INVESTIGATIVE REPORT

Pityriasis Rosea Recurrence is Much Higher than Previously Known: A Prospective Study

Mavise YUKSEL
Department of Dermatology, Istanbul Medipol University, Medical Faculty, Istanbul, Turkey

Pityriasis rosea is a common acute exanthema of unknown aetiology, which causes severe anxiety. In this study, the demographic data of pityriasis rosea patients, who presented to our clinic between 2013 and 2017, were prospectively recorded. The patients with a confirmed pityriasis rosea diagnosis were followed up for 4 years in order to investigate the recurrence rate. Of the clinically suspected patients, having a typical history of pityriasis rosea manifestations, a herald patch, and/or secondary coloured squamous lesions, 400 were confirmed by biopsy to have pityriasis rosea. The 4-year follow-up was completed in 212 patients, of whom 136 (64.2%) were female and 76 (35.8%) were male. The recurrence rate was determined as 25.9% at the end of the 4-year follow-up period.

Key words: pityriasis rosea; recurrence; prospective studies.

Accepted Mar 8, 2019; E-published Mar 8, 2019

Acta Derm Venereol 2019; 99: 664–667.

Corr: Mavise Yuksel, Department of Dermatology, Istanbul Medipol University, Medical Faculty, Istanbul, Turkey. E-mail: mavisey107@gmail.com

SIGNIFICANCE

Pityriasis rosea is a self-limiting acute exanthem of unkown causes. Pityriasis rosea is known to recur in some patients. In two retrospective studies involving large case series, the frequency of recurrence was reported as 3.7% and 2.8%. Between the years of 2013–2017, 212 patients admitted to the dermatology outpatient clinic of Istanbul Medipol University were included in the study. In the current prospective study, we found this rate to be 25.9%. It is considered that the rate of pityriasis rosea recurrence is actually greater than reported in the literature.

Pityriasis rosea (PR) is a self-limiting acute exanthema of unknown aetiology. Despite this fact, infectious agents are considered responsible for the pathogenesis of PR, with the most implicated infectious factors being human herpes virus (HHV)-6 and HHV-7. The role of HHV-7 in the pathogenesis of PR was first demonstrated by Drago et al. in 1997 (1). In addition to the proof that PR is associated with the endogenous reactivation of HHV-6 and HHV-7 (2), there are also studies which suggest that it is an active, systemic, infectious disease caused by these viruses (1).

In 15–90% of cases, typical PR begins with a medallion-like erythematous plaque, called a herald patch (3). A herald patch is an ovoid, erythematous, slightly raised patch 2–10 cm in diameter, typically with a coloured squamous edge. A few days to weeks after the herald patch appearance, smaller, salmon-coloured, ovoid, slightly raised lesions 5–10 mm in diameter are observed and some also present with coloured squamous edges. These secondary lesions take the shape of a Christmas tree when they are arranged along the Langer's lines on the back (4). Papulosquamous lesions in PR are usually located on the trunk and proximal extremities (5). Exanthema spreads and peaks within two weeks. This disseminated phase generally begins to decline within 2 to 4 weeks; however, in some cases, it may take more than 3–5 months (6). Itching is variable, with moderate to severe itching occurring in 25% of the patients (4). Prodromal symptoms and upper respiratory tract findings, such as sore throat, weakness, loss of appetite, and mild fever are present in more than 69% of patients before or during the eruption phase (3). PR can be seen all year round, but it is more frequent in winter, spring and autumn. Mucous membrane lesions occur in 16% of patients, but are usually overlooked or rarely reported since they are mostly asymptomatic (7). Although oral mucous lesions mostly present in the form of ulcerations, they may also occur as erythematous macules or plaques, and punctate haemorrhagic or erythematous lesions (3). Involvement of the oral mucosa is more commonly seen in paediatric, pregnant, relapsing and persistent cases than in classical PR (8). In adults, hands and feet are generally spared (6).

METHODS

A total of 400 patients presented to the Istanbul Medipol Mega University Hospital Dermatology Clinic between 2013 and 2017 and were diagnosed with PR. Of these, 212 patients completed the 4-year follow-up with the same physician and were included in the study. Detailed anamnesis was obtained from the patients. Age, sex, history of atopy, stress level before the disease, history of upper respiratory tract infection that might trigger the disease, and the duration of complaints were recorded. The diagnosis of PR was based on patients' detailed medical history and the findings on physical examination.

This study was approved by the ethics committee of Istanbul Medipol University Hospital (number: 10840098, date: March 10, 2017).

Diagnostic criteria

In this study, the following diagnostic criteria proposed by Chuh were used for a PR diagnosis (9):

doi: 10.2340/00015555-3169
Acta Derm Venereol 2019; 99: 664–667

Essential clinical features: (*i*) Discrete circular or oval lesions. (*ii*) Scaling on most lesions. (*iii*) Peripheral collarette scaling, with central clearance, of at least two lesions.

Optional clinical features: (*i*) Truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh. (*ii*) Distribution of most lesions along the ribs. (*iii*) A herald patch (not necessarily the largest) appearing at least two days before the generalized eruption.

Exclusion clinical features: (*i*) Multiple small vesicles at the center of two or more lesions. (*ii*) Most lesions on palmar or plantar skin surfaces. (*iii*) Clinical or serological evidence of secondary syphilis, such as generalized lymphadenopathy.

According to these criteria, a diagnosis of PR can be made if a patient has all the essential clinical features, at least one of the optional clinical features, and none of the exclusion clinical features. The histopathology of PR is not the gold standard (9). PR manifests with superficial perivascular dermatitis, epidermal changes, mild hyperplasia, focal spongiosis, and focal parakeratosis. Lymphocytes, histiocytes, and eosinophils can be present in a superficial perivascular dermal infiltrate. Papillary dermal oedema and extravasated erythrocytes in varying number can also be observed (6).

The differential diagnosis for PR includes secondary syphilis, guttate psoriasis, erythema dyschromicum perstans, lichen planus, nummular eczema, parapsoriasis, pityriasis alba, seborrhoeic dermatitis, tinea corporis, and tinea versicolor. In the current study, PR was confirmed by taking a biopsy from the suspicious lesions, conducting the VDRL (venereal disease research laboratory) test in cases suspected of secondary syphilis, and performing a fungal culture and direct examination in patients, suspected to have pityriasis versicolor. The patients with additional eczema, psoriasis, fungal infection and secondary syphilis were excluded from the study. None of the patients included in the study had any systemic diseases or used any medication. The patients were followed up to evaluate remission and recurrence. Only those that had very severe itching were given symptomatic drugs (antihistamines and local steroids).

The data were collected by the relevant clinician, transferred to Microsoft Excel, and adjusted for analysis. Data analysis was performed using the Statistical Package for Social Science v. 25.0 (SPSS, IBM Corp.). Non-parametric Wilcoxon and chi-square tests were employed for the analyses.

RESULTS

Of the 212 patients included in the study, 136 (64.2%) were female and 76 (35.8%) were male. The median age was 26.0 and 30.0 for female and male patients, respectively. It was found that 49.0% of the patients had presented to the hospital 7 days after the onset of the rash. More than half of the patients applied in the February–May period (51.4%), and some in March (24.5%).

At the time of onset of PR symptoms, a medallion lesion was observed in 98 patients (46.2%) and was not present in 114 patients (53.8%). Among the patients presenting with a medallion, this lesion was located on the trunk for 45 patients (45.9%), back for 19 (19.4%), leg for 12 (12.2%), neck for 9 (9.3%), arm for 6 (6.1%), armpit for 3 (3.1%), hip for two (2.0%), pubic region for one (1.0%), and wrist for one (1.0%). In 10 patients (4.7%), oral mucosa involvement was detected in the form of painless ulcers.

Table I. Relationship between disease recurrence and history of atopy

	History of atopy			
	0	1	Total	*p*
Disease recurrence				
0				
Total, *n*	127	30	157	
Disease recurrence, %	80.9	19.1	100	
History of atopy, %	78.4	60.0	74.1	
1				
Total, *n*	35	20	55	0.016
Disease recurrence, %	63.6	36.4	100	
History of atopy, %	21.6	40.0	25.9	
All patients, *n*	162	50	212	
Disease recurrence	76.4	23.6	100	
History of atopy	100	100	100	

At the time of presentation, 89 patients (42.6%) did not have itching, 60 (28.7%) had mild itching, 28 (13.4%) had moderate itching and 32 (15.3%) had severe itching. Fifty-six patients (26.4%) had a history of atopy. Nearly half the patients (49.0%) reported attending hospital one week after the onset of symptoms. There were no accompanying or preceding prodromal symptoms in 197 patients (92.9%) whereas the remaining 15 patients (7.1%) had signs of an influenza infection. Of the 212 patients, 142 (67.0%) reported to have undergone psychological stress prior to the development of the rash. In the 4-year follow-up, 157 patients (74.1%) did not have a PR recurrence. During this period, PR recurred once in 20 patients (9.4%), twice in 11 patients (5.1%), 3 times in 17 patients (8.0%), 4 times in 4 patients (1.9%), and 5 times in 3 patients (1.4%). When the relationship between the disease recurrence and atopy history was examined, the result was statistically significant ($p=0.016$). The patients with a history of atopy had a significantly higher recurrence rate (40.0%) (**Table I**).

In this study, the relationship between the disease recurrence and severity of itching with the primary disease was also investigated, but no statistically significant relationship was observed ($p=0.605$) (**Table II**).

The relationship between the disease recurrence and presence of a medallion lesion was also examined, but no relationship has been established ($p=0.793$) (**Table III**). However, the disease recurrence was found to be associated with the repeated occurrence of the medallion lesions ($p<0.05$); i.e., as the number of recurrences increased, the presence of medallion lesions also increased (**Table IV**). The mean ± SD primary disease time was 34.15 ± 56.3

Table II. Relationship between disease recurrence and severity of itching

	Itching					
Disease recurrence	No itching *n* (%)	Mild itching *n* (%)	Moderate itching *n* (%)	Severe itching *n* (%)	Total *n* (%)	*p*
0	68 (43.6)	43 (27.6)	19 (12.2)	26 (16.7)	156 (100)	0.605
1	21 (39.6)	17 (32.1)	9 (17.0)	6 (11.3)	53 (100)	
Total	89 (42.6)	60 (28.7)	28 (13.4)	32 (15.3)	209 (100)	

days. The earliest recurrence was seen after 3 weeks and the latest after 4 years. The mean ± SD duration of first recurrence was calculated as 33.20 ± 34.08 days (**Table V**).

The mean duration of the recurrent disease was shorter compared to the primary disease, and this was statistically significant for the third recurrence ($p<0.05$). However, no significant difference was found between the primary disease duration and other recurrence times ($p>0.05$) (**Table VI**). Furthermore, as the number of recurrences increased, the mean duration of the disease became shorter. There was a statistically significant difference between the first and second recurrence times, and the second and third recurrence times ($p<0.05$). However, no significant difference was observed when comparing the remaining recurrence times ($p>0.05$) (**Table VII**).

Table III. Evaluation of primary medallion lesion and recurrence (chi-square test)

	Primary medallion lesion		
Treatments, *n*	0 *n* (%)	1 *n* (%)	*p*
0	81 (51.6)	76 (48.4)	0.793
1	12 (60)	8 (40)	
2	7 (63.6)	4 (36.4)	
3	11 (64.7)	6 (35.3)	
4	2 (50)	2 (50)	
5	1 (33.3)	2 (66.7)	
Total	114	98	

Table IV. Comparison Disease recurrence and medallion lesion recurrence (chi-square test)

	Medallion recurrence		
Disease recurrence, *n*	0 *n* (%)	1 *n* (%)	*p*
0	156 (99.4)	1 (0.6)	0.000*
1	18 (90)	2 (10)	
2	9 (81.8)	2 (18.2)	
3	16 (94.1)	1 (5.9)	
4	2 (50)	2 (50)	
5	3 (100)	0 (0)	
Total	204	8	

*Statistically significant at 0.05 level.

Table V. Descriptive statistics

Disease/recurrence	Duration, days Mean ± SD
Duration of disease	
Primary disease	34.15 ± 56.43
First recurrence	33.20 ± 34.08
Second recurrence	20.27 ± 12.31
Third recurrence	19.95 ± 14.94
Fourth recurrence	15.40 ± 7.67
Fifth recurrence	23.33 ± 14.57
Time to recurrence	
First recurrence	210.71 ± 253.75
Second recurrence	457.59 ± 294.61
Third recurrence	521.81 ± 173.35
Fourth recurrence	624.38 ± 105.96
Fifth recurrence	907.50 ± 265.17

SD: standard deviation.

Table VI. Comparison of primary disease duration and recurrence time (day) (Wilcoxon test)

Variable	Mean (*n*) ± SD	*p*
Primary disease	34.15 (212) ± 56.43	–
First recurrence	33.20 (55) ± 34.08	0.879
Second recurrence	20.27 (30) ± 12.31	0.064
Third recurrence	19.95 (20) ± 14.94	0.030*
Fourth recurrence	15.40 (5) ± 7.67	0.416
Fifth recurrence	23.33 (3) ± 14.57	0.276

*statistically significant at 0.05 level.
SD: standard deviation.

Table VII. Comparison of recurrens times (day) (Wilcoxon test)

Variable 1	Variable 2	I	J	J-I	*p*
First recurrence	Second recurrence	33.200	20.270	−16.930	0.002*
First recurrence	Third recurrence	33.200	19.950	−17.250	0.007*
First recurrence	Fourth recurrence	33.200	15.400	−21.800	0.680
First recurrence	Fifth recurrence	33.200	23.330	−13.870	0.285
Second recurrence	Third recurrence	20.270	19.950	−0.320	0.825
Second recurrence	Fourth recurrence	20.270	15.400	−4.870	0.705
Second recurrence	Fifth recurrence	20.270	23.330	−3.060	0.180
Third recurrence	Fourth recurrence	19.950	15.400	−4.550	0.414
Third recurrence	Fifth recurrence	19.950	23.330	−3.380	0.276
Fourth recurrence	Fifth recurrence	15.400	23.330	−7.930	0.180

*statistically significant at 0.05 level.

DISCUSSION

The frequency of PR varies between 0.5 to 2%. The aetiology of PR has not yet been fully elucidated. Due to its seasonal predominance and epidemic incidence in the community, viral, bacterial and fungal infective agents are considered to be responsible for this papulosquamous disease, but non-infective aetiologic agents, such as atopy, autoimmunity and certain drugs have also been implicated (10, 11).

PR has attracted the attention of researchers since it was first reported in detail by Halkier-Sørensen in 1990 (12). Although the reason for the recurrences is not yet fully understood, there are some reports demonstrating PR recurrence after an upper respiratory tract infection, hepatitis B and influenza A (H1N1) vaccines, and HHV6 and 7 reactivation (10, 13, 14).

PR recurrence is generally considered to be rare. In two retrospective studies involving large case series, the frequency of recurrence was reported to be 3.7% and 2.8%, respectively (15, 16). In another study conducted with 939 PR patients over 10 years, the rate of recurrence was 1.8% (17). In the current prospective study, we found this rate to be 25.9%.

The recurrent PR cases in the literature manifest in different clinical forms. In studies on recurrent PR, conflicting results have been reported, concerning the severity, compared to the primary disease, distribution of rash, morphology, presence or absence of a herald patch, and time between and duration of recurrences. In their retrospective study with 570 PR patients, Drago et al. (15) found the relapse rate to be 3.7%. Most cases only had a single relapse, with the maximum number of relapses being 3. A herald patch was not detected in relapses, the number and size of the lesions decreased and the duration was shorter compared to the primary disease

(15). In a 24-year-old man, Chuah et al. (18) observed 3 attacks, each manifesting with a herald patch, but the form and severity of the lesions were milder compared to the primary disease. In contrast, Zawar & Kumar. (13) did not detect a herald patch in any of the attacks. Halkier-Sørensen (12) presented a case of a 39-year-old woman, who had an attack every year in spring for 5 years. The authors found the presence of a herald patch in episodes and the average duration of the recurrence was 6 weeks (12). In another case report published in 1998, Singh et al. (19) demonstrated that a 25-year old man had a total of 5 attacks over 4 years, each manifesting with a herald patch.

In the current study, patients with recurrent PR had fewer and smaller lesions compared to the primary disease. As the number of recurrences increased, the probability of a herald patch also increased, but the mean disease duration was reduced. A single, painless ulcer over the buccal mucosa was observed in one patient during the third recurrence. The same patient had several painless oral ulcers present in primary disease. We identified 3 patients that had a maximum of 5 attacks over 4 years, and in each of these attacks, we observed a herald patch lesion. Most recurrences were within the first year of the primary disease. The majority of the recurrent cases (78.2%) belonged to the female patients, and the mean ± SD age of the patients with recurrent PR was 28 for women and 31.1 for men. For the primary disease, the mean age of female and male patients was calculated to be lower (27.68 ± 9.928 and 28.56 ± 11.443, respectively).

In the literature, after the primary episode, the earliest and latest recurrence cases were reported to be two weeks (18) and two years (20), respectively. In the current study, the earliest recurrence occurred after 3 weeks and the latest after 4 years. In the literature, multiple relapses have been reported in a limited number of cases: Drago et al. reported a maximum of 3 attacks (15), Singh et al. 5 attacks over 4 years in a 25-year-old patient (19), Halkier- Sørensen 5 attacks in 5 years in a 39-year-old patient (12), Engelmann et al. multiple relapse attacks every year for 7 years in an 11-year-old girl (20).

In a population-based study, 16.0% of the 939 patients were found to have a history of atopy (17). In the current study, this rate was 26.4%, and we found a significant relationship between the history of atopy and disease recurrence ($p = 0.018$). This indicates a higher risk of recurrence in patients with a history of atopy. It is known that in allergic diseases, the increase in the T-helper 2 response coupled with an elevated type 2 cytokines cause an increase in the level of IgE, mast cells, basophils, and eosinophils, leading to a susceptibility to inflammatory diseases (21). Considering that PR is an inflammatory disease (22), the higher number of recurrences in patients with atopy may be attributed to the increasing susceptibility to inflammatory diseases caused by atopy.

It is considered that the incidence of PR recurrence is actually greater than reported in the literature probably because patients attend a different health centre when the disease relapses or do not visit a doctor at all due to the milder severity of the recurrent disease. The reason for the higher PR recurrence rate in this study, compared to the literature, may be due to the prospective nature of the study and the same physician doing the follow-up.

REFERENCES

1. Drago F, Ranieri E, Malaguti F, Battifoglio ML, Losi E, Rebora A. Human herpesvirus 7 in patients with pityriasis rosea. Electron microscopy investigations and polymerase chain reaction in mononuclear cells, plasma and skin. Dermatology 1997; 195: 374–378.
2. Broccolo F, Drago F, Careddu AM, Foglieni C, Turbino L, Cocuzza CE, Gelmetti C, Lusso P, Rebora AE, Malnati MS. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. J Invest Dermatol 2005; 124: 1234–1240.
3. Drago F, Ciccarese G, Rebora A, Broccolo F, Parodi A. Pityriasis rosea: A comprehensive classification. Dermatology 2016; 232: 431–437.
4. Stulberg DL, Wolfrey J. Pityriasis rosea. Am Fam Physician 2004; 69: 87–91.
5. Truhan AP. Pityriasis rosea. Am Fam Physician 1984; 29: 193–196.
6. González LM, Allen R, Janniger CK, Schwartz RA. Pityriasis rosea: an important papulosquamous disorder. Int J Dermatol 2005; 44: 757–764.
7. Parija M, Thappa DM. Study of role of streptococcal throat infection in pityriasis rosea. Indian J Dermatol 2008; 53: 171–173.
8. Ciccarese G, Broccolo F, Rebora A, Parodi A, Drago F. Oropharyngeal lesions in pityriasis rosea. J Am Acad Dermatol 2017; 77: 833–837.
9. Chuh AA. Diagnostic criteria for pityriasis rosea: a prospective case control study for assessment of validity. J Eur Acad Dermatol Venereol 2003; 17: 101–103.
10. Li A, Li P, Li Y, Li W. Recurrent pityriasis rosea: a case report. Hum Vaccin Immunother 2018; 14: 1024–1026.
11. Chuh A, Chan H, Zawar V. Pityriasis rosea – evidence for and against an infectious aetiology. Epidemiol Infect 2004; 132: 381–390.
12. Halkier-Sørensen L. Recurrent pityriasis rosea. New episodes every year for five years. A case report. Acta Derm Venereol 1990; 70: 179–180.
13. Zawar V, Kumar R. Multiple recurrences of pityriasis rosea of Vidal: a novel presentation. Clin Exp Dermatol 2009; 34: e114–116.
14. Eisman S, Sinclair R. Pityriasis rosea. BMJ 2015; 351: h5233.
15. Drago F, Ciccarese G, Rebora A, Parodi A. Relapsing pityriasis rosea. Dermatology 2014; 229: 316–318.
16. Bjornberg A, Hellgren L. Pityriasis rosea. A statistical, clinical, and laboratory investigation of 826 patients and matched healthy controls. Acta Derm Venereol 1962; Suppl 50: 1–68.
17. Chuang TY, Ilstrup DM, Perry HO, Kurland LT. Pityriasis rosea in Rochester, Minnesota, 1969 to 1978. J Am Acad Dermatol 1982; 7: 80–89.
18. Chuah SY, Chia HY, Tan HH. Recurrent and persistent pityriasis rosea: an atypical case presentation. Singapore Med J 2014; 55: e4–6.
19. Singh SK, Singh S, Pandey SS. Recurrent pityriasis rosea. Indian J Dermatol Venereol Leprol 1998; 64: 237.
20. Engelmann I, Ogiez J, Ogiez L, Alidjinou EK, Lazrek M, Dewilde A, Hober D. Relapsing pityriasis rosea with HHV-7 reactivation in an 11-year-old girl. Pediatrics 2018; 141: e20173179.
21. Miescher SM, Vogel M. Molecular aspects of allergy. Mol Aspects Med 2002; 23: 413–462.
22. Neoh CY, Tan AW, Mohamed K, Sun YJ, Tan SH. Characterization of the inflammatory cell infiltrate in herald patches and fully developed eruptions of pityriasis rosea. Clin Exp Dermatol 2010; 35: 300–304.