Association of pityriasis rosea with Human Herpesvirus-6

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Background: Pityriasis rosea (PR) is a common papulosquamous skin disorder that is suspected to have an infectious etiology. We aimed to study the role of human herpesvirus-6 (HHV-6) in the pathogenesis of PR.

Method: We used immunohistochemical (IHC) assays to detect HHV-6 in patients with PR. Fifty-one patients with PR and 35 age and sex matched healthy control samples were enrolled in the study. The intensity and percentage of cell staining for HHV-6 infection were evaluated and recorded.

Result: The intensity of IHC staining was negative in 25 (49.01%) patients and 24 (68.58%) control samples while it was +1 in 6 (11.77%) patients and 11 (31.42%) control samples, +2 in 4 (7.85%) patients and +3 in 16 (31.37%) of them. The incidence of moderate and intense staining for HHV-6 was significantly higher among patients with PR than the control group (P value < 0.01).

Conclusion: We concluded that HHV-6 infection may play a role in some patients with PR. The rate of HHV-6 infection was significantly higher in PR patients than the control group.

Keywords: human herpes virus-6 (HHV-6), immunohistochemistry, pityriasis rosea

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INTRODUCTION

Pityriasis rosea (PR) is a common skin disorder with a self-limited papulosquamous presentation. The spontaneous regression of skin changes are seen within 6-12 weeks without any therapy [1]. The association of some prodromal symptoms (fatigue, headache, vomiting, and diarrhea), clustering in families, and occurrence in the spring and fall suggest a viral pathogenesis for PR [2-5]. Various infectious agents have been considered as the cause of PR. Although the etiology of PR is still not known, viral agents may be a culprit [6].

Human herpesvirus-6 (HHV-6) and HHV-7 were discovered during the last three decades. There are some controversial results on the detection of HHV-6 and HHV-7 in PR [1].

Viral DNA has been found in blood mononuclear cells and in 80-100% of the involved skin of pityriasis rosea patients. HHV-7 is found with higher prevalence than HHV-6 but both viruses exist [7,8]. HHV-6 or HHV-7 is found in 10-40% of the control group. This shows that these viruses do not always lead to clinical disease. The presence of these viruses has not been confirmed in some studies [9,10] and a definite relationship has not been demonstrated in others [11]. Because of these controversial results, we aimed to investigate the role of HHV-6 in PR patients in this study.

PATIENTS & METHODS

This cross-sectional descriptive-analysis study was performed on patients with pityriasis rosea

who attended the Dermatology Clinic of Ghaem Hospital, Mashhad, Iran, in a 9-month period. The relationship between HHV-6 and pityriasis rosea was evaluated in these patients.

Patients with a clinical diagnosis of PR entered the trial. All patients were visited by one expert dermatologist and a skin biopsy was also obtained. The study was approved by the Ethics Committee of the Faculty of Medicine before the trial started, and all patients signed written informed consent. After histological confirmation of PR, the patients were enrolled in the trial on the basis of histopathology inclusion criteria which included a combination of the following criteria: focal parakeratosis, decreased granular layer, irregular acanthosis, exocytosis, and superficial perivascular infiltration of mononuclear cells. Immunohistochemical (IHC) assays were used to determine viral infection in the epidermis and papillary dermis cells. Then, the intensity and percentage of cell staining were evaluated and recorded. Thereafter, viral infection was investigated by immunohistochemical assays in the control group taken from nonspecific skin biopsy samples (which were taken from the pathology department archive). The Novo Castra protocol of staining was used for IHC assays. Pathologic studies of samples were carried out by one expert pathologist. The results were recorded according to the intensity and percentage of cell staining as the following:

Lack of staining was considered as negative or trivial staining scored as +1 while moderate and intense staining (+2 and +3) was regarded as positive. According to the percentage of cells stained, they were divided in 4 groups: 0-25%, 25-50%, 50-75%, and more than 75% staining. Statistical analysis was done using T-test and Mann-Whitney test.

RESULTS

Fifty-one patients with pityriasis rosea and 35 healthy control samples from free margins of excised melanocytic nevus and also psoriatic patients were evaluated for HHV-6 infection. Two groups were matched in terms of sex and age. The intensity of IHC staining was +1 in 6 (11.77%) patients and 11 (31.42%) control samples. It was +2 in 4 (7.85%) PR patients and +3 in 16 (31.37%) of them while it was negative in 25 (49.01%) patients and 24 (68.58%) control samples. The incidence of moderate and intense staining for HHV-6 was significantly higher among PR patients than the control group (P value < 0.01, Table1). The percentage of IHC staining was between 0-25% in 4 patients with PR and 11 control samples while 5 patients showed 25-50% staining. Also, 6 patients with PR presented 50-75% of staining and finally, the percentage of staining was more than 75% in 11 (21.57%) patients. The percentage of staining for HHV-6 was considerably higher in PR patients than the control group (P< 0.01, Table1).

DISCUSSION

In 2005, Broccolo et al measured the DNA load of HHV-6 and HHV-7 in the plasma, peripheral blood mononuclear cells, and tissue by the PCR method. Also, specific antigens of these viruses were evaluated in the skin tissue using IHC. In this study, the load of HHV-7 DNA but not HHV-6 was higher in PR patients than the control group. These two viruses were detected only in the skin of PR patients. The data indicates a clear association between PR and active HHV-7 infection and to lesser extent with HHV-6 infection [12]. According

Table 1. Comparison between control and pityriasis rosea patients regarding IHC percentage and intensity of staining for HHV-6 virus

	Control group	Pityriasis rosea group
IHC percentage of staining for HHV-6		
%0	24 (68.58%)	25 (49.01%)
1-25%	11 (31.42%)	4 (7.85%)
25-50%	0	5 (9.8%)
50-75%	0	6 (11.77%)
>75%	0	11 (21.57%)
IHC intensity of staining for HHV-6		
Negative	24 (68.58%)	25 (49.01%)
+	11 (31.42%)	6 (11.77%)
++	0	4 (7.85%)
+++	0	16 (31.37%)

to this article, there is evidence for an infectious etiology in this disease including its distinctive clinical course, lack of recurrence in many patients, clustering of disease which supports an infectious cause, seasonal occurrence, association with respiratory tract infections, low socioeconomic status of the patients, and a history of previous contact with PR patients in some patients [13].

In 2006, Drago et al evaluated the efficacy of acyclovir in PR patients considering that acyclovir is effective against HHV-6 and HHV-7. They noticed that acyclovir might be effective in the treatment of PR, especially in patients treated in the first week from the onset when the replicative viral activity of HHV is probably very high [14]. In 2011, Rassai et al conducted a similar study but they used low dose acyclovir compared to the previous study. They also found acyclovir to be effective in reducing the duration of the lesions of PR even at low doses [15].

In another study performed by Watanabe et al, nested PCR was used to detect HHV-6, HHV-7, and CMV DNA in the lesional skin, healthy skin, peripheral blood mononuclear cells, serum, and saliva. Control samples were obtained from healthy people and psoriatic patients. Samples of the patients were positive in more than 80% of the cases while the control samples were rarely positive. This study showed that PR was associated with systemic HHV-6 and HHV-7 infections [16]. In 2009, Canpolat Kirac found a relationship between HHV-6 and HHV-7 infection and PR disease [17]. In the current study, 26 PR patients and 11 control samples had positive IHC staining for HHV-6; the rate of positivity was significantly higher in PR patients than the control group. This finding approves the results of the previous study and shows high rate of HHV-6 infection in PR patients in comparison with healthy controls. In 2002, a study conducted in Turkey showed that the incidence of HHV-7 infection in PR patients was 28.57% [18]. In another study done in 2004 from Turkey, blood samples of 35 patients with acute PR and 30 healthy volunteers were evaluated for HHV-6 and HHV-7 antibody titers. Anti HHV-6 and HHV-7 IgG antibodies were detected using indirect fluorescent antibody (IFA) test. No significant relationship was found between PR and HHV-6 or HHV-7 but the authors agreed that the acute phase timing of sample collection was an important problem in detection of herpes viruses and HHV-7 infection could be hidden from serologic tests [1]. Chuh et al did not detect any evidence of HHV-6 or HHV-7 infection in 15 PR patients using the plasma PCR method [19]. In three separate studies performed by Kosuge et al, Kempf et al, and Wong et al, no evidence of HHV-6 or HHV-7 infection was found in PR patients [20-22]. Moreover, no association was detected between PR and HHV-7 or HHV-8 infection in another study in 2006 [23].

As mentioned earlier, different studies have evaluated the association of HHV-6 and 7 infections in PR patients. Some studies have showed positive results while others failed to confirm any association. This may be related to different methods of virus detection or sampling at different stages of the disease. Our study showed the higher incidence of HHV-6 in PR patients than the control group but we still believe that future studies with larger sample sizes and more accurate methods of virus detection are required to clarify the exact role of these viruses in this common disease. If a definitive association is found, appropriate antiviral medications can be used to treat patients with more severe or protracted forms of the disease.

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