Crazy 8: Unraveling Human Herpesvirus 8 Seroprevalence

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(See the article by Chen et al. on pages 1052–8)

The most beautiful thing we can experience is the mysterious.
Albert Einstein

The eighth and most recently discovered human herpesvirus was first detected in proliferating lymphatic endothelial cells of the skin tumor known as Kaposi sarcoma (KS) [1]. Since then, this virus, which is now known both as human herpesvirus 8 (HHV-8) and KS-related herpesvirus (KSHV), has been detected in a number of other sites, including malignant B cells of AIDS-associated primary effusion lymphoma (PEL), occasional large B cells in the plasma cell variant of Castleman disease, peripheral blood B cells and monocytes in patients with KS, and saliva specimens obtained from patients with AIDS [2–7].

Unlike most infectious agents, herpesviruses maintain an asymptomatic persistent latent infection in the host following primary infection. Lifelong persistence of virus is accompanied by lifelong persistence of both humoral and cellular antiviral immunity. Serologic detection of herpesvirus antibodies has proved to be of immense value not only in the diagnosis of primary infection, but also for determination of the prevalence of infection in various population groups. The high rates of adult seropositivity reported from various regions of the world indicate that most herpesvirus infections are highly prevalent and not geographically restricted. In an early landmark study, Lennette et al. [8], using an indirect immunofluorescence assay (IFA) for detection of both latent and lytic viral antigens, reported HHV-8 seroprevalence in the general adult population from the San Francisco area of ∼25%. In contrast, other early studies of HHV-8 seroprevalence that used an IFA for detection of antibody to latency-associated nuclear antigen (LANA) indicated that infection was highly restricted to a few specific groups at high risk for development of KS, such as HIV-infected homosexual males and adults from regions of KS endemicity [9–11]. Although the theory that HHV-8 infection is sexually transmitted was consistent with the high seropositivity noted in homosexual males, it was inconsistent with the high seropositivity in older heterosexual Mediterranean men and young African children. Evidence in support of an oral route of transmission was subsequently provided by studies in which saliva specimens obtained from patients with AIDS were shown to contain HHV-8 [6, 7]. Although these findings provided an alternative mechanism for virus spread in groups other than homosexual males, the low seroprevalence in regions of the world in which KS is not endemic reported in early studies that used the LANA assay was puzzling. One explanation that was offered was that HHV-8 had only recently spread to regions of nonendemicity via the HIV epidemic. However, because all other human herpesviruses are ubiquitous in their worldwide distribution, this explanation was not entirely convincing.

Determination of viral seroprevalence is highly dependent on the characteristics of the assay that is used. Great care must be taken to select an assay that is not only highly specific but also highly sensitive. High sensitivity is particularly important when the assay is used to determine seroprevalence in healthy populations in which antibody titers from past exposure may be quite low. HHV-8 serological analysis was originally performed with an anti-LANA IFA by means of AIDS-associated PEL cell lines that were latently infected with HHV-8 and adapted to cell culture [9–11]. The LANA assay revealed an HHV-8 seroprevalence of 2%–27% (median, 10%) in 6 studies of adult blood...
donors from KS-endemic regions [12–17] and 0%–15% (median, 4%) in 10 studies of adult blood donors from regions in which KS is not endemic [15,18–26].

Because of low titers of LANA antibody in many healthy HIV-negative persons with HHV-8 infection, the LANA IFA may not be ideal for determination of HHV-8 seroprevalence in these groups [27]. For this reason, more-sensitive assays for detection of antibodies to virus lytic antigens have been employed. Because only 10%–20% of the cells in most PEL cell lines normally express lytic antigens, PEL cells may be cultured for a few days with the tumor promoter TPA to induce lytic antigen expression in a majority of the cells. The lytic IFA assay revealed an HHV-8 seroprevalence of 23%–29% in 3 studies of healthy US blood donors [8, 20, 28]. In 5 studies, a direct comparison of LANA and lytic IFA results for HIV-negative adults was reported [12, 15, 20, 23, 25]. As expected, seroprevalence determined with the lytic assay was significantly higher than that determined with the LANA assay in all 5 studies, with LANA IFA seroprevalences of <1%–5% and lytic IFA seroprevalences of 16%–28%. Thus, it seems that HHV-8 infection in healthy adults from regions in which KS is not endemic is much more common than was originally suspected and is likely spread not only by sexual means, but by nonsexual means as well.

In this issue, Chen et al. [29] report on HHV-8 seroprevalence in northern Thailand, a region notable for a very low incidence of KS despite a relatively high incidence of HIV/AIDS, and lend further support to the related concepts that HHV-8 infection is not uncommon in HIV-negative adults in regions of the world in which KS is not endemic and that transmission of HHV-8 often occurs by nonsexual means. Using a sensitive lytic IFA, Chen et al. [29] report an overall HHV-8 seroprevalence among 400 HIV-negative men and women of 20.5%, a result that is remarkably similar to those described elsewhere for US blood donors [8, 20, 28].

Perhaps the most curious result in this report is the finding that HHV-8 seroprevalence among HIV-negative female subjects (23.8%) is significantly higher than that among HIV-negative male subjects (13%). Not only is this intriguing result difficult to explain, but it contrasts with results of studies involving HIV-negative US blood donors, in which no sex-based difference in seroprevalence were noted [20, 30]. Another interesting finding reported by Chen et al. [29] is the lack of correlation between the relatively high incidence of HIV/AIDS and HHV-8 infection and the very low incidence of KS. As the authors suggest, it is very likely that there are unrecognized cofactors involved in KS pathogenesis that have yet to be accounted for. The issues brought forth by the results of Chen et al. [29] are important and only further deepen the mystery of the complex relationship between HHV-8 and KS. We certainly have much more to learn from this peculiar herpesvirus.

References
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