Pityriasis Rosea Is Not Associated With Human Herpesvirus 7

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Objective: To examine the proposed association between pityriasis rosea and human herpesvirus 7 (HHV-7).

Design: A retrospective cross-sectional survey.

Setting: University medical center in Switzerland.

Patients: Thirteen patients with pityriasis rosea and 14 persons with normal skin (control subjects).

Main Outcome Measures: Detection of HHV-7–specific DNA sequences and antigen (85-kd phosphoprotein [pp85]) by nested polymerase chain reaction and immunohistochemical analysis, respectively.

Results: Human herpesvirus 7 DNA sequences and expression of the HHV-7–specific immunodominant pp85 antigen were found in 1 (8%) of 13 lesional skin biopsy specimens of pityriasis rosea. The prevalence of HHV-7 DNA sequences and antigens is even slightly lower in lesional skin of patients with pityriasis rosea than in clinically and morphologically normal skin of 14 control persons, in 2 of whom (14%) HHV-7 DNA sequences and antigens could be detected.

Conclusion: The low detection rate of HHV-7 DNA sequences and antigens argues strongly against a causative role for HHV-7 in the pathogenesis of pityriasis rosea.

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PARTICIPANTS AND METHODS

We examined 13 skin biopsy specimens of PR lesions (including 4 herald patches) from 13 patients with clinically and histologically proven PR and specimens of histologically normal skin from 14 subjects undergoing plastic surgery. In all cases, the diagnosis of PR was based on a consideration of clinical and histological features. Of 13 patients with PR, 12 showed the typical clinical manifestation, with the development of multiple patchy erythematous and scaling skin lesions within days or as much as 2 weeks after the occurrence of a primary plaque. The spontaneous resolution of the lesions within 2 months was observed in all patients. Only 1 patient presented with an atypical manifestation of multiple papular lesions, but the lesions showed histologically typical features of PR and regressed spontaneously after 6 weeks. The histological features of all specimens were compatible with the diagnosis of PR. The median age of patients with PR was 25.8 years (age range, 17-49 years), whereas the median age of the control subjects was 24.3 years (age range, 16-44 years).

On histological examination, all PR lesions showed spongiosis, focal parakeratosis, and some dyskeratotic cells of the epidermis and a mixed perivascular inflammatory infiltrate in the upper dermis. The median time between the onset of the disease and a skin biopsy was 9.3 days (range, 2-17 days). The tissue specimens were routinely fixed in 10% buffered formalin and embedded in paraffin. Informed consent was obtained from all patients. Blood specimens were not available for the evaluation of viral presence in serum or PBMCs.

POLYMERASE CHAIN REACTION

DNA was extracted by proteinase K digestion according to standard procedures as previously described. To avoid contamination and product carryover, the microtome blade was cleaned with xylene after each cut, and DNA extraction, PCR, and gel electrophoresis were done in separate laboratories. Successful amplification of a β-globin phosphoprotein encoded by the U14 gene of HHV-7 and is suitable for detecting HHV-7 in archival, formalin-embedded tissues. Because it is directed to a structural component of the virion, reactivity is indicative of active viral infection.

RESULTS

DETECTION OF HHV-7 DNA SEQUENCES

Human herpesvirus 7 DNA sequences were detected in only 1 (8%) of the 13 PR skin biopsy specimens by nested PCR (Figure) and in 2 (14%) of 14 specimens of normal skin. All specimens contained amplifiable β-globin sequences. We note that the prevalence of HHV-7 in normal skin specimens in the present study is lower than that reported previously (63%). The major difference in the 2 groups of specimens relates to the location of the biopsy specimens, which were collected from various body areas of both male and female persons in the present study, in contrast to the use in a previous study of pectoral skin biopsy specimens from women undergoing breast reduction.

IMMUNOHISTOCHEMICAL TECHNIQUE

For immunohistochemical study, we used the monoclonal antibody Mab5E1, which is directed against a phosphorylated protein (85-kd phosphoprotein [pp85]) of the virion tegument of HHV-7. The sensitivity of the amplified products was determined to be about 1 × 10^3-ng DNA by serial 10-fold dilutions of the amplifier of the first PCR, followed by the second nested PCR and analysis by agarose gel electrophoresis. The specificity of the amplified products was confirmed by direct sequence analysis (data not shown).

EXPRESSION OF HHV-7–SPECIFIC ANTIGENS

The expression of HHV-7–specific antigen was detected only in the PR skin biopsy specimens that contained the viral DNA sequences and in 1 of 2 specimens of normal skin harboring the HHV-7 DNA sequence. In all cases, the cells expressing HHV-7 viral antigen pp85 were perivascular cells. Based on morphologic features, the cells expressing HHV-7 antigen represent mononuclear inflammatory cells such as lymphocytes and histiocytes.

COMMENT

Human herpesvirus 7 DNA sequences and cells infected with HHV-7 are present in lesional skin specimens of patients with PR and in clinically and histologically normal skin specimens of healthy persons at comparable levels (1 of 13 persons and 2 of 14 persons, respectively) and with an overall low incidence. The reliability of our experimental approach stems from the findings that PCR and immunohistochemical analysis concordantly detected HHV-7 in the same specimens—those with disease and specimens of normal skin. Current
results sharply contrast with those of Drago et al, who found HHV-7 DNA sequences in all skin and PBMC specimens analyzed and in plasma specimens from patients with PR at a higher frequency than from healthy persons.

The reasons for the discrepancy are unclear. Whereas in our study, authenticity of the PCR data was provided by sequencing of the amplified fragments and was substantiated by immunohistochemical analysis, PCR was the only analytic technique used in the preceding study. So whether DNA sequences other than those of HHV-7 were amplified cannot be excluded, in particular because skin specimens of healthy persons were not investigated as negative controls and, furthermore, because PCR amplification products were not sequenced. The PCR is well known to produce false-positive results due to contamination. Recently, in a PCR-based study on the presence of human herpesvirus-8, contamination occurred even in circumstances in which the control experiments did not indicate contamination of investigated specimens. In the preceding study, the presence of HHV-7 in cell-free plasma specimens from patients with PR was interpreted to support a causal relationship. In our study, plasma and PBMC specimens were not available for the detection of viral sequences. For a pathogenetic association between HHV-7 and PR, however, the virus is expected to be present in the lesions. Given that in our study, HHV-7 DNA and antigens were not detected in PR specimens at a frequency compatible with a pathogenetic association, the presence of viral DNA in plasma or in PBMCs would have been indicative only of viral replication at sites other than those involved by the disease under examination rather than of a causal relationship. Alternative explanations for the presence of viral DNA in serum are conceivable. Thus, HHV-7 reactivation may be the consequence of a transient immunodepressive state, as is often observed with herpesviruses. For example, herpes labialis and herpes zoster lesions are frequently observed as a consequence of reactivation of herpes simplex and varicella-zoster viruses in persons with immunodepressive states.

Conclusions

Inasmuch as a consistency of findings from different groups of investigators is crucial to demonstrate a causal association between an infectious agent and a disease, current results argue strongly against a causative role for HHV-7 in the pathogenesis of PR.

Since the manuscript was submitted for publication, we became aware of a study reported by Yasukawa et al. In addition, anti-HHV-7 IgG levels in the serum of patients with PR were not higher than that of normal control subjects. These data confirm our findings and do not support a causal association of HHV-7 and PR.

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