And then there were eight ...

In the 22 years following the discovery of the Epstein-Barr virus (EBV) in 1964 (1), five human herpesviruses were known: herpes simplex type 1, herpes simplex type 2, varicella zoster virus, cytomegalovirus and EBV. In 1986, Salahuddin et al (2) reported the isolation of a novel herpesvirus from peripheral blood leukocytes of six individuals. Because of the tropism of this new virus for B lymphocytes, the virus was initially called human B lymphotropic virus but was subsequently named human herpesvirus-6 (HHV-6). As with the five previously recognized human herpesviruses, the seroprevalence of antibodies to HHV-6 was found to be very common (3). Shortly thereafter, Yamanishi et al (4) demonstrated that HHV-6 was the long-sought cause of roseola infantum, also known as exanthema subitum. Further studies have demonstrated that most episodes of HHV-6 infection are not manifest clinically as roseola infantum, but rather as an undifferentiated febrile illness in children under the age of three years, many of whom are given a clinical diagnosis of otitis media (5,6). HHV-6 may also cause heterophile-negative infectious mononucleosis (7). Just as the five previously recognized human herpesviruses are capable of causing more severe disease in individuals with impaired cell-mediated immunity, it is not surprising that there have been several reports of life-threatening HHV-6 infection in immunocompromised patients, particularly in those who have undergone bone marrow transplantation (8,9).

In 1990, Frenkel et al (10) isolated a new herpesvirus from peripheral blood mononuclear cells of a healthy individual. This new herpesvirus is known as human herpesvirus-7 (HHV-7). HHV-7 is a ubiquitous virus against which antibodies develop in early childhood in a majority of individuals (11). Although the site of shedding of HHV-7 is known to be saliva (12), HHV-7 is still considered to be a virus in search of a natural reservoir. Recently, Asano et al (13) described a roseola-like illness in a 13-month-old boy in association with the isolation of HHV-7, seroconversion to HHV-7 and previously documented HHV-6 roseola.

The newest addition to the human herpes family, tentatively called human herpesvirus-8 (HHV-8), was initially reported by Chang et al (14) in December 1994 when she and her colleagues identified herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma (KS) tissue. Although this virus has not yet been cultured, its sequences are homologous to, but distinct from, genes of the gammaherpesvirinae, herpesvirus saimiri and EBV (14). Subsequently, this research team and others have confirmed the detection of HHV-8 sequences in nearly all samples of KS, whether from persons with AIDS, human immunodeficiency virus (HIV)-seronegative homosexual men, HIV-seronegative individuals with classic KS, HIV-seronegative individuals with endemic KS or immunosuppressed organ transplant recipients. It is virtually never detected in skin samples from healthy individuals without KS (15-21).

The finding of an infectious agent in KS tissue is not surprising. It has long been observed that KS occurs much more frequently among those who acquire HIV infection sexually than among those who acquire HIV infection parenterally (22). Among men who have sex with men, the risk of developing KS was shown to correlate with the number of sexual contacts during 1978 to 1982 in San Francisco, Los Angeles and/or New York in one cohort (23), and with the frequency of insertive oral-anal contact in another (24). It is also not surprising that a human herpesvirus can play an important role in malignancy in AIDS patients. It is well established that seroprevalence data for HHV-8 are not currently available. If HHV-8 is similar to other human herpesviruses, one would speculate that there is a high seroprevalence of HHV-8 and that immunosuppression is a major trigger for reactivation to clinically recognizable disease (29).

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HHV-8 has also been strongly associated with body cavity-based lymphomas (pleural, pericardial or peritoneal lymphomatous effusions) in both HIV-infected individuals (30) and an HIV-negative individual (31). In addition, HHV-8 DNA sequences have been demonstrated in basal cell carcinomas,
cutaneous squamous cell carcinomas, actinic keratoses, verruca vulgaris, seborrhoeic keratoses and atypical squamous proliferations in organ transplant recipients (32).

It remains to be determined whether HHV-8 actually causes KS or is an innocent bystander (33). The recognition that HHV-8 is the probable cause of KS raises the possibility that KS could be prevented or treated by antiviral therapy. Glesby et al (34) analyzed data from 135 homosexual men with AIDS from the Multicenter AIDS Cohort Study and found no evidence that acyclovir reduced the risk of developing KS. However, they found that both intravenous ganciclovir and foscarnet were associated with an approximately 50% reduction in risk of KS, although the difference was not statistically significant for either drug. There are no data to indicate whether prophylactic oral ganciclovir has an effect on preventing KS.

While a causal relationship has not been definitively proven, the available data are consistent with a causal role for HHV-8 in KS and possibly for body cavity-based lymphomas. If a causal relationship is confirmed, it is possible that future antiviral strategies could reduce the risk of developing KS.

REFERENCES


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