

Herpes virus type 8 and interstitial lung disease with

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What is known about human herpes virus type 8?

John M. Routes: Human Herpesvirus Type 8 (HHV8) is a γ -herpes virus also known as Kaposi's Sarcoma Associated Virus that is closely related to the Epstein-Barr Virus. In the absence of immunodeficiency, primary infection with HHV8 is usually self-limited. In contrast, in patients with impaired cellular immune responses, such as infection with HIV-1 or iatrogenic immunosuppression, HHV8 infection is an important, opportunistic pathogen. HHV8 is linked to the development of Kaposi's Sarcoma and lymphoproliferative diseases such as primary effusion lymphoma and Castleman's disease (1).

Epidemiologic studies indicate that the prevalence of HHV8 infection varies by geographic location and is influenced by behavioral risk factors. In the United States, antibodies to the HHV8 antigens are present in approximately 33% of homosexual men without KS, 8% of HIV-1 uninfected patients attending STD clinics and 0.1-3% of HIV-1 uninfected blood donors (1). In countries where the prevalence of HHV8 infection is low such as the United States, infection is thought to be primarily through sexual intercourse. In contrast, in countries where HHV8 infection is endemic, saliva is likely the most common mode of spread (1).

How is the diagnosis of the primary immunodeficiency, common variable immunodeficiency (CVID) made?

John M. Routes: Common variable immunodeficiency (CVID) is a primary immunodeficiency of unknown etiology. CVID is characterized by low levels of serum immunoglobulin G (IgG) and an inability to make specific antibodies in response to exogenous antigens (2). The diagnosis of CVID is made in the context of hypogammaglobulinemia and the exclusion of other B cell disorders. Unlike X-linked agammaglobulinemia (XLA), which is caused by mutations within the B cell specific Btk gene leading to a pure B cell disorder, CVID is not a distinct disease entity but rather a clinical syndrome with protean manifestations. T lymphocyte

abnormalities are somewhat common and are hypothesized to contribute to the increased incidence neoplastic diseases seen in these patients.

Patients with CVID are predisposed to infection particularly those involving the respiratory tract and gastrointestinal tract (2). Treatment with high dose gamma-globulin coupled with aggressive antimicrobial therapy has dramatically reduced the prevalence, morbidity and mortality associated with bacterial infection in CVID. Presently, the major causes of death in patients with CVID include progressive lung disease and malignancies, in particular B cell lymphomas(2).

Why does HHV8 preferentially infect patients with CVID?

John M. Routes: Based on observations in patients with infected with HIV-1 and HHV8 CD4⁺ T cells are a critical host defence against the virus. To date, there are no systematic studies examining the prevalence of HHV8 infection in patients with primary immunodeficiencies. However, there are case reports documenting HHV8 infection in

patients with diverse primary immunodeficiencies including DiGeorge Syndrome, interferon- γ -r1 deficiency and perforin deficiency. The CVID patients infected with HHV8 exhibit CD4 lymphopenia. We hypothesize that the combination of antibody deficiency and T cell dysfunction predispose patients with CVID to infection with HHV8.

How does HHV8 infection cause interstitial lung disease (ILD) in patients with CVID?

John M. Routes: The molecular mechanisms whereby HHV8 infection causes ILD in patients with CVID is unknown. However, studies on the closely related murine γ -herpesvirus, MHV68, provides insight into this issue. Recent studies indicate that the wood mouse is the natural host for MHV68 and the lung is the predominant site of viral infection and latency (3). Interestingly, the lung pathology found in MHV68-infected wood

mice closely mimics the lung pathology found in HHV8 infected patients with CVID (4,5). Mora *et al.* demonstrated that chronic MHV68 infection of IFN γ receptor-deficient mice resulted in progressive interstitial lung disease (pulmonary fibrosis) (6). Progressive pulmonary fibrosis is a major cause of death in CVID patients with ILD. Therefore, MHV68 may provide an important tool to understand HHV8-induced human disease.

How does HHV8 cause human malignancies?

John M. Routes: Although other mechanisms are undoubtedly involved, the current paradigm for HHV8 induced oncogenesis is similar to the molecular mechanisms that small DNA tumor viruses use to transform cells. HHV8 encodes a viral cyclin (v-cyclin) that functions in concert with other cellular cyclins to phosphorylate the tumor suppressor protein, pRb, thereby activating the transcription factor E2F and abrogating the G1/S cell cycle checkpoint. Activation of the E2F pathway also increases

the transcription of the tumor suppressor gene, p53. p53 induces the transcription of genes that induce cell cycle arrest and cellular apoptosis, providing an important cellular checkpoint to the dysregulated activation of E2F. However, HHV8 encodes two proteins (LANA-1, LANA-2) that block p53 function and inhibit p53-mediated apoptosis. Thus, HHV8 promote cellular transformation by inducing cellular proliferation and inhibiting p53 function

Is there an effective antiviral therapy against HHV8?

John M. Routes: Unfortunately, there is no effective antiviral therapy at the present time.

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