ASSOCIATION OF PITYRIASIS ROSEA WITH HUMAN HERPESVIRUS-6 AND HUMAN HERPESVIRUS-7 IN TAIPEI

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Pityriasis rosea (PR) is prevalent worldwide, irrespective of climate or race. It has been estimated to account for 0.3 to 4.8% of dermatologic outpatient visits [1, 2]. Most epidemiologic data on PR have been obtained from western populations, and little information is available for Asian populations. PR is an acute, self-limited inflammatory disorder that most commonly affects otherwise healthy children and young adults [3]. PR typically begins with a herald patch, a solitary expanding oval pink scaly plaque (Fig. 1A), and then secondary eruptions appear in groups over the next 10 to 14 days (Fig. 1B) [3]. Since the initial description of PR as a separate clinical entity by Gilbert in 1860 [as referenced in 4], the existence of an infectious origin has received occasional consideration [4–10]. However, the etiology of the disease is still unknown. Several epidemiologic and clinical features, including seasonal variation in incidence, clustering of cases, recent upper respiratory tract infection, household concurrences, and increased rate in dermatologists suggests a possible viral etiology [11–14]. Previous studies have excluded a link between PR and picornavirus or parvovirus B19 [6, 7]. Although human herpesvirus-6 and -7 (HHV-6 and HHV-7) have been suggested as causative agents of PR [5, 15], no definitive evidence has been found. In this study, the clinical features of PR patients from two hospitals in northern Taiwan were studied. The association between HHV-6 and HHV-7 and PR was assessed using polymerase chain reaction (PCR) of skin biopsy specimens.
Patients and Methods

Patients with PR treated at the Departments of Dermatology of Chang Gung Memorial Hospital in Taipei or Taoyuan were enrolled in the study between April 1999 and March 2000. In all cases, the diagnosis of PR was made by a dermatologist based on clinical features of typical pink scaly oval patches arranged in a Christmas-tree like pattern and was further supported by histopathologic findings of hyperkeratosis, focal parakeratosis, acanthosis, exocytosis, spongiosis, and perivascular mononuclear cell infiltrates in the upper dermis (Fig. 2). Clinical characteristics were studied and skin biopsies were taken during the acute stage of the illness (within 2 weeks after onset). Data on demographic characteristics, seasonal variation, occurrence of a herald patch, disease duration, recent upper respiratory tract infection, and household concurrences were collected. Skin biopsy specimens from PR lesions of 24 patients were obtained. The specimen was taken by an incisional biopsy from the center of an individual oval PR lesion to peripheral normal skin. The specimen was then divided into two parts. The central...
portion was processed for viral culture and PCR, while the peripheral part was taken for pathologic evaluation. Blood samples from these 24 PR patients were subjected to Veneral Disease Research Laboratory (VDRL) test. Skin biopsy specimens from age- and sex-matched controls with other dermatoses were also subjected to PCR study.

Skin specimens were ground and suspended in 200 µL lysis buffer (NaCl 75 mM, EDTA 25 mM, pH 8.0) and 20 mL proteinase K (20 mg/mL; QIAGEN, Hilden, Germany). The mixture was incubated at 56°C overnight. DNA was extracted using the QIamp® viral RNA mini kit according to the manufacturer’s instructions (QIAGEN).

The sequences of the HHV-6 primers were 5’-GTGTTTCCATTGRACGAAACCGGT-3’ and 5’-TAAACATCAATGGGTTGCATACAGT-3’. The sequences of the HHV-7 primers were 5’-TAT-CCGAGCTTTTCATATAGTAAC-3’ and 5’-GCC-TTGCGGTAGCACTAGATTTTTG-3’ [16]. The thermocycling procedure (Thermal Cycler 9600, Perkin-Elmer Cetus, Norwalk, CT, USA) consisted of initial denaturation at 94°C for 2 minutes, 30 cycles of denaturation at 94°C for 1 minute, annealing at 60°C for 45 seconds, extension at 72°C for 2 minutes, and final extension at 72°C for 2 minutes. HHV-6 and HHV-7 positive control DNA was obtained by DNA extraction of HHV-6 strain U1102-infected T-cells and the HHV-7 infected SupT1 cell line. PCR products were visualized under ultraviolet light after electrophoresis on 1% agarose gels containing ethidium bromide.

Results

A total of 41 PR patients, 11 males and 30 females (ratio 1:2.7), were included in the study. Their ages ranged from 8 to 62 years with a peak (17/41) in the 20 to 29 years age group (Fig. 3A). PR was seen all year round but episodes peaked during the spring season (March–May, 18/41) (Fig. 3B). About one-quarter of patients reported a history of upper respiratory tract infection such as runny nose, sore throat, or cough shortly before or during the occurrence of the rash. Only one household concurrence within the same family was noted. A history of recurrent PR was reported by two patients. A herald patch was observed in eight patients, usually on the trunk or shoulder. Eruptions resolved within 12 weeks in 33 patients, but prolonged cases of up to 6 months were also noted (2 patients). All VDRL tests were negative.

Among the 20 controls (5 males, 15 females), there were 10 with melanocytic nevus, three with blue nevus, two with seborrheic keratosis, and one each with dermatofibroma, hemangioma, epidermal inclusion cyst, and nodular fasciitis.

Discussion

Epidemiologic studies on PR in the USA, Turkey, Nigeria, and Singapore as well as the present study have shown
similar demographic characteristics among PR patients (Table 1) [2, 17–19]. Most studies showed an equal or a slight female predominance, though a male preponderance was reported in the study from Singapore [19]. Our study found a higher prevalence in females (female:male, 2.7:1) than in previous studies. Our patients were enrolled into the study when they were seen at the outpatient clinic, rather than selected randomly from the general population of patients with PR. The higher incidence of PR in females may have been due to the fact that most PR lesions are asymptomatic and that female patients tend to be more aware of skin changes on their bodies, thus leading a greater percentage of female patients with PR to seek medical help. Study of a larger sample of patients is needed for a more accurate determination of gender prevalence. The peak age group in the present study was 20 to 29 years, which agrees with most reports that children and young adults are the most frequently affected group. The incidence of PR episodes in the present study peaked during the spring months. Several studies have reported that PR episodes are most frequent during the spring and fall seasons [2, 18]. A history of upper respiratory tract infection preceding or during the occurrence of the rash was reported in 11 of our 41 patients. This finding is similar to results from studies in Singapore and Rochester, Minnesota, where 25% and 21% of the patients had upper respiratory infection shortly before the onset of PR [17, 19].

Although many epidemiologic and clinical features suggest a viral etiology for PR, confirmatory results for this hypothesis have not been reported despite several studies on this topic (Table 2). Studies that support a viral etiology have reported the observation of cytopathic effects on cells co-cultured with PR skin lesions [20, 21], the presence of viral particles or viral-like particles in electron microscopic studies of PR skin lesions [9, 22, 23], and the identification of viral DNA in PR skin lesions by PCR analysis [5, 15, 24]. Possible causative roles for picorna virus, adenovirus, influenza virus A, influenza virus B, parainfluenza 1, 2, or 3 virus, and parvovirus B19 were all excluded by serologic studies, in situ hybridization, or PCR analysis [6, 7, 25].

HHV-6 and HHV-7, two newly identified members of the family herpesviridae, have been reported as causative agents in PR. As with other herpesviruses, they may cause a primary infection, establish latent infection in a specific set of cells of their host, and then reactivate if conditions of altered immunity develop. Primary HHV-6 and HHV-7 infection may present as exanthem subitum in children [26, 27]. HHV-6 genome was detected in peripheral blood mononuclear cells (PBMCs) from six of 14 PR patients and was suggested to be associated with PR [15]. The possibility of a causative role for HHV-7 in PR was reported in 1997 by Drago et al [5]. Using PCR analysis, they identified HHV-7 DNA in plasma, PBMCs, and skin biopsy specimens from 12 PR patients. In addition, a cytopathic effect in co-cultured PBMCs and HHV7-like particles in the supernatant of co-cultured PBMCs were noted [5]. However, subsequent studies could not confirm these results [15, 28–31], and thus the causative role of HHV-7 remains controversial. The explanation for inconsistent results from studies of HHV-6 and HHV-7 infection in PR skin specimens may be the reactivation of various severities in patients with diverse immunity profiles.

In the present study, HHV-6 and HHV-7 DNA levels were below the limit of detection in all skin biopsy specimens from PR patients and from healthy control

![Detection of human herpesvirus-7 by polymerase chain reaction (PCR).](image)

**Fig. 5.** Detection of human herpesvirus-7 by polymerase chain reaction (PCR). PCR products were subjected to electrophoresis on 2% agarose gel and stained with ethidium bromide. A) Lane M, size marker; lane (+), positive control; lanes 1–20, sample from PR patients; lane (-), negative control. B) Lane M, size marker; lane (+), positive control; lanes 1–20, samples from control individuals.

### Table 1. Summary of epidemiologic studies of pityriasis rosea in different populations

<table>
<thead>
<tr>
<th>Area</th>
<th>N</th>
<th>Duration</th>
<th>Male:Female</th>
<th>Peak age</th>
<th>Peak months</th>
<th>Herald patch</th>
<th>Recent URI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minnesota, USA [17]</td>
<td>939</td>
<td>10 years</td>
<td>1:1.8</td>
<td>20–24</td>
<td>December–February</td>
<td>NM</td>
<td>21%</td>
</tr>
<tr>
<td>EA, Turkey [18]</td>
<td>391</td>
<td>3 years</td>
<td>1:1.2</td>
<td>20–29</td>
<td>October–February</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Singapore [19]</td>
<td>368</td>
<td>1 year</td>
<td>1:2.1</td>
<td>20–29</td>
<td>Evenly distributed</td>
<td>17.1%</td>
<td>25%</td>
</tr>
<tr>
<td>Taipei, Taiwan [19]</td>
<td>41</td>
<td>1 year</td>
<td>1:2.7</td>
<td>20–29</td>
<td>March–May</td>
<td>8/41</td>
<td>26.8%</td>
</tr>
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URI = upper respiratory tract infection; NM = not mentioned; EA = Eastern Anatolia.

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individuals. Although failure to detect a virus in a tissue does not establish that the disease is not associated with that virus, our data does not lend support to a possible role for HHV-6 and HHV-7 in the pathogenesis of PR. Since HHV-7 is cytopathic for CD4 T-cells, its sequence can be found in PBMCs of 80% of healthy individuals who harbor the virus in a latent form [32, 33]. It has been suggested that the detection of HHV-7 DNA in PBMCs indicates infection, although neither its activity nor its causal role in diseases such as PR or exanthem subitum has been substantiated [5, 33, 34]. However, the cell-free viral DNA in body fluids such as plasma represents a productive infection [5, 34]. Regrettably, we failed to collect patients’ plasma for PCR study. The etiology of PR is likely to be heterogeneous and not caused by a single infectious agent. Additional study is needed to confirm the pathogenic role of HHV-6 and HHV-7 in PR and the possible etiologic role of other viruses in PR.

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References