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Türkiye'den Pitriazis Rosea Hastalarıyla İlgili 2 Yıllık Bir Tecrübe: Alerjinin Patogenezdeki Rolü Nedir?

Two Years of Experience Related to Pitriazis Rosea Patients From Turkey: Where to Place Allergy Topics in The Pathogenesis?

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ÖZET

Amaç: Pitriazis Rosea (PR), etiyolojisi bilinmeyen papüloskuamöz bir deri döküntüsüdür. Etyopatogenezde enfeksiyöz ajanların, genetik faktörlerin ve otoimmünitenin rol oynadığı öngörülmektedir. Çalışma kapsamında PR ile ilişkili demografik ve klinik özellikler ile altta yatan etiyolojik faktörlerin belirlenmesi amaçlanmıştır. Ayrıca PR'nin atopi öyküsü ve alerjen maruziyeti ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Çalışmaya 2018-2020 yılları arasında PR tanısı konan 170 hasta dâhil edilmiştir. Yaş ve cinsiyet uyumlu 170 sağlıklı katılımcı çalışmaya katılmıştır. Hastaların komorbiditeleri, meslekleri, etiyolojik faktörleri, atopi öyküleri ve biyopsi örneklerinin histopatolojik özellikleri de kaydedilmiştir.

Bulgular: Hastaların yaş ortalaması 27.8±1.04, ortalama hastalık süresi 29.3±5.24 gün olarak tespit edilmiştir. En sık tetikleyici faktörler stres (% 44,1) ve enfeksiyonlar (%33,5) olmuştur. 26 hasta (%15.2), kendilerinin bitkilerle temaslarına neden olan bahçe işi öyküsü tariflemiştir. Stres anamnezi veren olgu sayısı kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek çıkmıştır ($p<0.001$). Atopi öyküsü 28 hastada (%16.4) tespit edilmiştir. Atopi sıklığı açısından gruplar arasında istatistiksel olarak anlamlı farklılık tespit edilmemiştir ($p=0,765$). Ancak PR nüksü olan hastalarda atopi sıklığı nüks olmayan hastalara göre istatistiksel olarak anlamlı derecede yüksek çıkmıştır ($p=0,002$). Bitki teması öyküsü tanımlayan hastaların histolojisinde nispeten daha yüksek sayıda eozinofil görülmüştür ($p<0.001$).

Sonuç: Sonuç: Bu çalışmada PR en sık stres ve üst solunum yolu enfeksiyonları ile ilişkili bulunsa da, kronik progresyon ve rekürrens gösteren PR'li hastalarda allerjen maruziyetinin önemli bir tetikleyici faktör olabileceği sonucuna ulaşılmıştır.

Anahtar Kelimeler: : Pitriazis rosea, allerjen, tetikleyici.

ABSTRACT

Aim: Pityriasis rosea (PR) is a papulosquamous skin eruption with an etiology of unknown origin. Infectious agents, genetic factors, and autoimmunity are suspected to play a role in the etiopathogenesis. The study was designed to evaluate the demographic and clinical characteristics and underlying etiologic factors associated with PR. It was also aimed to evaluate the relationship between PR and history of atopy and allergen exposure.

Materials and Methods: Materials and Methods: The study included 170 patients diagnosed with PR between 2018 and 2020. Age and gender-matched 170 healthy participants participated in the study. Comorbidities, occupations, etiological factors, atopy history and the histopathological features of the biopsy specimens of the patients were also recorded.

Results: Results: The mean age of the patients was 27.8±1.04, the mean disease duration was 29.3±5.24 days. Stress was the most common triggering factor (44.1%) followed by infections (33.5%). Twenty-six patients (15.2%) had gardening history that brought them in contact with plants. The number of cases describing stress was significantly higher than control group ($p<0.001$) . 28 patients (16.4%) had a history of atopy. Between the groups, atopy frequency was not statistically significantly different ($p=0.765$). Nonetheless, atopy frequency was significantly higher in patients who had PR recurrence than the patients without recurrence ($p=0.002$). Relatively higher numbers of eosinophils were seen in the histology of the patients describing a history of plant contact ($p<0.001$).

Conclusion: Although PR was found most frequently associated with stress and upper respiratory tract infections in this study, it should be considered that allergen exposure may be a crucial triggering factor in patients with PR who have chronic progression and recurrence.

Keywords: Pityriasis rosea, allergen, trigger.

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INTRODUCTION

Pityriasis rosea (PR) is an acute exanthem, characterized by multiple, oval macules, papules, plaques, and occasional vesicles, 1 The etiopathogenesis of the disease is poorly understood. A probable viral etiology has been proposed, supported by the presence of prodromal symptoms in some patients, the spontaneous resolution of the eruption.1,2

Genetic factors and autoimmunity have been suggested to have a role in disease's etiopathogenesis. 3 Atopy has also been implicated in the etiology as atopy prevalence has been found to be higher in patients with recurrent PR.4 Furthermore, PR-like eruptions related to chemical use also exist in literature.5 The present study aimed to investigate the demographic and clinical features of PR patients and to evaluate the etiological causes related to PR. We also aimed to evaluate the relationship of PR with atopy history and allergen exposure.

Statistical analysis

IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Normality was tested using the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as numbers and percentages. Fisher's exact test was used to analyse categorical variables.

MATERIALS AND METHODS

This retrospective descriptive study included 170 patients admitted to our clinic between January 2018 and May 2020 and was conducted with Institutional Review Board protocol approval (dated: 22.06.2020; number: 06/16 from the local committee of Human Research Ethics Committees at Aksaray University). The patient characteristics including age, sex, occupation, comorbidities, residence, month and season of disease onset, recurrence numbers, resolution time, factors in etiology, atopy history, medication use, prodromal symptoms, clinical PR type, and a herald patch's presence and location were documented. PR diagnosis was made in patients when they had three essential features and at least one out of three optional features. The essential features consisted of circular or oval lesions, scaling on the majority of lesions, and a peripheral collarette of scale with central clearance on at least two lesions. Optional features were truncal and proximal limb distribution with less than 10% of lesions distal to the mid-upper arm and mid thighs, the majority of lesion being distributed among the ribs, and a herald patch appearing minimum two days prior the eruption. The exclusion criteria consisted of multiple small vesicles at the center of two or more lesions, the majority of lesions being on palmar and plantar skin surfaces, and clinical or serologic evidence of secondary syphilis.6 The diagnosis of thirty-four patients were also confirmed by histopathology. The patients' histopathology results were classified into three groups per the eosinophil numbers in overall investigated biopsy areas (HEX200): group 1: no eosinophils, group 2: Containing 1-5 eosinophils, group 3: 6-10 eosinophils, group 4: 10 or more eosinophils in biopsy area. The results were also classified according to the degree of spongiosis. Group 1: mild intercellular bridges, group 2: increase in the number of mild intercellular bridges group 3: Vesicle and bulla formation.

RESULTS

61 (35.8%) male and 109 (64.2%) female patients were recruited, with a male/female ratio of 0.55. The mean age of the patients was 27.8±1.04, ranging from 2 to 64 years. The main disease duration was 29.3±5.24 days and ranged between 1 and 365 days. The mean resolution time was 39±17.7 days, ranging between 21 and 120 days.

137 patients (80.5%) resided in a city and 33 (19.5%) lived in rural areas. The vast majority of the patients were students (40%) followed by housewives (33.5%), construction workers (14.1 %), teachers (3.5%), officers (2.9%), farmers (2 %), police (1.5 %), market worker (1.5 %), marble worker (1 %), caffee worker (0.5 %), cargo worker (0.5 %), paperprocessing worker (0.5 %), hammam worker (0.5 %), textile worker (0.5 %), oil worker (0.5 %), driver (0.5 %), forester (0.5 %), guard (0.5 %) (Table 1).

Table-1. Occupational distribution of the study population.

Occupation	Number of patients	Percentage
Student	68	40
Housewife	47	33.5
Construction worker	24	14.1
Teacher	6	3.5
Officer	5	2.9
Farmer	4	2
Police	3	1.5
Market worker	3	1.5
Marbleworker	2	1
Cafeworker	1	0.5
Cargo worker	1	0.5
Paperprocessing worker	1	0.5
Hammam worker	1	0.5
Textile worker	1	0.5
Oil worker	1	0.5
Driver	1	0.5
Forester	1	0.5
Guard	1	0.5

75 patients had a history of stress (44.1%), 57 (33.5 %) patients had a history of infection. 26 (15.2%) patients had a gardening history and plant contact. These plants included tomato, chickpea, pepper, grass, cucumber, beans, lentil, sunflower, apple and plum. The patients contacted with these plants with hands for at least 30 minutes. PR occurred in 6 (3.5%) patients following particular food consumption, in 6 patients no causal factor was identified. (Table 2) Anemia was the most common comorbid disease. Table 3 presented the other comorbid diseases in detail. Fatigue (20.5%), arthralgia (16.4%), and headache (15.2%) were the major accompanying symptoms.

Table-2. Percentage of patients according to triggering factors.

Etiology	Number of patients	Percentage
Stress	75	44.1%
Infection	57	33.5%
Plant contact	26	15.2%
Tomato	6	23.07%
Chickpea	6	23.07%
Pepper	4	15.3%
Grass	3	11.5%
Cucumber	2	7.6%
Beans	1	3.8%
Lentil	1	3.8%
Sunflower	1	3.8%
Apple	1	3.8%
Plum	1	3.8%
Food Consumption	6	3.5%
Honey	1	16.6%
Sunflowerseed	1	16.6%
Beer	1	16.6%
Mussel	1	16.6%
Cheese	1	16.6%
Meat	1	16.6%

Table-3. Comorbidites accompanying pitriasis rosea.

Comorbidity	Number of Patients
Goitre	1
Chronic urticaria	4
Servix ca	1
Anemia	5
Gastritis	1
Asthma	2
Bone tumor	1
Diabetes	3
Allergic rhinitis	1
Hypertension	2

There was a herald patch in 107 patients (62.9%); most herald patches were on the trunk (in 59 patients ,55.14%), followed by extremities in 48 patients (44.8%). The classic PR type was present in 157 patients (94.1%), and 13 (5.9%) had an atypical PR type [the segmental type in two (1.1%), the purpuric type in two (1.1%), and the inverse type in nine (5.2%)]. There was facial involvement in one patient (0.9%).

Only one disease episode was observed in 144 patients (84.7%), 21 (12.3%) had two episodes, 4 (2.3%) had three episodes, and 1 (0.58%) had five episodes. 28 patients (16.4%) had a history of atopy . The most common month of PR onset was May (13.5%) and spring was the season in the most cases (28.8%). (Table 4)

Table-4. The distribution of patients according to months

Months	Number of patients	Percentage %
January	15	8.8
February	8	4.7
March	10	5.8
April	12	7
May	23	13.5
June	21	12.3
July	20	11.7
August	14	8.2
September	13	7.6
October	13	7.6
November	12	7
December	9	5.3
Seasons		
Spring	49	28.8
Summer	48	28.2
Winter	35	20.5
Autumn	38	22.35

The patients having a histopathology concordant with group 2 and 3, which consist relatively higher eosinophil numbers, constituted 28.6 % of the patient group with a history of plant contact. The histopathology of the patients without plant contact were consistent with either group 1 or group 2. In the patients with plant contact the percentage of cases in according to eosinophil numbers groups,the total number of the patient numbers in the groups 2,3 and 4 was statistically significantly higher than that of the patients without plant contact ($p<0.001$) (Table 5). In the spongiosis grades groups, the percentage of the total number of cases in the plant contact groups 2 and 3 was statistically significantly higher than the group without plant contact ($p = 0.03$) (Table 6).

Table-5. The histopathological classification according to eosinophil numbers.

Eosinophil numbers in histopathology	Group 1 No eosinophil	Group 2 1-5 eosinophils	Group 3 6-10 eosinophils	Group 4 10 or more eosinophils	Group 2+3+4	P value
PR related to plant contact	2 (14.3%)	8 (57.1%)	3 (21.5%)	1 (7.1%)	12 (85.7%)	
PR unrelated to plant contact	15 (75%)	5 (25%)	0	0	5 (25%)	0,001*

*Fischer's exact test, $p<0.05$ was considered statistically significant

Table-6. The histopathological classification according to spongiosis.

	Group 1	Group 2	Group 3	Group 2+3	p value
PR related to plant contact	2 (14.3%)	5 (35.7%)	7 (50%)	12 (85.7 %)	0.03*
PR unrelated to plant contact	10 (50%)	9 (45%)	1 (5 %)	10 (50%)	

DISCUSSION

Characterized by erythematous scaly plaques, PR is a self-limited cutaneous eruption. The disease incidence was approximately 0.5–2%, and maximum incidence was observed between 10 and 35 years. 7,8 In this regard, the patients' mean age was 27.8±1.04 in our study. Although female predominance was demonstrated in some studies, others reported no gender predilection.,9

PR etiopathogenesis remains unclear. Infective agents, such as viruses, bacteria, fungi and noninfectious causes including drugs and vaccines were emphasized in the etiology.10 Investigations examining the viral etiology of PR mostly focused on Human Herpes virus 6 (HHV-6) and HHV-7. In lesional skin, nonlesional skin, saliva, peripheral blood mononuclear cells, and serum of patients with PR, Watanabe et al. demonstrated evidence of both systemic active HHV-6 and HHV-7 infections.11 However, Kosuge reported that most PR patients demonstrated no significant differences in HHV-6 and HHV-7 antibody titers compared to patients with other skin diseases. This finding suggested that HHV-6 and HHV-7 may play a role in the etiology but other causative agents could also play a role in PR. It is also possible that latent activation of HHV-6 and HHV-7, which can be triggered by stress and a state of immunosuppression, may play a role in the etiopathogenesis of PR. 12 Stress was the most common triggering factor reported by the patients in our study (44.1%).

In 8% to 20% of patients, PR is related to recent upper respiratory tract infections.13 31.7% of the population had a previous upper respiratory tract infection in our study. Furthermore, in up to 69% of PR patients, prodromal symptoms have been observed. 13 78.3% of patients had prodromal symptoms in our study, being mostly fatigue. The possible role of viral etiology in PR has been supported by the high proportion of prodromal symptoms in our study.

In addition, some studies in the literature have suggested that extrinsic factors can trigger PR. Accordingly, a study by Egwin showed that 20% of the patients had new garment use history. The mechanism of this causal association has not been clear. 14 Suggesting that atypical cases of PR may actually represent a contact reaction, Zawar et al. revealed a PR-like eruption after the application of mustard oil, confirmed by a patch test.5 Twenty-six patients (15.2%) had gardening history and contact with plants in our study.

It is also striking that higher degree of spongiosis and higher numbers of eosinophils were seen in the histopathology of the biopsy specimens in this group. Spongiosis develops as a result of various immunological reactions and passage of the extravasated edema fluid from dermis into the epidermis resulting with osmotic pressure to epidermis. The severity of spongiosis may range from microscopic changes to macroscopic vesicle and bulla formation dependent on the amount of the allergen exposed.15 Higher degrees of spongiosis accompanying with high numbers of eosinophils may also highlight the role of allergic mechanisms in PR development in these patients. The lack of patch testing, which would further support an allergic etiology, is a limitation of our study.

In several studies, the relationships between PR and environmental factors such as air temperature, air humidity, and rainfall were investigated. An increased incidence of PR during fall, winter, and spring was found in some studies, which suggests an infectious cause. 1 Reports indicating no association between PR and seasonal variations also exist in the literature. 16 ,17 In our study, most cases occurred in the spring and summer; there was an association with plant contact in 29.1% of cases that developed in the summer and 10.2% of those developed in spring. Since relatively higher eosinophil numbers suggested an allergic mechanism in the histopathology of these patients, it is possible that plant allergens may have caused the high occurrence rate of PR in the summer.

Although PR etiopathogenesis has not been fully clarified, PR has been mostly related to viral etiology. One of the factors supporting the viral etiology of the disease is the low PR recurrence rate.18 Nonetheless, a recent study by Yüksel et al. determined the recurrence rate of PR as 25.9%, which was higher than previously reported, and disease recurrence was related to atopy.4 Similarly, patients with PR recurrence had a higher atopy frequency in our study. Increased susceptibility to PR, which is an inflammatory disease, may be caused by an increase in Immunglobulin E (IgE), mast cells, basophils, and eosinophil levels during the T helper 2 (Th2) inflammatory response in allergic diseases .4,19 There are also studies showing that there are pathways similar to cytokine traffic in allergic skin diseases in PR. Recent studies show that Th17 cells are involved in both allergic mechanisms and pityriasis rosea. 20,21 Contact reactions, which may play a role in PR etiology, are also frequently reported in atopic patients. 22

Viral genetic markers including HHV-6, HHV-7 on lesional and nonlesional skin specimens and in serum were not investigated in our study since it is a retrospective analysis. This is a limitation of the study.

In this study, in which we evaluated the clinical characteristics of patients with PR, the most common triggering factor reported by patients was stress, followed by upper respiratory tract infections. Plant contact may also be a triggering factor for PR by allergenic mechanisms as supported by the relatively high number of eosinophils and higher degree of spongiosis in the histopathology comparing with the histopathology of PR related to other causes. In this regard, we believe that PR may have a multifactorial pathogenesis in which atopy and allergic mechanisms may also be involved. More studies investigating the possible allergic etiology of PR are needed.

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