Prevalence of Human Herpesvirus 8 Infection Measured by Antibodies to a Latent Nuclear Antigen in Patients With Various Dermatologic Diseases

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Background: Human herpesvirus 8 (HHV-8) has been detected in all epidemiological forms of Kaposi sarcoma (KS). The role of HHV-8 in dermatologic diseases other than KS is controversial. Some studies based on polymerase chain reaction findings suggest an association between HHV-8 and epithelial tumors of the skin, lymphoproliferative disorders, or pemphigus.

Objective: To assess the prevalence of antibodies against a latent nuclear antigen of HHV-8 in patients with various dermatologic diseases.

Design: An indirect immunofluorescence assay was used to search for HHV-8 antibodies.

Setting: Ambulatory or hospitalized patients from a university hospital associated with a research laboratory.

Patients: Eighty-three patients with various non-KS dermatologic diseases and 16 patients with KS who were seronegative for the human immunodeficiency virus. Controls were 100 healthy subjects living in the same area.

Results: Antibodies to HHV-8 were found in 100% (16/16) of the patients with KS and 3.6% (3/83) of the patients with non-KS dermatologic diseases: 1 patient with pemphigus vulgaris, 1 with discoid lupus erythematosus, and 1 with bullous pemphigoid. The prevalence of antibodies to HHV-8 in controls was 2% (2/100) and was not significantly different than the prevalence in patients with dermatologic diseases other than KS (P = .28).

Conclusions: Our serologic study confirms the higher prevalence of HHV-8 antibodies in patients with KS and demonstrates that contrary to other human herpesviruses, HHV-8 is not a ubiquitous virus in France. We could not determine any causal association between HHV-8 and pemphigus or lymphoproliferative disorders of the skin.

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Kaposi sarcoma (KS)—associated herpesvirus, also known as human herpesvirus 8 (HHV-8), is consistently found in all epidemiological forms of KS. Human herpesvirus 8 genomes are present in endothelial and spindle cells, the histological hallmark of KS. The frequency of detection of HHV-8 in other dermatologic diseases is controversial. Some authors report that HHV-8 may be found in other dermatologic diseases, such as epithelial tumors, cutaneous T-cell lymphoma, or pemphigus vulgaris, and that HHV-8 could be a widespread virus reactivated in some tumoral or immunological conditions. However, we and others have not confirmed the presence of HHV-8 in lymphoproliferative disorders of the skin or in epithelial tumors either in immunocompetent or immunosuppressed patients. Such discrepancies could reflect the variation of the distribution of HHV-8 infection by geographical area. Some serologic study results suggest that, at least in western countries, HHV-8 infection is largely confined to individuals with or at risk for KS. However, one study of antilytic HHV-8 antibodies suggests that the prevalence of HHV-8 could be as high as 25% in the general population in the United States. Nevertheless, using an antilytic assay cross-reactive against other human herpesviruses, notably Epstein-Barr virus (HHV-4), could lead to an overestimation of the prevalence of HHV-8 antibodies. The aim of our study was to assess the prevalence of antibodies against a latent nuclear antigen of HHV-8 in patients with various cutaneous diseases and to compare it with the prevalence in patients with KS and in healthy control subjects.

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PATIENTS AND METHODS

Serum samples were collected from 83 patients with various dermatologic diseases: cutaneous T-cell lymphoma (n = 17), pseudolymphoma (n = 4), B-cell lymphoma (n = 1), anaplastic T-cell lymphoma (n = 1), malignant melanoma (n = 5), discoid lupus erythematosus (n = 6), psoriasis (n = 8), pemphigus (n = 13, including 4 with pemphigus foliaceus and 9 with pemphigus vulgaris), vasculitis (n = 5), erythema multiforme (n = 4), bullous pemphigoid (n = 11), and other dermatologic diseases (urticaria [n = 2], pruritus [n = 2], erythema nodosum [n = 2], cutaneous sarcoidosis [n = 1], and morphea [n = 1]). We also studied serum samples from 14 patients with classic KS, including 2 homosexual patients with KS who were seronegative for the human immunodeficiency virus (HIV) and 3 partners of patients with KS: 1 HIV-negative homosexual man whose partner was an HIV-negative homosexual man with stage I KS and 2 HIV-negative partners of 2 patients with stage I classic KS. Serum samples were collected at the patient’s first visit or before the initiation of immunosuppressive therapy, except in 4 patients with autoimmune bullous diseases who were undergoing therapy with prednisone at a low level (5-20 mg/d). The samples were stored at −80°C until needed for processing. Serum samples from 100 healthy subjects served as controls.

Antibodies to a latent nuclear antigen (LNA-1) of HHV-8 were searched for using an immunofluorescence assay on a primary effusion cell line (BCP-1) latently infected with HHV-8 but not with the Epstein-Barr virus. The immunofluorescence assay was performed as previously described. Briefly, BCP-1 cells were fixed in 4% paraformaldehyde, rendered permeable with detergent (0.2% Triton X-100, Sigma-Aldrich, Dorset, England), incubated with human sera (1:100) for 30 minutes at room temperature, washed in a combined solution of phosphate-buffered saline and 3% fetal calf serum, incubated for 30 minutes with anti-human IgG–fluorescein isothiocyanate conjugate (Dako, Carpinteria, Calif), and then washed again and examined using fluorescence microscopy.

RESULTS

Antibodies to HHV-8 were found in the serum samples of all 14 patients with classic KS and in the 2 HIV-negative homosexual patients with KS. Antibodies to HHV-8 were also found in the serum samples of 3 tested partners of patients with KS. Serum samples of 2 (2%) of the 100 controls were found to be positive for HHV-8. Among the patients with dermatologic diseases, the prevalence of antibodies to HHV-8 was as follows: 0 (0%) of 23 patients with lymphoproliferative disorders of the skin, 0 (0%) of 5 patients with malignant melanoma, 1 (16%) of 6 patients with discoid lupus erythematosus, 0 (0%) of 8 patients with psoriasis, 1 (7%) of 13 patients with pemphigus, 0 (0%) of 5 patients with vasculitis, 0 (0%) of 4 patients with erythema multiforme, 1 (9%) of 11 patients with bullous pemphigoid, and 0 (0%) of the 8 patients with other dermatologic diseases. The prevalence of antibodies to HHV-8 in patients with dermatologic diseases other than KS was not statistically different than the prevalence in controls (3.6% vs 2%, respectively; Fisher exact test, P = .28).

COMMENT

Our study was based on results of an immunofluorescence assay that detects antibodies against a latent nuclear antigen of HHV-8. This is the most sensitive and specific serologic assay available for determining past or present infection with this virus. The same serologic assay has enabled researchers to establish a strong correlation between HHV-8 infection and KS, to identify populations at risk for KS, and to question the pathogenic role of HHV-8 in multiple myeloma.10,17 Our results confirm that, in the area of Paris, France, HHV-8 is not a ubiquitous virus and is largely confined to patients with KS. The prevalence of antibodies to HHV-8 that we found in patients with KS is similar to the prevalence previously reported in such patients.12-15 Moreover, serologic studies provide explicit and confirmatory epidemiological data about HHV-8: the link between all epidemiological forms of KS and HHV-8; the preferential sexual transmission of this agent as suggested by a high prevalence in populations exposed to sexually transmitted diseases (eg, syphilis or HIV); and the restricted distribution in the general population in western countries and a higher prevalence in African countries.12-15 Thus, serologic assays give the best indication of prevalence of HHV-8. According to the findings of our serologic assay, the implication of HHV-8 in dermatologic diseases other than KS, such as cutaneous lymphoma or pemphigus, is uncommon. Previous studies based on findings of polymerase chain reaction suggest that HHV-8 could be implicated in the pathogenesis of epithelial tumors of the skin. However, these results have not been confirmed by other reports.7,8 Concerning the role of HHV-8 in lymphoproliferative disorders of the skin, one study reported the presence of HHV-8 DNA sequences in 7 of 48 cutaneous T-cell lymphomas, including 2 cases of mycosis fungoides, 2 peripheral T-cell lymphomas, 2 cases of parapsoriasis en plaque, and 1 lymphomatoid papulosis.4 These results were not confirmed in following studies, suggesting that HHV-8 is not directly implicated in the pathogenesis of either cutaneous T-cell or B-cell lymphoma.4,11 Results of our serologic study confirm the absence of any direct or indirect role of HHV-8 in the pathogenesis of lymphoproliferative disorders of the skin.

The role of HHV-8 in pemphigus vulgaris has been suspected in one case.5 Recently, HHV-8 DNA sequences were detected in 4 of 6 skin lesions from patients with pemphigus vulgaris and in all 6 skin lesions from patients with pemphigus foliaceus.18 These findings could not be explained by a cross-contamination of DNA according to the DNA sequencing analysis, and these results contrast with our own, which suggest that there is no link between HHV-8 and...
pemphigus. However, some argue that such discrepancies could result from the variation of the geographical distribution of HHV-8 infection. However, contrary to KS, which is associated with HHV-8 regardless of the patient’s geographical origin, we could not determine any causative role of HHV-8 in pemphigus. Moreover, the presence of HHV-8 DNA sequences does not unambiguously signify that HHV-8 is directly implicated in the pathogenesis of pemphigus. In fact, this result could be explained by the presence of these sequences in the patients’ peripheral blood mononuclear cells, which could have contaminated the skin samples. This hypothesis needs to be explored by further studies that compare HHV-8 DNA load in both lesional skin and normal skin in the same patient and include an evaluation of the presence of HHV-8 viremia.

The prevalence of antibodies to HHV-8 reported herein in healthy controls and in patients with non-KS dermatologic diseases is similar to the prevalence previously reported in the general population in western countries.12,13 Thus, our study reinforces the hypothesis of a link between HHV-8 and KS. Moreover, the fact that 3 partners of 3 different patients with KS were found to be seropositive for HHV-8 suggests that this virus could be sexually transmitted, as recently reported.19

In conclusion, using an immunofluorescence assay, we detected antibodies to a latent nuclear antigen of HHV-8, suggesting that contrary to other human herpesviruses, HHV-8 is not a widespread virus in France and that HHV-8 infection is limited to patients with or at risk for KS. Thus, we maintain that, HHV-8 is not involved in the pathogenesis of lymphoproliferative disorders of the skin or pemphigus.

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