Persistent Pityriasis Rosea: An Unusual Form of Pityriasis Rosea with Persistent Active HHV-6 and HHV-7 Infection

Francesco Drago, Francesco Broccolo, Giulia Ciccarese, Alfredo Rebora, Aurora Parodi

Introduction

Pityriasis rosea (PR) is an acute, self-limiting exanthematous disease associated with the reactivation of the human herpesvirus 6 (HHV-6) and/or human herpesvirus 7 (HHV-7), whose overall incidence is estimated to be 0.68% in dermatological patients. PR usually lasts 6–8 weeks, although durations as short as 2 weeks have also been reported. A persistent form of PR has been reported only in 1 patient so far. Here, we report on 12 patients in whom the features of PR lasted longer than 12 weeks, defining this form of the disease as persistent PR (PPR). As in typical PR, in most of the PPR patients the disease begins with a herald patch, but compared to typical PR, systemic symptoms and oral lesions are more common. Moreover, in PPR we found a persistent reactivation of HHV-6 and/or HHV-7 with higher viral loads than in typical PR, accounting for the unusual persistence of the illness, the more frequent and severer systemic symptoms and the oral lesions. In conclusion, we describe an unusual persistent form of PR, whose prevalence has probably been underestimated so far and which should be added to the other variants of PR.

Methods

Twelve patients with PPR (i.e. 2.0%), were selected from our series of 585 PR patients recruited between 2003 and 2013 at the Department of Dermatology, University of Genoa. They were 8 females and 4 males aged between 21 and 37 years (median age: 30.08 years). They were bloodsampled for specific anti-HHV-6 and anti-HHV-7 serology at their first visit, at the follow-up and after recovery. Both the HHV-6 and the HHV-7 DNA loads were assessed in 32 blood samples using a calibrated quantitative real-time PCR as previously described.

Results

Clinical Features

The typical herald patch, or mother patch, with slightly elevated scaling borders and central resolution was found on the trunk or lower/upper limbs of 9 patients (75%). The mean time lapse between herald patch and generalized eruption was 13 days. The skin eruption was characterized by oval erythematous-squamous lesions of the trunk and limbs with a typical Christmas tree distribution (fig. 1) in all but 3 patients (cases 2, 3 and 7) who presented a generalized distribution of the lesions without the herald patch. Therefore, a skin biopsy was performed in these patients, and the histological examination showed mild acanthosis, focal parakeratosis and spongiosis in the epidermis with extravasated red blood cells and a perivascular infiltrate of lymphocytes in the upper dermis, confirming the diagnosis of PR. The duration of the exanthem...
Eleven patients (92%) complained of systemic symptoms during the course of their PPR, with different degrees of severity and duration. In all patients but one, the symptoms were severe from the prodromal phase up to the clearance of the exanthem, and even longer than that in patients 3, 5, 10 and 12 (table 1). Of these symptoms, fatigue was the commonest (in all patients but one, 92%), and in 3 cases it was so severe that it compelled these patients to discontinue their occupation. Other symptoms were headache, insomnia, irritability and difficulty to concentrate. Oral lesions were present in 9 patients (75%), namely strawberry tongue, erythematous macules, vesicular lesions (fig. 2) and petechiae (fig. 3).

Serology

Laboratory investigations yielded results that were all within normal limits, and the venereal disease research laboratory results were negative in all serum samples. IgG antibodies to HHV-6 and HHV-7 were present in all patients with a titer that ranged between 1:20 and 1:80 for HHV-6 and between 1:20 and 1:320 for HHV-7; 2 patients also had IgM antibodies to HHV-6 and 2 to HHV-7 (table 1). In the patients with IgM, the IgG antibody titer was not reduced by a denaturing agent, proving that these were high-avidity antibodies synthesized during a past or recurrent infection. In all cases, IgM antibodies became negative after the full recovery of the patients.

Viral Load of HHV-6 and HHV-7 in Blood Samples

The cell-free HHV-6 and HHV-7 viral load in the plasma was determined by calibrated quantitative real-time PCR assays; contaminations due to cell lysis and/or the presence of chromosomally integrated HHV-6 were excluded utilizing a quantitative real-time PCR assay for the quantitative detection of genomic DNA content [3]. HHV-6 and HHV-7 plasma viremia, a specific marker of active infection, was detected in all patients and in 30/32 of the plasma samples from the various phases of the illness. The viral loads were lower towards the healing phase, and the only 2 samples that proved negative were obtained during convalescence. Plasma viremia for both HHV-6 and HHV-7 was codetected in 3 patients. The level of plasma viremia ranged between 10 and 438 genome equivalents/ml for HHV-6 (mean 55 genome equivalents/ml) and between 10 and 250 for HHV-7 (mean 58 genome equivalents/ml) (table 1). HHV-6 and HHV-7 plasma viremia, a marker of active infection, was not detected in any of the healthy subjects of similar age, as previously described [3].

Discussion

The typical course of PR lasts 6–8 weeks, but atypical courses are probably more common than imagined and may pose a diagnostic challenge. Relapsing PR, for example, accounts for 1.8–2.8% of cases (3.7% in our experience [8]) and the persistent form for about 2% of all PR cases. We define PPR as a form of PR that lasts for over 12 weeks without interruption, regardless of the presence of constitutional symptoms. There is no real gold standard method for the diagnosis of PPR, but the persistence of HHV-6 and/or HHV-7 plasma viremia measured by calibrated quantitative real-time PCR in all the phases of the illness is highly suggestive.

PPR patients have some clinical features in common. As in typical PR and in contrast to relapsing PR [8], in most of the PPR patients the disease begins with the herald patch (75%). Interestingly, the 3 patients of our study in whom the herald patch was absent (cases No. 2, 3 and 7) developed a PR exanthem that was atypical for the morphology and distribution of the lesions and showed a simultaneous reactivation of HHV-6 and HHV-7. Possibly, the simultaneous viral reactivation may have led to the clinical atypical forms of PPR.

All patients but 1 had systemic symptoms, and fatigue was always present. Compared with typical and relapsing PR, systemic symptoms were more common (92 vs. 69% of cases), and this is in accordance with the persistent systemic reactivation of HHV-6 and HHV-7. Oral lesions, resembling Nagayama’s spots described in primary HHV-6 infection [9], were also more common than in PR (75 vs. 16% of cases) [10], a further sign of active HHV-6 infection [11].

Overall, the persistence of signs and symptoms is consistent with the persistence of the HHV-6 and/or HHV-7 reactivation (100% of cases), a rate definitely higher than in typical PR (48%) [3]. In addition, even the average level of plasma viremia was higher in PPR than in PR (49 vs. 17 genome equivalents/ml for HHV-6 and HHV-7).

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50 vs. 18 genome equivalents/ml for HHV-7). Three patients were coinfected with both HHV-6 and HHV-7 and developed severer systemic symptoms and oral lesions. Fatigue was so severe that it prevented them from attending to their usual occupations. Furthermore, serology disclosed IgM antibodies in 4 patients which, together with the simultaneous presence of IgG high-avidity antibodies in the same sample, confirmed that both HHV-6 and HHV-7 infection had been reactivated.

In conclusion, we have described an unusual persistent form of PR, whose prevalence has probably been underestimated so far and which should be added to the other variants of PR. Overall, our data indicate that in PPR we have a persistent reactivation of HHV-6 and/or HHV-7 with higher viral loads than in typical PR, accounting for the unusual persistence of the illness, the more frequent and severe systemic symptoms and the oral lesions.

**Disclosure Statement**

The authors declare that they have no conflicts of interest nor funding sources.

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**Table 1. Clinical and virological features of the patients with PPR**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender, age (years)</th>
<th>HP site, time lapse until eruption</th>
<th>Skin eruption, lesion morphology and distribution</th>
<th>Duration (weeks)</th>
<th>Mucosal lesions</th>
<th>Systemic symptoms</th>
<th>Sampling (weeks)</th>
<th>DNA copies/ml HHV-6</th>
<th>Serology at diagnosis HHV-6</th>
<th>HHV-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 31</td>
<td>trunk, 15 days</td>
<td>typical, trunk and limbs</td>
<td>18</td>
<td>palatal petechiae</td>
<td>fatigue, difficulty to concentrate</td>
<td>6</td>
<td>&lt;20</td>
<td>IgG 1:80; IgG 1:80; IgM neg.</td>
<td>IgG 1:80; IgM neg.</td>
</tr>
<tr>
<td>2</td>
<td>F, 34</td>
<td>absent, atypical</td>
<td>oral petechiae and erosions</td>
<td>21</td>
<td>fatigue, depression, inappetence</td>
<td>12</td>
<td>&lt;127</td>
<td>IgG 1:80; IgM 1:80</td>
<td>IgG 1:40; IgM 1:80</td>
<td>IgM neg.</td>
</tr>
<tr>
<td>3</td>
<td>F, 37</td>
<td>absent, atypical</td>
<td>oral papules, strawberry tongue</td>
<td>19</td>
<td>fatigue, headache, irritability</td>
<td>13</td>
<td>&lt;70</td>
<td>IgG 1:20; IgG 1:160</td>
<td>IgG 1:160; IgM neg.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F, 27</td>
<td>lower limb, 15 days</td>
<td>typical, trunk</td>
<td>24</td>
<td>none</td>
<td>fatigue, pruritus, headache, insomnia, irritability, difficulty to concentrate</td>
<td>16</td>
<td>118</td>
<td>IgG 1:40; IgG 1:40; IgM neg.</td>
<td></td>
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<tr>
<td>5</td>
<td>M, 25</td>
<td>trunk, 21 days</td>
<td>typical, trunk</td>
<td>20</td>
<td>oral petechiae, papules</td>
<td>fatigue, difficulty to concentrate</td>
<td>14</td>
<td>165</td>
<td>IgG 1:40; IgG 1:160</td>
<td>IgM neg.</td>
</tr>
<tr>
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<td>F, 35</td>
<td>upper limb, 10 days</td>
<td>typical, trunk</td>
<td>23</td>
<td>palatal erosions and petechiae</td>
<td>fatigue</td>
<td>12</td>
<td>15</td>
<td>IgG 1:80; IgG 1:40; IgM neg.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M, 21</td>
<td>absent, atypical</td>
<td>strawberry tongue and oral papules</td>
<td>19</td>
<td>strawberry tongue and oral papules</td>
<td>fatigue, pruritus, headache</td>
<td>8</td>
<td>20</td>
<td>IgG 1:60; IgG 1:40; IgM neg.</td>
<td></td>
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<tr>
<td>8</td>
<td>F, 30</td>
<td>lower limb, 10 days</td>
<td>typical, trunk</td>
<td>16</td>
<td>none</td>
<td>fatigue, pruritus</td>
<td>7</td>
<td>10</td>
<td>IgG 1:80; IgG 1:40; IgM neg.</td>
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<td>9</td>
<td>F, 28</td>
<td>lower limb, 8 days</td>
<td>typical, trunk</td>
<td>19</td>
<td>none</td>
<td>none</td>
<td>8</td>
<td>20</td>
<td>IgG 1:80; IgG 1:20; IgM neg.</td>
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<tr>
<td>10</td>
<td>M, 32</td>
<td>lower limb, 14 days</td>
<td>atypical</td>
<td>22</td>
<td>oral petechiae, strawberry tongue</td>
<td>fatigue, irritability, difficulty to concentrate</td>
<td>12</td>
<td>438</td>
<td>IgG 1:80; IgG 1:160</td>
<td>IgM neg.</td>
</tr>
<tr>
<td>11</td>
<td>F, 31</td>
<td>trunk, 18 days</td>
<td>typical, trunk</td>
<td>20</td>
<td>palatal petechiae and erosions</td>
<td>fatigue, irritability, inappetence</td>
<td>7</td>
<td>35</td>
<td>IgG 1:80; IgG 1:80; IgM neg.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F, 30</td>
<td>trunk, 7 days</td>
<td>typical, trunk</td>
<td>21</td>
<td>oral petechiae, strawberry tongue</td>
<td>fatigue, insomnia</td>
<td>8</td>
<td>15</td>
<td>IgG 1:80; IgG 1:320; IgM neg.</td>
<td></td>
</tr>
</tbody>
</table>

HP = Herald patch.
References


