Acta Dermatovenerol Croat 2018;26(2):109-118 CLINICAL ARTICLE

General Characteristics and Comorbidities in Patients with Palmoplantar Pustulosis

Magdalena Misiak-Galazka[1], Hanna Wolska[1], Adam Galazka[2], Bartłomiej Kwiek[3], Lidia Rudnicka [1]

[1]Department of Dermatology, Medical University of Warsaw, Warsaw, Poland; [2] Head and Neck Cancer Department, Maria Sklodowska–Curie Cancer Center, Warsaw, Poland; [3]Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland

Corresponding author:
Professor Lidia Rudnicka, MD, PhD
Department of Dermatology
Medical University of Warsaw
Koszykowa 82A
02-008 Warsaw
Poland
lidiarudnicka@gmail.com

Received: February 9, 2017;
Accepted: May 15, 2018

ABSTRACT The aim of this prospective study was to analyze comorbidities in patients with palmoplantar pustulosis (PPP). The current study comprised 63 consecutive patients with palmoplantar pustulosis. The control group consisted of 37 patients with psoriasis vulgaris (PSV). The study included a standardized anamnesis, a clinical examination, blood tests for thyroid hormones, as well as calcium, magnesium, antiendomysial antibody, and patch tests.
Hypertension was observed in 28/63 (44.44%) patients with PPP. Eight (12.7%) had ischaemic heart disease, and 7/63 (11.11%) had type 2 diabetes mellitus. There was no statistically significant difference between the patients with PPP and those in the control group. Metabolic syndrome was diagnosed in 19/63 (30.16%) patients with PPP and in 12/37 (32.43%) patients with PSV. Thyroid disease was more prevalent among patients with PPP in comparison to patients with PSV (31.75% vs. 13.51%; p=0.0421). Body mass index was statistically significantly higher in patients with PSV (28.25 vs. 25.86 kg/m^2, p=0.0144). BMI was higher than 25 kg/m^2 in 18.03% patients with PPP and 26.47% patients with PSV (p=0.333). Positive patch tests were observed in 12/39 (30.77%) patients with PPP. The most common allergens were nickel chloride (5/12, 41.67%) and fragrances (5/12, 41.67%). In the control group, patch tests were positive in 2/11 (18.18%) cases (p<0.05). Patients with PPP, like patients with PSV, often presented with hypertension and metabolic syndrome. Given that many studies have focused on cardiovascular risk in PSV, there is a need for further research on the association between PPP and cardiovascular risk. In addition, patients resistant to PPP treatment should be screened for contact allergies.

KEY WORDS: internal disease associated with dermatology, psoriasis, patch testing

INTRODUCTION

Palmoplantar pustulosis (PPP) is an entity of unknown nosological origin. Some authors claim that it belongs to the spectrum of psoriasis, whereas others suggest it is of a different nature and a distinct disease. Palmoplantar pustulosis is characterized by an eruption of pustules on an erythemato-desquamative background on the palms and/or the soles. Not much has been reported in the literature about this condition. The term palmoplantar pustulosis was introduced by Lever in 1967 (1). In the 1970s and 1980s, differences between PPP and vulgar psoriasis (PSV) were noticed, but greater interest was taken in PPP only in the 1990s. Subsequent immunological and immunohistochemical studies proposed the concept of PPP as an autoimmunological disease (in contrast to chronic plaque psoriasis) (1-6). Recently, Becher *et al.*

(7) published a retrospective review of comorbidities in patients with PPP. However, there is still a need for further studies on comorbidities in patients with PPP.

PATIENTS AND METHODS

The study was conducted in the Department of Dermatology, Medical University of Warsaw, Poland, between 2011 and 2014.

A total of 63 patients with skin lesions corresponding to those seen in palmoplantar pustulosis were enrolled in the study. The control group consisted of 37 patients with skin lesions corresponding to those associated with chronic plaque psoriasis (PSV) occasionally occurring on the hands or feet. The control group was matched to the study group by age and sex to compare concomitant diseases and the results of laboratory tests.

The characteristic skin lesions (Fig. 1) were the inclusion criterion. The exclusion criterion was an unspecific clinical presentation. None of the patients received biological treatment prior to or during the study.

The study included:

1. Self-designed standardized anamnesis containing questions about the disease, concomitant diseases, and treatment.

2. Clinical examination that described skin and nail changes.

a. Body Mass Index (BMI = mass (kg)/ height^2 (m^2)) was measured.

b. Metabolic syndrome was diagnosed according to specific criteria (8).

3. Laboratory tests were conducted for thyroid hormones, calcium, magnesium, and antiendomysial antibodies.

4. Data regarding the treatment regimen were obtained from the medical documentation.

5. Patch testing was conducted using one of two sets of allergens (Table 1):

a. the first set of allergens by Polish Patch Test Company I (mgr farm. Edmund Jaworski, Katowice, Poland),

b. the second set of allergens with TRUE TEST panels 1 and 2 by SmartPractice Denmark Aps

The interpretation of the patch tests was as follows: negative reaction (–); doubtful (+/–) faint erythema; weak positive (+) erythema, discrete papules; strong positive (++) papules, discrete vesicles; and extreme positive (+++) coalescing vesicles/bullous reaction.

The study protocol was approved by the Bioethical Committee at the Medical University of Warsaw (KB 13/2011). All study participants provided writtne informed consent to the survey.

Table 1. Two sets of allergens used for patch testing

Set of allergens Polish Patch Test Company, mgr farm. Edmund Jaworski, Katowice, Poland	TRUE TEST panel 1and 2 by SmartPractice Denmark Aps
Budezonid	Nickel sulphate
Fragrance cocktail A	Wool alcohols
Potassium dichromate	Neomycin sulphate
Nickel chloride	Potassium dichromate
p-Phenylenediamine	Caine mix
Formalin	Fragrance mix
IPPD= Nonox ZA	Colophony
Balsam of Peru	Epoxy resin
Mercaptobenzothiazole	Quinoline mix
Anestesin	Balsam of Peru
Colophony	Ethylenediamine dihydro-cloride
Eucerin	Cobalt chloride
Cobalt (I) chloride	P-tert butylphenol formalde-hyderesin
Fragrance cocktail P	Paraben mix
Thiuram mix	Carba mix
Terpentine	Black rubber mix
Neomycin	Kathon CG
Quaternium-15	Quaternium-15
	Mercaptobenzothiazole
	P-phenylenediamine
	Formaldehyde
	Mercapto mix
	Thiomersal
	Thiuram mix

Statistical analyses

The results were computed with Statistica 8.0 software (StatSoft Inc.) licensed to the Medical University

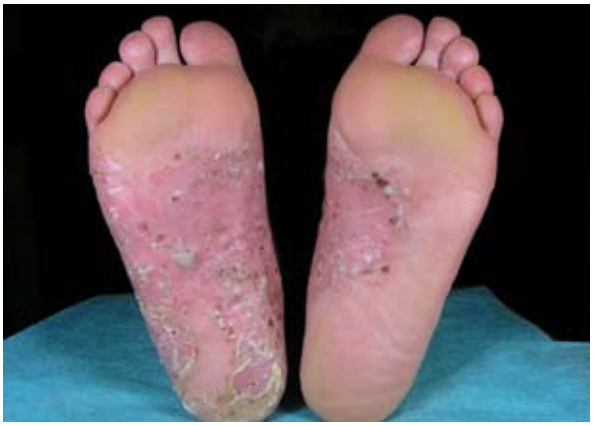

Figure 1. Clinical presentation of PPP skin lesions.

Table 2. Baseline demographics and clinical disease characteristics.

Variable	PPP n=63	PSV n=37	P
Female (%)	58 (92,06)	34 (89,19)	0,9444
Age mean ± SD, years	58,51 ± 12,4	57,03 ± 14,39	0,7330
Disease onset ± SD, years	**48,51 ± 13,06**	**38,73 ± 20,97**	**0,0379**
Triggering factors: No of pts (%)			
stres	**11 (17,46)**	**15(40,54)**	**0,0111**
infections	16 (25,40)	15 (40,54)	0,1139
smoking	**60 (95,23)**	**23 (62,16)**	**0,001**
packyears of smoking	**24,04**	**15,97**	**0,0095**
Positive family history of PSV, No of pts (%)	**14 (22,22)**	**15 (40,54)**	**0,0502**
Finger nail involvement, No of pts (%)	28 (44,44)	22 (59,46)	0,1471
Toe nail involvement, No of pts (%)	26 (41,27)	14 (37,84)	0,7352
Systemic treatment, No of pts (%)			
Acitretin	**25 (39,7)**	**4 (10,81)**	**0,0021**
Methotrexate	11 (17,5)	3 (8,11)	0,1932
Local- PUVA	**13 (20,6)**	**2 (5,41)**	**0,0395**
Re-local PUVA	2 (3,2)	0	
UVB 311	**2 (3,2)**	**10 (27,03)**	**0,0004**
CsA	1 (1,6)	2 (5,41)	0,2799
Fumarans	1 (1,6)	0	
Glucocorticosteroids	8 (12,7)	0	

of Warsaw. The Kolmogorov-Smirnov, Shapiro-Wilk test and visual analyses were used for assessing the normal distribution of the sample. Continuous variables were tested for statistically significant differences using the Student's t-test and the Mann-Whitney test where appropriate. Spearman rank correlation coefficients were computed to estimate possible interrelations. Fisher's exact test was used for testing binary variables. A p-value below 0.05 was considered statistically significant.

RESULTS

The study group comprised 63 patients with palmoplantar pustulosis, of which 58 (92.06%) were women. The control group comprised 37 patients with PSV – 34 (89.19%) women and three men. There was no difference between the groups regarding age and sex. (Table 2).

The onset of the disease in patients with PPP was between 14 and 75 years of age, on average at 48.5 [95% confidence interval (CI)13.06]. This was statistically significantly later than in the patients with PSV who were in the control group (38.73±20.97; p=0.038). In the PPP group, one peak in incidence was observed; this was in contrast to two peaks in the PSV group (Fig. 2 & 3). The mean duration of the disease was 10.0 ± 11.59 years. In 15 patients, skin lesions appeared first on the palms; in 29, on the soles; and

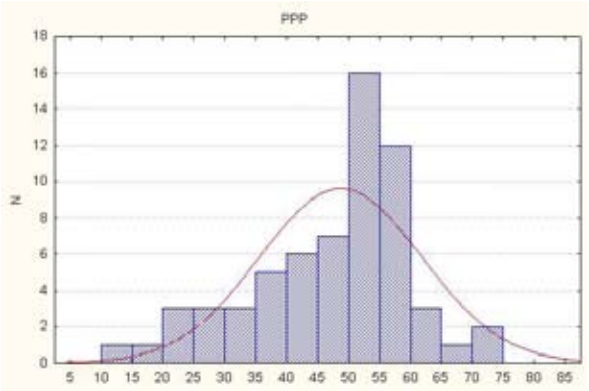

Figure 2. Age at the onset of the disease in PPP patients (years).

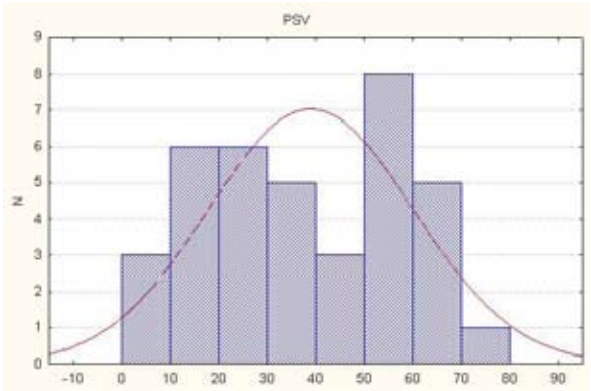

Figure 3. Age at the onset of the disease in PSV patients (years).

Table 3. Comorbidities in patients with PPP and PSV

Variable	PPP n=63	PSV n=37	p
	N (%)	N (%)	
Thyroid diseases	**20 (31.75)**	**5 (13.51)**	**0.0421**
Diabetes mellitus type 2	7 (11.11)	7 (18.92)	0.2773
Hypertension	28 (44.44)	17 (45.95)	0.8841
Ischaemic heart disease	8 (12.7)	6 (16.21)	0.624
Metabolic syndrome	19 (30.16)	12 (32.43)	0.8124
BMI (kg/m^2)	**25.86**	**28.25**	**0.0144**
BMI > 25 kg/m^2; No of pts	11/61 (18.03)	9/34 (26.47)	0.333
COPD	2 (3.17)	1 (2.70)	0.8937
Atopy	12 (19.05)	3 (8.11)	0.1391
Atopic dermatitis	1 (1.59)	0 (0)	0.4412
Hay fever	11 (17.46)	2 (5.41)	0.0835
Allergic conjunctivitis	8 (12.70)	1 (2.70)	0.0917
Asthma	1 (1.59)	1 (2.70)	0.7233
Psychiatric disorders	11 (17.46)	6 (16.22)	0.8730
Depression	9 (14.28)	4 (10.81)	
others	2 (3.18)	2 (5.4)	
Arthralgia, No of pts	36 (57.14)	15 (43.24)	0.1792
The onset of arthralgia, years	51.32	48.21	0.1946
The intensity of joint pains, 0-10	**5.37**	**1.58**	**0.0001**

BMI—body mass index; COPD—Chronic Obstructive Pulmonary Disease

in 11 on the palms and soles simultaneously. During the period of exacerbation, pustules were observed on the palms in 52 subjects and on the soles in 61 subjects.

In 24/54 (44.44%) patients with PPP, the disease presented with a chronic course. Long remissions of more than 6 months were noted in 13/37 (35.14%) cases. In 9/13 (69.23%) cases, there was a long-lasting symptom-free period of at least 18 months after the first flare-up.

TRIGGERING FACTORS

The most common triggering factors (Table 2) in the study group were stress and infections, as in PSV; however, existing skin lesions in PSV patients were more frequently exacerbated by stress (40.54% vs. 17.46%; p=0.0111).

Forty-five (45) patients with PPP were smokers, and 15 had smoked in the past (a total of 60 subjects, 95.23%). In addition, two patients were passive smokers at home. On the contrary, 23/37 (62.16%) PSV patients reported smoking during the study (37.84%) or in the past (p=0.001). The patients with PPP had

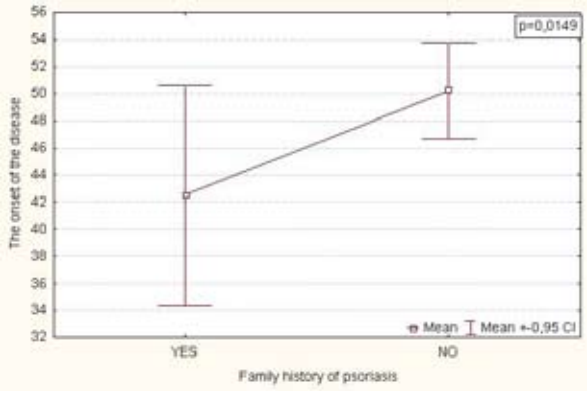

Figure 4. The onset of the disease in PPP patients with a positive family history of PSV.

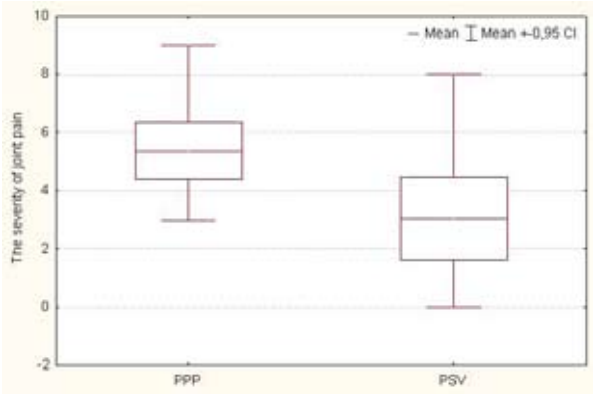

Figure 5. A comparison of the severity of joint pain evaluated on a 0–10 scale, in PPP and PSV patients.

Table 4. The results of patch tests in patients with PPP

Alergen	N (%)	Alergen	N (%)
Nickel chloride	5 (41.67%)	Colophony	1 (8.33%)
Potassium dichromate	1 (8.33%)	Eucerin	1 (8.33%)
Cobalt chloride	2 (16,67%)	Formalin	2 (16.67%)
Fragrance cocktail P	2 (16.67%)	Terpentinepara	1 (8.33%)
Fragrance cocktail A	3 (25%)	p-Phenylenediamine	1 (8.33%)
Balsam of Peru	2 (16.67%)	Neomycin	1 (8.33%)

smoked for a statistically significantly longer time (for 29.7 vs. 19.3 years; p=0.0022) and had smoked for a higher number of pack-years (24.03 vs. 15.97; p<0.01) than the patients with PSV.

In the study group (PPP), the onset of the disease was observed before menopause in 24/58 (41.38%) female patients with PPP, in 7/58 (12.07%) during perimenopause, and in 27/58 (46.55%) after menopause. In addition, postmenopausal exacerbations were observed in 3/58 (4.76%) female patients. Menopause did not influence the course of the disease in 9 (14.29%) patients.

Two patients were pregnant. Remission of the disease was observed in one patient during pregnancy and up to 6 months after delivery. For the other patient, the course of the disease did not change during pregnancy, but an exacerbation of skin lesions was observed after delivery.

In the control group (PSV), the onset of the disease was observed in 21/33 (63.64%) female subjects before menopause, in 3/33 (9.09%) during perimenopause, and in 10/33 (30.3%) after menopause. In addition, exacerbations after menopause were observed in 5/33 (15.15%) patients.

ASSOCIATION WITH PSV

In the PPP group, patients reported a positive family history of PPP (3/63, 4.76%) and PSV (14/63, 22.22%). PSV skin lesions were observed periodically in 17/63 (26.98%) patients with PPP. However, no occurrence of scalp lesions, generalized skin lesions, or psoriatic erythroderma was observed in any of the subjects with PPP. Patients with PPP and positive family history of the disease presented with an earlier onset in comparison to the group without a PSV family history (at the age of 42.5 vs. 50.22, p=0.0149) (Figure 4).

In the study group, fingernail involvement was observed in 44.44% cases, and toenail involvement in 41.27% cases. Among the most common changes were nail pitting (17.46%), followed by onycholysis and subungal changes (pustules, hyperkeratosis) (11.11% for both) – all typical for PSV. Less frequently occurring uncharacteristic nail changes were also reported (7.95%). There was no statistically significant difference in fingernail changes between the group with PPP and the one with PSV (44.44% vs. 59.46%, p=0.1471), except for onycholysis – PSV vs. PPP (36.11% vs 11.11%; p=0.0029).

COMORBIDITIES

Among 63 patients with PPP, 28 (44.44%) had hypertension, 8 (12.7%) had ischaemic heart disease (IHD), and 7 (11.11%) had type 2 diabetes mellitus (Table 3).

Metabolic syndrome was diagnosed in 19/63 (30.16%) patients with PPP and in 12/37 (32.43%) patients with PSV. There was no statistical difference (p=0.8124).

Eleven (11/61 (18.03%)) patients with PPP and 9/34 (26.47%) patients with PSV had a BMI greater than 25kg/m^2 (p=0.333). Although the mean BMI was statistically significantly higher in patients with PSV (28.25 vs. 25.86 kg/m^2, p=0.0144), the mean body mass index was elevated in both groups of patients (PPP and PSV), indicating overweight.

No statistically significant difference in the incidence of hypertension, IHD, type 2 diabetes mellitus, chronic obstructive pulmonary disease, or atopy was observed (Table 3).

Thyroid disease was more prevalent among patients with PPP in comparison to patients with PSV (31.75% vs. 13.51%; p=0.0421). The most common were thyroiditis (Hashimoto, Graves-Basedow disease) and goiter.

Thirty-six (36/63, 57.14%) PPP patients suffered from joint pain. The beginning of arthralgia started on

average at the age of 51.32 [CI 95% ±14.95], (age range 20–78). No statistical difference was found in the frequency of the onset of joint pain in the two groups. However, it was discovered that the intensity of joint pain, evaluated on a 0–10 scale (Figure 5), was higher in patients with PPP (5.374 vs. 1.584; p=0.0001). Most often, pain affected the knee joints, followed by ankle and shoulder joints. Among the patients with arthralgia, seven had been diagnosed with arthritis prior to the study – psoriatic arthritis (4), rheumatoid arthritis (1), SAPHO syndrome (1), arthritis of the jaw (1), and one (1) during the diagnostic procedures. According to the rheumatological observation, the remaining 28 patients with arthralgia were suspected of psoriatic arthritis, but did not fulfill the diagnostic criteria.

PATCH TESTING

The results of the patch tests (Table 4) were positive in 12/39 (30.77%) patients with PPP. The most common allergens were nickel chloride (5/12, 41.67%) and fragrances (a total of 5/12, 41.67%). Multivalent allergies were present in eight cases. In the control group, patch tests were positive in 2/11 (18.18%) cases (p<0.05). In both cases, multivalent allergies were present (nickel, dichromate, and p-phenylenediamine).

LABORATORY TESTS

None of the 24 subjects with PPP had detectable IgA or IgG antiendomysial autoantibodies.

No statistical difference in the levels of calcium (9.11 vs. 9.05mg/dL; p=0.6603) or magnesium (2.06 vs. 2.05 mg/dL; p=0.7041) was found in patients with PPP and PSV. In 48 (88.89%) patients with PPP, calcium levels were within the normal range. It was lower in 3 (5.56%) and elevated in 3 (5.56%) patients.

TREATMENT

The treatment of PPP was based on topical agents: potent glucocorticosteroids, exfoliating agents (salicylic acid), retinoids (tazarotene), Vitamin D_3 derivatives (calcipotriol), and emollients. Thirty-six (36/63, 57.14%) subjects were treated with systemic methods. The most common systemic methods included acitretin (25/63, 39.7%), local-PUVA (13/63, 20.6%), and methotrexate (Mtx) (11/63, 17.5%). Eight patients (12.7%) were treated with systemic glucocorticosteroids by rheumatologists because of accompanying arthritis.

Acitretin was administered in 20-40 mg doses per day. The treatment lasted between 3 weeks and 3 years, but usually 1-3 months. An improvement of more than 75% was noted in about 50% of the cases of skin lesions. A rapid recurrence of the disease (5/12) and short remissions of up to three months were observed (4/12) in the study group. In 10/24 cases, side effects resulted in the discontinuation of treatment.

Medical documentation was available for only 5/13 subjects treated with local-PUVA. An improvement of more than 75% was observed in 3/5 patients with lesions, including one for whom a 5-month remission was observed. In the remaining two subjects, no remission was observed. A single dose ranged from 0.75 to 4.0 J/cm^2, and the total dose ranged from 59.5 to 104 J/cm^2.

Methotrexate was administered in doses of 12.5 to 25 mg/week because of skin lesions (4/10) or arthritis (6/10). Rheumatologists treated three patients without skin lesions with Mtx and systemic glucocorticosteroids. In only one subject to whom Mtx was administered in a dose of 25 mg/week for 12 months one year of remission of skin lesions was achieved. No clinical change was observed in 4/7 (57.14%) subjects.

DISCUSSION

A review of the literature identified the general characteristics of patients with palmoplantar pustulosis in various populations, e.g., Swedish, Japanese, German, Austrian or Spanish (9-14). Despite some similarities among these populations, a few differences were described. The presence of anti-gliadin antibodies and coeliac disease, as well as an elevated level of calcium, was characteristic for Swedish patients with PPP (9, 15, 16). Pustulotic arthro-osteitis (PAO) was prevalent in Japanese patients. In one study, 70/469 (14.9%) of patients presented with PAO (10). Interestingly, a high incidence of PPP was not observed among Japanese females (10, 17). The prevalence of PPP in the Japanese population at large was estimated at 0.12% (95% confidence interval (CI), 0.12% to 0.12%) (18).

In our study of Polish patients with PPP, more than 90% of the subjects were women, with an average age of 58.5 years. In addition, the results regarding the association between smoking and thyroid disease were consistent with a majority of the characteristics of PPP cases described in the literature (9, 11, 19).

In comparison to the studies in the Swedish population (9, 16), our study found no antiendomysial autoantibodies or celiac disease in any of the 24 subjects in the PPP group who presented with IgA or IgG. The results were consistent with the observations of Weisenseel *et al*. (20). Moreover, there was no statistical difference in the calcium or magnesium levels of the subjects with PPP or PSV. The results did not confirm the observations of Hagforsen *et al*. (15).

Acta Dermatovenerol Croat
2018;26(2):109-118

Concomitant diseases

Metabolic syndrome is the name for a group of risk factors that lead to an increased risk of cardiovascular disease and type 2 diabetes. The new criteria for the diagnosis of metabolic syndrome were published in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (8).

Many reports have been published about metabolic syndrome in individuals with psoriasis. A meta-analysis of 41,853 PSV cases revealed that a patient with metabolic syndrome has twice the risk for developing psoriasis in comparison to individuals in the general population, for developing psoriasis (21). In another study, Langan *et al*. (22) showed that the severity of psoriasis was positively correlated with metabolic syndrome. In patients with mild psoriasis (BSA <2%), metabolic syndrome was diagnosed in 32% of cases. In subjects with moderate psoriasis (BSA 2–10%), it was diagnosed in 36% of cases, and in subjects with severe psoriasis (BSA > 10%), it was diagnosed in 40% of cases (22).

In the current study, metabolic syndrome was diagnosed in the PPP group in 30.16% of the cases and in the control group (PSV) in 32.43% of the cases, with no statistically significant difference (p=0.8124). There was no statistically significant difference in the percentage of subjects with elevated BMI (>25kg/m2) in the PPP and PSV groups, although the mean BMI was higher in subjects with PSV in comparison to those with PPP (28.25 vs. 25.86 kg/m^2, respectively, p=0.0144). In the Tratter H. *et al*. study the metabolic syndrome was observed in 26% (24, 41) of patients with PPP (14).

In addition, there was no statistical difference in the prevalence of ischaemic heart disease, hypertension, or type 2 diabetes mellitus between the groups. The results were consistent with the study of Atas and Gonul (23). They did not find the difference between the fasting glucose, insulin and the homeostatic model assessment (HOMA index) between the PPP and control groups (23).

It might be interesting to compare the prevalence of metabolic syndrome in patients with PPP and those in the general population.

Joint pain quite often accompanied PPP. It was present in 57.14% of the PPP cases in the our study. Knee joints were affected most often. Among the subjects with arthralgia, arthritis was diagnosed in more than 20% of cases. The SAPHO syndrome was observed in one case. No pustulotic arthro-osteitis (PAO), which was a characteristic in Japanese populations (10), was observed in our study group. The literature related to joint pain in PPP mostly describes rare diseases like Sonozoki syndrome, SAPHO syndrome, or chronic recurrent multifocal osteomyelitis (24-26). Reports regarding the concomitance of arthralgia and PPP are rare. In one study, arthralgia was reported in 25/59 (42.37%) cases, mostly in hand joints (9).

A review of the literature revealed only a few studies describing the association between PPP and contact allergies. In a study of a group of 40 subjects with PPP, positive patch tests were observed in 6 (15%) cases (19). In another study, 9/15 (60%) patients with PPP presented with positive patch tests, with 7 cases exhibiting polyvalent allergies (27). Fragrances were the most common allergens. Interestingly, in 7/9 subjects with positive patch tests, the avoidance of allergens caused an improvement of skin lesions.

Case studies have suggested that flare-ups of PPP lesions might be associated with treatments with dental fillings. In one case, the development of skin lesions on the palms and soles started after dental treatment with medications, including zinc. The replacement of the dental fillings with those without zinc resulted in the remission of the lesions (28). In another case, PPP skin lesions resistant to treatment regressed following the removal of dental amalgams. In those cases, patch tests were positive for metal allergens (29, 30).

In our study, positive patch tests were found in 30.77% patients with PPP. Polyvalent allergies were noted in 8 cases. The most common allergens were nickel chloride and fragrances.

These observations all indicate that patients with PPP might need screening for contact allergies.

Treatment

In our study, the majority of patients were treated with systemic methods, including acitretin (39.7%), local-PUVA (20,6%), and methotrexate (17.5%). Acitretin had high efficacy, although recurrences of lesions were observed very soon after the withdrawal of the drug.

There are a few reports about the effectiveness of local-PUVA in PPP (31-34). However, the combined treatment of retinoid and PUVA (Re-PUVA) seems to be the most effective method (35).

Based on single reports, Mtx could be the second- or third-line treatment in PPP, especially in patients with arthritis and contraindications to acitretin (36).

Sevrain *et al*. published a systematic literature review and recommendations for the treatment of PPP (37). For the first-line treatment of PPP without

PsA, potent or very potent topical glucocorticosteroids were proposed. For the second-line treatment, a combination therapy of acitretin and local phototherapy or monotherapy of one of the methods was suggested. For the third-line treatment, ciclosporin and methotrexate were recommended (37). These recommendations were consistent with our clinical observations with one exception–namely, that topical benzoyl peroxide or retinoids could be an alternative for topical glucocorticosteroids.

Other studies have documented the use of biological treatments for PPP. In one open study, Bissonnette *et al*. showed that etanercept might be effective in some patients with PPP (38). In another study, a randomized controlled trial with a group of 33 patients with PPP, ustekinumab did not show significant efficacy (39). In an observational descriptive study, a complete or partial response to treatment without adverse events was observed in only 5/11 (45%) subjects with PPP (40).

Recently, many new report about the treatment in PPP were published, including excimer laser, calcipotriol- clobetasol propionate combination (41), apremilast (42), ustekinumab (43) and guselkumab (44) as well as a systematic review on biologic therapy (45).

Nosological position of PPP

The nosological position of PPP has already been discussed by authors of this paper in (46). In this context, the biggest question arises about the relationship between PPP and PSV. What distinguishes PPP and PSV is undoubtedly the high incidence among women patients, the association with smoking and thyroid disease, as well as the statistically significantly later onset of PPP, which has already been described (9, 11) and confirmed in our study of Polish patients.

Although PSV skin lesions were observed periodically in 17/63 (26.98%) patients with PPP, none of them presented with scalp involvement, generalized skin lesions, or psoriatic erythroderma. This would have been quite unusual in 63 patients with PSV. In addition, onycholysis was statistically less prevalent in PPP patients despite the seemingly similar frequency of the occurrence of nail changes in PPP and PSV patients (36.11% vs. 11.11%). The above observations, as well as those in genetic studies (47, 48), point to a distinction between PPP and PSV.

Nevertheless, some observations lead to a hint that there might be a relationship between PPP and PSV. A positive family history of vulgar psoriasis, PSV skin lesions, and many types of nail changes characteristic of PSV were reported for the study group. In both groups of patients, joint pain was observed with similar frequency. It is worth noting that PSV and PPP are the most common side effects affecting the skin from therapies with biologicals, especially anti-TNF-α (43-46). This implies some shared etiopathological pathways.

In our study, the group of patients with PPP was heterogeneous. We did not find any condition that influenced the course of the disease or the response to treatment. Only a positive PSV family history resulted in the onset of the disease being eight years earlier than in other patients. In our opinion, we can distinguish at least two groups among PPP patients: one with a chronic course of the disease and significant resistance to treatment and the other with a mild course of the disease.

In approximately 25-30% of subjects, PPP was associated with vulgar psoriasis; however, in the remaining 70-75% of patients, no association was found between PPP and PSV. In addition, the disease in these patients showed features that were distinct from those associated with PSV.

CONCLUSION

Patients with PPP, like patients with PSV, often presented with hypertension and metabolic syndrome. Given that many studies have focused on the cardiovascular risk in PSV (53), there is a need for more research on the association between PPP and the risk for cardiovascular disease. In addition, patients resistant to PPP treatment should be screened for contact allergies.

References:

1. Lever WF, editor. Histopathology of the skin. Philadelphia: J.B. Lippincott; 1967. p. 149
2. Thomsen K, Osterbye P. Pustulosis palmaris et plantaris. Br J Dermatol. 1973;89:293-6.
3. O'Doherty CJ, MacIntyre C. Palmoplantar pustulosis and smoking. Br Med J (Clin Res Ed). 1985;291:861-4.
4. Eriksson MO, Hagforsen E, Lundin IP, Michaelsson G. Palmoplantar pustulosis: a clinical and immunohistological study. Br J Dermatol. 1998;138:390-8.
5. Akiyama T, Seishima M, Watanabe H, Nakatani A, Mori S, Kitajima Y. The relationships of onset and exacerbation of pustulosis palmaris et plantaris to smoking and focal infections. J Dermatol. 1995;22:930-4.
6. Hagforsen E. The cutaneous non-neuronal cholinergic system and smoking related dermatoses: studies of the psoriasis variant palmoplantar pustulosis. Life Sci. 2007;80:2227-34.
7. Becher G, Jamieson L, Leman J. Palmoplantar pustulosis--a retrospective review of comor-

bid conditions. J Eur Acad Dermatol Venereol. 2015;29:1854-6.

8. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-421.
9. Eriksson MO, Hagforsen E, Lundin IP, Michaelsson G. Palmoplantar pustulosis: a clinical and immunohistological study. Br J Dermatol. 1998;138:390-8.
10. Akiyama T, Seishima M, Watanabe H, Nakatani A, Mori S, Kitajima Y. The relationships of onset and exacerbation of pustulosis palmaris et plantaris to smoking and focal infections. J Dermatol. 1995;22:930-4.
11. Gimenez-Garcia R, Sanchez-Ramon S, Cuellar-Olmedo LA. Palmoplantar pustulosis: a clinicoepidemiological study. The relationship between tobacco use and thyroid function. J Eur Acad Dermatol Venereol. 2003;17:276-9.
12. Brunasso AM, Puntoni M, Aberer W, Delfino C, Fancelli L, Massone C. Clinical and epidemiological comparison of patients affected by palmoplantar plaque psoriasis and palmoplantar pustulosis: a case series study. Br J Dermatol. 2013;168:1243-51.
13. Wilsmann-Theis D, Jacobi A, Frambach Y, Philipp S, Weyergraf A, Schill T, *et al*. Palmoplantar pustulosis - a cross-sectional analysis in Germany. Der matol Online J. 2017;23:4.
14. Trattner H, Bluml S, Steiner I, Plut U, Radakovic S, Tanew A. Quality of life and comorbidities in palmoplantar pustulosis - a cross-sectional study on 102 patients. J Eur Acad Dermatol Venereol. 2017;31:1681-5.
15. Hagforsen E, Michaelsson K, Lundgren E, Olofsson H, Petersson A, Lagumdzija A, *et al*. Women with palmoplantar pustulosis have disturbed calcium homeostasis and a high prevalence of diabetes mellitus and psychiatric disorders: a case-control study. Acta Derm Venereol. 2005;85:225-32.
16. Michaelsson G, Kristjansson G, Pihl Lundin I, Hagforsen E. Palmoplantar pustulosis and gluten sensitivity: a study of serum antibodies against gliadin and tissue transglutaminase, the duodenal mucosa and effects of gluten-free diet. Br J Dermatol. 2007;156:659-66.
17. Noda K, Kodama S, Suenaga S, Suzuki M. Tonsillar focal infectious disease involving IgA nephropathy, pustulosis, and ossification. Clin Exp Nephrol. 2007;11:97-101.
18. Kubota K, Kamijima Y, Sato T, Ooba N, Koide D, Iizuka H, *et al*. Epidemiology of psoriasis and palmoplantar pustulosis: a nationwide study using the Japanese national claims database. BMJ Open. 2015;5:e006450.
19. Thomsen K, Osterbye P. Pustulosis palmaris et plantaris. Br J Dermatol. 1973;89:293-6.
20. Weisenseel P, Kuznetsov AV, Ruzicka T, Prinz JC. Palmoplantar pustulosis is not inevitably associated with antigliadin antibodies. Br J Dermatol. 2007;156:1399-400.
21. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol. 2013;68:654-62.
22. Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, *et al*. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol. 2012;132(3 Pt 1):556-62.
23. Atas H, Gonul M. Insulin resistance, diabetes mellitus and thyroid dysfunction in patients with palmoplantar pustulosis: a case-controlled study. Postepy Dermatol Alergol. 2017;34:268-72.
24. Koshiba S, Ichimiya S, Nagashima T, Tonooka A, Kubo T, Kikuchi T, *et al*. Tonsillar crypt epithelium of palmoplantar pustulosis secretes interleukin-6 to support B-cell development via p63/p73 transcription factors. J Pathol. 2008;214:75-84.
25. Sonozaki H, Azuma A, Okai K, Nakamura K, Fukuoka S, Tateishi A, *et al*. Clinical features of 22 cases with "inter-sterno-costo-clavicular ossification". A new rheumatic syndrome. Arch Orthop Trauma Surg. 1979;95:13-22.
26. Zhao Z, Li Y, Zhao H, Li H. Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome with review of the relevant published work. J Dermatol. 2011;38:155-9.
27. Yiannias JA, Winkelmann RK, Connolly SM. Contact sensitivities in palmar plantar pustulosis (acropustulosis). Contact Dermatitis. 1998;39:108-11.
28. Yanagi T, Shimizu T, Abe R, Shimizu H. Zinc dental fillings and palmoplantar pustulosis. Lancet. 2005;366:1050.
29. Liu F, Zhang M, Lou Y, Liu H, Sang H. The spontaneous regression of palmoplantar pustulosis following removal of dental amalgams: A report of two cases. Australas J Dermatol. 2016;57:e93-6.
30. Ito T, Mori T, Fujiyama T, Tokura Y. Dramatic exacerbation of palmoplantar pustulosis following strongly positive nickel patch testing. Int J Dermatol. 2014;53:e327-9.
31. Agren-Jonsson S, Tegner E. PUVA therapy for

palmoplantar pustulosis. Acta Derm Venereol. 1985;65:531-5.

32. Paul R, Jansen CT. Suppression of palmoplantar pustulosis symptoms with oral 8-methoxypsoralen and high-intensity UVA irradiation. Dermatologica. 1983;167:283-5.
33. Sezer E, Erbil AH, Kurumlu Z, Tastan HB, Etikan I. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. J Dermatol. 2007;34:435-40.
34. Lassus A, Lauharanta J, Eskelinen A. The effect of etretinate compared with different regimens of PUVA in the treatment of persistent palmoplantar pustulosis. Br J Dermatol. 1985;112:455-9.
35. Matsunami E, Takashima A, Mizuno N, Jinno T, Ito H. Topical PUVA, etretinate, and combined PUVA and etretinate for palmoplantar pustulosis: comparison of therapeutic efficacy and the influences of tonsillar and dental focal infections. J Dermatol. 1990;17:92-6.
36. Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? Br J Dermatol. 2011;164:942-6.
37. Sevrain M, Richard MA, Barnetche T, Rouzaud M, Villani AP, Paul C, *et al*. Treatment for palmoplantar pustular psoriasis: systematic literature review, evidence-based recommendations and expert opinion. J Eur Acad Dermatol Venereol. 2014;28:13-6.
38. Bissonnette R, Poulin Y, Bolduc C, Maari C, Provost N, Syrotuik J, *et al*. Etanercept in the treatment of palmoplantar pustulosis. J Drugs Dermatol. 2008;7:940-6.
39. Bissonnette R, Nigen S, Langley RG, Lynde CW, Tan J, Fuentes-Duculan J, *et al.* Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. J Eur Acad Dermatol Venereol. 2014;28:1298-305.
40. Bertelsen T, Kragballe K, Johansen C, Iversen L. Efficacy of ustekinumab in palmoplantar pustulosis and palmoplantar pustular psoriasis. Int J Dermatol. 2014;53:e464-6.
41. Thakur A, Bishnoi A, Dogra S, Narang T. Comparison of effectiveness and safety of excimer lamp vs topical calcipotriol-clobetasol propionate combination in the treatment of palmoplantar psoriasis. Photodermatol Photoimmunol Photomed. 2018 Feb 8 doi: 10.1111/phpp.12378. [Epub ahead of print].
42. Haebich G, Kalavala M. Successful treatment of refractory palmoplantar pustulosis with apremilast. Clin Exp Dermatol. 2017 Feb 27 doi: 10.1111/ced.13065. [Epub ahead of print].
43. Hegazy S, Konstantinou MP, Bulai Livideanu C, Tauber M, Uthurriague C, Paul C. Efficacy of ustekinumab in palmoplantar pustulosis. J Eur Acad Dermatol Venereol. 2018;32:e204-e206. doi: 10.1111/jdv.14718.
44. Terui T, Kobayashi S, Okubo Y, Murakami M, Hirose K, Kubo H. Efficacy and Safety of Guselkumab, an Anti-interleukin 23 Monoclonal Antibody, for Palmoplantar Pustulosis: A Randomized Clinical Trial. JAMA Dermatol. 2018;154:309-16.
45. Sanchez IM, Sorenson E, Levin E, Liao W. The Efficacy of Biologic Therapy for the Management of Palmoplantar Psoriasis and Palmoplantar Pustulosis: A Systematic Review. Dermatol Ther. 2017;7:425-46.
46. Misiak-Galazka M, Wolska H, Rudnicka L. What do we know about palmoplantar pustulosis? J Eur Acad Dermatol Venereol. 2017;31:38-44.
47. Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaelsson G, Evans J, *et al*. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. J Invest Dermatol. 2003;120:627-32.
48. Mossner R, Kingo K, Kleensang A, Kruger U, Konig IR, Silm H, *et al*. Association of TNF -238 and -308 promoter polymorphisms with psoriasis vulgaris and psoriatic arthritis but not with pustulosis palmoplantaris. J Invest Dermatol. 2005;124:282-4.
49. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9:1-14.
50. Shmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-alpha inhibitors: the Mayo Clinic experience, 1998 to 2010. J Am Acad Dermatol. 2012;67:e179-85.
51. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. Arthritis Rheum. 2007;56:2715-8.
52. Gonzalez-Lopez MA, Martinez-Taboada VM, Gonzalez-Vela MC, Fernandez-Llaca H, Val-Bernal JF. New-onset psoriasis following treatment with the interleukin-1 receptor antagonist anakinra. Br J Dermatol. 2008;158:1146-8.
53. Baran A, Kiluk P, Mysliwiec H, Flisiak I. The role of lipids in psoriasis. Dermatol Rev/Przegl Dermatol. 2017;104: 619-35.