for KS, as highlighted by Drs. Susan Krown of Memorial Sloan-Kettering Cancer Center and Patrick Hennessey of New York University Medical Center, while not discussed in this article, can be found in the previously published summary.

**Background: KS and HIV**

Kaposi’s sarcoma (KS) was first described in 1872 by the Austro-Hungarian dermatologist Moritz Kaposi. He described five new cases of “idiopathic multiple pigmented [skin] sarcomas” of the lower extremities in elderly men (Kaposi, 1872). One patient died of gastrointestinal bleeding 15 months after the initial appearance of the skin lesions, and an autopsy showed visceral lesions in the lungs and the gastrointestinal tract. Subsequently, other investigators described four clinical variants of KS that had identical histologic features but developed in specific populations and had different sites of involvement and rates of progression.

Classic KS is characterized by indolent, purple-blue or reddish-brown skin lesions of the extremities seen in elderly white males of Ashkenazi or Mediterranean descent. While rarely fatal and slow in its progression—it can take years or decades for lesions to spread centrally from the hands and feet—approximately 10% of individuals with classic KS can go on to experience mucosal or systemic involvement.

Endemic KS, first described in 1934, typically involves African children and adults—usually males. There are two clinical types: cutaneous and lymphoproliferative. While most cases of endemic KS involve the cutaneous variety, tumors are more aggressive than the classic variety and are often associated with a poor prognosis. This is especially true of the lymphoproliferative type, with death usually occurring secondary to disease within two to three years.

There have also been numerous reports of KS occurring in patients receiving treatments for AIDS- and non-AIDS-related KS lesions. At its progression—it can take years or decades for lesions to spread centrally from the hands and feet—approximately 10% of individuals with classic KS can go on to experience mucosal or systemic involvement.

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**Summary**

The tree was derived by comparing the amino acid sequences of the major capsid protein gene. Kaposi’s sarcoma–associated herpesvirus/human herpesvirus 8 (KSHV; HHV-8) is a member of the subfamily of gammaherpesviruses, genus *Rhadinovirus*. EBV denotes Epstein–Barr virus, HHV-2 equine herpesvirus type 2, HSV herpesvirus saimiri, HSV-1 herpes simplex virus type 1, HSV-2 herpes simplex virus type 2, PRV pseudorabies virus, VZV varicella–zoster virus, HCMV human cytomegalovirus, HHV-6 human herpesvirus 6, and HHV-7 human herpesvirus 7.

TABLE 1. Patterns of Infection with KSHV and KS Among Persons without HIV

<table>
<thead>
<tr>
<th>Regions</th>
<th>Incidence of KS</th>
<th>Prevalence of KSHV</th>
<th>Route of Transmission</th>
<th>Groups at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, northern Europe, Asia</td>
<td>Low</td>
<td>0% to 5%</td>
<td>Sexual, iatrogenic</td>
<td>Men who have sex with men (MSM), those with STDS, transplant recipients</td>
</tr>
<tr>
<td>Mediterranean, Middle East, Caribbean</td>
<td>Intermediate</td>
<td>5% to 20%</td>
<td>Sexual, iatrogenic, nonsexual?</td>
<td>MSM, those with STDS, transplant recipients, older adults</td>
</tr>
<tr>
<td>Africa, parts of Amazon basin</td>
<td>High</td>
<td>&gt;50%</td>
<td>Nonsexual, sexual</td>
<td>Children, older adults, persons of low socioeconomic status</td>
</tr>
</tbody>
</table>


immunosuppressive drugs, mostly in the setting of organ transplantation to prevent rejection. This type of KS tends to be aggressive, involving lymph nodes, mucosa, and visceral organs in about half of patients, sometimes in the absence of skin lesions. Upon lowering or withdrawal of immunosuppressive therapy, however, lesions typically resolve, often completely.

Epidemic, or AIDS-associated, KS was first documented by Dr. Alvin Friedman-Kien—a longtime PRN member—and colleagues in what has come to be known as the world’s first official report of what would soon be called AIDS (Friedman-Kien, 1981). Additional reports established that AIDS-associated KS affected gay and bisexual men with HIV-related immune-suppression 20 times as frequently as it did male patients with hemophilia and AIDS. Although the incidence of KS, at least in the United States, has decreased dramatically in recent years, it remains the most common of all the AIDS-related cancers.

KSHV and KS

A number of microorganisms have been indicted over the years as the causative agent of KS. These include cytomegalovirus (which was proposed as the pathogen responsible for endemic KS in Africa); hepatitis B virus; human herpesvirus 6 (HHV-6); human papillomavirus 16 (HPV-16); Mycoplasma penetrans; HIV itself (most notably the HIV transactivation gene [tat]); and a furiously debated suspect, amyl nitrates (poppers). Countless studies attempted to isolate these pathogens in KS lesions, most of which were unpersuasive at best.

In 1994, the tide turned with the discovery of sequences of two small fragments of DNA in an AIDS KS lesion, which was reported in a landmark issue of Science by Dr. Chang and her dedicated team (Chang, 1994). The nucleotide sequence of these two fragments shared homology with genes of the minor capsid and tegument proteins of two known gamma-herpesviruses, the Epstein-Barr virus (EBV) and herpesvirus saimiri (see Figure 1). This finding led to the identification of a new human herpesvirus, which has now come to be known, descriptively, as KSHV, and formally, as HHV-8.

In 1995, two additional studies published in the New England Journal of Medicine and Nature Medicine went on to confirm the presence of KSHV in virtually all AIDS-related KS tissues and, in most cases, non-AIDS-related KS specimens, including those collected from African individuals (Moore, 1995; Schallling, 1995).

Serologic assays for HIV-8 antibodies are now used to test for the presence of the virus, bypassing the need for contamination-prone PCR-based techniques. The assays depend on cell lines derived from body cavity-based primary effusion lymphomas, which are infected with up to 100 copies of the virus and are a rich source of a viral latency-associated nuclear antigen (LANA). Studies using LANA seroassays have found that KSHV-specific antibodies are detectable in 70% to 90% of all patients with KS and almost 100% of immuno competent patients with the disease. “In AIDS-related KS,” Dr. Chang explained, “there is a lower LANA positivity rate as measured by existing seroassays, probably due to decreased antibody production in patients with late-stage HIV disease.”

Epidemiology of KSHV

Results of serologic studies show that, unlike other human herpesviruses, KSHV is not ubiquitous. Instead, the infection rate appears to correlate with the risk of KS within different populations, including those with different geographical regions of the world (see Table 1). The rates of KSHV infection in the general population of Mediterranean countries (e.g., Italy, Greece, Israel, Saudi Arabia) are typically between 5% and 20%, where classic KS is seen with relatively high frequency. Lower rates of KSHV seropositivity are seen among general populations of the United States, northern Europe, and throughout Asia. In Japan, for example, the seroprevalence of KSHV among blood donors is approximately 0.2%, where KS is rare (Fuji, 1999). In contrast, high KSHV seroprevalence—in excess of 50%—has been reported in various African cohorts, including those in Uganda (Gao, 1996), Zambia (Olsen, 1998), and South Africa (Sitas, 1999).

Irrespective of geography, there are certain at-risk populations with particularly high KSHV seroprevalence rates (see Table 2). In HIV-negative blood donors in the United States, KSHV seropositivity rates have been estimated to be between 1% and 2%, compared to prevalence rates in excess of 30% in gay and bisexual men, regardless of their HIV serostatus (Martin, 1998). The KSHV seropositivity rate among HIV-positive hemophiliacs or transfusion recipients, on the other hand, has been reported to be only 2% to 3%. Similarly, only 3% to 4% of HIV-positive heterosexual women participating in the Women’s Interagency HIV Study were KSHV-positive (Kedes, 1997).

The concordance of positive KSHV
TABLE 2. Patterns of Infection with KSHV Among Persons with and without HIV: Risk-Factor Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Francisco Men’s Health Study (Martin, 1998)</td>
<td></td>
</tr>
<tr>
<td>Gay and bisexual</td>
<td>38%</td>
</tr>
<tr>
<td>Heterosexual (exclusively)</td>
<td>0%</td>
</tr>
<tr>
<td>Women’s Interagency HIV Study (Kedes, 1997)</td>
<td>HIV-positive or at high risk</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>4%</td>
</tr>
<tr>
<td>HIV-negative</td>
<td>1%</td>
</tr>
<tr>
<td>Other Populations (Kedes, 1996)</td>
<td>HIV-negative blood donors</td>
</tr>
<tr>
<td>HIV-positive heterosexual hemophiliacs</td>
<td>HIV-negative blood donors with syphilis</td>
</tr>
<tr>
<td>HIV-negative</td>
<td>8%</td>
</tr>
<tr>
<td>HIV-positive, gay and bisexual blood donors</td>
<td>13%</td>
</tr>
<tr>
<td>HIV-positive, gay and bisexual blood donors</td>
<td>35%</td>
</tr>
</tbody>
</table>


higher titers in saliva (Koelle, 1997; Vieira, 1997). To help make sense of this, Dr. Chang discussed a study conducted by Dr. John Pauk and his colleagues of the University of Washington in Seattle, which was designed to determine the mode of transmission and to identify risk factors in two groups of gay and bisexual men without KS (Pauk, 2000).

In the first group, Dr. Pauk’s team collected mucosal, PBMC, seminal, anal, and prostatic fluid samples and tested them for KSHV using quantitative PCR and in situ assays. His team detected KSHV in mucosal samples from 30/50 (60%) gay and bisexual men with mixed HIV serostatuses who were seropositive for KSHV. KSHV shedding was found in 30% of oropharyngeal samples, but in just 1% of anal and genital samples (P<0.001). Levels of KSHV were 2.5 times greater in secretions of the oral cavity than in all other sites. The buccal mucosa had the highest titers in the mouth.

To identify risk factors for KSHV infection, Dr. Pauk’s team analyzed a second group of 92 men, 26 of whom were HIV-8 seropositive; only HIV-negative men were included in this analysis, as HIV-related immunosuppression may confound risk factors for the acquisition of HIV-8. Risk factors included older age; a greater number of sexual partners, particularly partners who were HIV-positive; a history of sexually transmitted diseases, especially herpes simplex virus type 2; deep kissing; and the use of poppers.

While these data suggest that KSHV may be acquired by oral-oral contact and, quite possibly, the use of saliva as a sexual lubricant, important questions regarding the transmission of KSHV still remain. Why, for example, is KSHV infection in North America mainly restricted to gay and bisexual men? The observation that KSHV is not ubiquitous among all populations suggests that it may not be easily transmitted and that acquisition may depend on the degree of exposure to infected persons, especially to those who are immunocompromised. Alternatively, there may be unidentified cofactors that greatly increase either the shedding of infectious virus in KSHV-positive persons or the risk of infection in uninfected persons. “Until there is a better understanding of the mechanisms of KSHV transmission,” states Dr. Pauk’s team in its New England Journal of Medicine article, “it will be difficult to define the most effective approach to prevention.”

The Etiology and Pathogenesis of KSHV

There is still a great deal to be learned about the mechanism(s) by which KSHV leads to the development of KS lesions. Essentially, two schools of thought have come to dominate the field. The first hypothesis postulates that KSHV plays a crucial role in creating the necessary microenvironment for lesion development through autocrine and paracrine mechanisms. The second hypothesis holds that KSHV is more directly involved, particularly in the transformation of normal cells into malignant ones.

It is likely that KS begins as a hyperplastic proliferation mediated by growth factors and angiogenic factors, which, under certain conditions, becomes a true malignancy—a highly vascularized cell mass—...
The entire coding region is flanked by terminal-repeat sequences (hatched boxes). The gene encodes numerous proteins that are homologous to cell-signaling and regulatory-pathway proteins found in human cells (solid boxes) and that are unique to KSHV and related rhadinoviruses. The proteins encoded include viral complement-binding protein (vCBP), viral interleukin-6 (vIL-6), viral macrophage inflammatory protein type 1 (vMIP1) and type II (vMIP2), viral Bcl-2 (vBcl-2), viral interferon regulatory factor (vIRF), viral cyclin (vCYC), latency-associated nuclear antigen (LANA), viral adhesin (vADH), G-protein-coupled receptor (vGCR), dihydrolate reductase (DHFR), thymidylate synthase (TS), thymidine kinase (TK), and ribonucleotide reductase (RR). Stippled boxes indicate regions that are homologous to those of other herpesviruses. T1.1 and TO.7 denote nonhomologous open reading frames with undetermined activities.


FIGURE 2. The KSHV Genome

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oncogenic gene expression or the autocrine/paracrine mechanisms responsible for tumor formation and proliferation. At the present time, it is generally believed that immune suppression—whether it’s tied to HIV infection (e.g., epidemic KS), the use of immunosuppressive therapy (e.g., KS in transplant recipients), aging (e.g., classic KS), or poverty (e.g., endemic KS)—is the necessary cofactor for KS virus to unleash its opportunistic streak.

**Conclusion**

Although several outstanding questions regarding the natural history and pathogenesis of KS virus have yet to be answered, a great deal has been learned about the role of this wily virus in the development of KS, PEL, and MCD. Now that some of the key pieces of the puzzle have been found and put into place, it is hoped that research into the treatment and prevention—including a possible vaccine—of KS virus-related malignancies will get under way. “KS is obviously less of a problem in the developed world than it was before HAART became available,” Dr. Chang said. “But we still have a significant problem in other parts of the world and it’s not clear what we’ll be seeing here in the future.” It is precisely because of these uncertainties that the pathogenesis and medical management of KS must remain a research priority.

**References**


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**FIGURE 3. KSHV Proteins That Interact with the Tumor-Suppressor Pathways Governed by Retinoblastoma Protein and p53**

The viral interferon regulatory factor prevents interferon from repressing c-myc. FLICE denotes Fas-associated death domain—like interleukin-1β-converting enzyme. Red arrows indicate an inhibitory effect.