Pack-year cigarette smoking affects the course of palmoplantar pustulosis

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Abstract

Background. Palmoplantar pustulosis (PPP) is a chronic inflammatory disease with poorly understood pathogenesis. The disease has a chronic course with improvements and exacerbations. Due to palmoplantar location, PPP has a severely negative impact on patients' quality of life.

Objectives. To identify demographic and environmental factors, concomitant diseases, medications, and bacterial factors which may affect the course of PPP.

Materials and methods. A total of 51 patients suffering from PPP took part in the study. They were classified according to the Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI) into 3 groups due to the severity of the disease. Pack-year of smoking score was established as a quotient of packets smoked every 24 h and the years of being addicted. Diagnosis of metabolic syndrome was based on the IDF criteria from 2009. *Chlamydia trachomatis* was detected using enzyme-linked immunosorbent assay (ELISA) technique, *Staphylococcus aureus* by the culture swabs. Contact hypersensitivity was examined with the T.R.U.E. test.

Results. Significantly high severity of PPP was observed in patients addicted to smoking with a high pack-year score ($p = 0.03$). Significantly lower intensity of PPP lesions was observed in patients treated with ibuprofen ($p < 0.01$). There was no correlation between severity of PPP skin lesions and comorbidities.

Conclusions. Addiction to cigarette smoking and a high pack-year score aggravates the course of PPP. Treatment with ibuprofen can improve the course of the disease.

Key words: smoking addiction, pack-year score, comorbidities, ibuprofen, palmoplantar pustulosis

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Background

Palmoplantar pustulosis (PPP) is a chronic inflammatory disease with poorly understood pathogenesis. The lesions are localized on the palms and soles, usually symmetrically.[1,2] Sterile pustules on the erythematous skin, with superficial scaling and fissures are observed. The disease has a chronic course with improvements and exacerbations. Middle-aged women are more common affected than men. Palmoplantar pustulosis has a severely negative impact on quality of life. Clinical observations and research data indicate that genetic, immunological and environmental factors play a role in the development of PPP.[2] The disease is classified by some authors as a variant of psoriasis, and by others treated as a separate condition.[2–5] Some lesions are common for psoriasis and PPP. The co-occurrence of cutaneous psoriatic lesions and psoriatic nail changes is observed in patients with PPP. Some patients with PPP report arthralgia as well as a positive family history of psoriasis. Moreover, focal bacterial infections seem to play a role in the pathogenesis of both diseases.[1,6,7] On the other hand, there are differences between psoriasis and PPP. Palmoplantar pustulosis occurs more often in middle-aged women and it does not occur in children. Many publications confirm the relationship between PPP and cigarette smoking, as well as the co-occurrence of contact allergies[8–11] and other comorbidities.[8–15] Thyroid dysfunction in PPP patients is observed more frequently than in the case of psoriasis.[16,17]

Objectives

The objective of this study was to identify demographic and environmental factors, concomitant diseases, medications, and bacterial factors that may affect the course of PPP.

Materials and methods

A total of 51 people suffering from PPP, who had been hospitalized in the Dermatology Department of Wroclaw Medical University, Poland, took part in the study. The severity of PPP was assessed according to the Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI). The ppPASI is a modification of the PASI index with evaluation of erythema, vesicles/pustules and scaling/desquamation. Patients were classified into 3 groups due to the severity of the disease: mild (ppPASI: 0–9), moderate (ppPASI: 10–19) and severe (ppPASI: 29–72) disease. Pack-year of smoking score was established as a quotient of packets smoked every 24 h and the years of being addicted. The diagnosis of metabolic syndrome was based on the International Diabetes Federation (IDF) criteria from 2009.[18] *Chlamydia trachomatis* was detected in urethral specimens with enzyme-linked immunosorbent assay (ELISA) technique. *Staphylococcus aureus* (*S. aureus*) colonization of the nasal vestibule was established using culture swabs. Contact hypersensitivity was examined with the thin-layer rapid-use epicutaneous (T.R.U.E.) test with 35 allergens.

The influence of age, sex, co-occurrence of psoriatic lesions and metabolic syndrome, environmental factors such as: cigarette smoking, contact allergies, medications taken for other diseases, and infectious factors on the severity of PPP skin lesions were assessed.

The results obtained during the research were statistically analyzed using STATISTICA v. 12.0 (StatSoft Polska Sp. z o.o.; Kraków, Poland). Student's t-test, χ^2, Kolmogorov–Smirnov test, Pearson correlation, the Yates's correction, and the analysis of variance (ANOVA) were used. The analysis was performed at the significance level of $p = 0.05$.

The study was approved by the Ethics Committee of Wroclaw Medical University. All study participants signed informed consent forms.

Results

The results of the study are presented in Table 1. A total of 51 patients with PPP, 11 (22%) men and 40 (78%) women, aged 20–77 years (mean age: 54.2 years), were included in the study. The predominance of women among the patients was statistically significant ($p = 0.03$). Skin lesions were most often located on: hands and feet in 36 (70.6%) patients, in 5 (9.8%) patients only on the hands, and in 10 (19.6%) only on the feet. The values of ppPASI ranged from 2.4 to 72 with the average value of 21.64. Nine (17.65%) patients were classified into the group with mild disease (ppPASI < 10), 18 (35.29%) with moderate (ppPASI 10–19) and 24 (47.06%) with severe disease (ppPASI ≥ 20). There was no correlation between the severity of skin lesions and the age or sex of patients ($p = 0.66$; $p = 0.81$, respectively). The disease onset was between 45 and 65 years of age (mean: 47.1 years). The duration of the disease ranged from 1 year to 45 years. The age of onset and duration of the disease did no influence the severity of PPP skin lesions ($p = 0.63$; $p = 0.91$, respectively).

Concomitant psoriasis

In 14 (27.45%) patients with PPP, pustular lesions were accompanied by plaque psoriasis. The majority of these patients (8, 57.1%) suffered from severe PPP (ppPASI > 20), and only 1 patient (7.4%) had mild disease (ppPASI < 10); however, no significant correlation was established.

Cigarettes smoking

In the study group, 47 (92.2%) patients were active cigarette smokers. Four non-smoking patients had

Table 1. Severity of PPP symptoms depending on concomitant treatment

Medicines	Use of medications	Number of patients with different intensity of skin lesions in the course of PPP (n = 51)			p-value
		mild (ppPASI < 10) n (%)	moderate (ppPASI 10–19) n (%)	severe (ppPASI ≥ 20) n (%)	
β-blockers	no	8 (19.5%)	17 (41.5%)	16 (39%)	0.06
	yes	1 (10%)	1 (10%)	8 (80%)	
Angiotensin converting enzyme (ACE) inhibitors	no	8 (18.2%)	18 (40.9%)	18 (40.9%)	0.06
	yes	1 (14.3%)	0 (0%)	6 (85.7%)	
Statins	no	8 (20%)	14 (35%)	18 (45%)	0.69
	yes	1 (9.1%)	4 (36.4%)	6 (54.5%)	
Ibuprofen	no	6 (12.8%)	18 (38.3%)	23 (48.9%)	<0.01
	yes	3 (75%)	0 (0%)	1 (25%)	
Indapamide	no	8 (17.4%)	18 (39.1%)	20 (43.5%)	0.2
	yes	1 (20%)	0 (0%)	4 (80%)	
Hydrochlorothiazide	no	9 (18.8%)	17 (35.4%)	22 (45.8%)	0.66
	yes	0 (0%)	1 (33.3%)	2 (66.7%)	
Acetylsalicylic acid (ASA)	no	9 (19.6%)	17 (37%)	20 (43.5%)	0.27
	yes	0 (0%)	1 (20%)	4 (80%)	
Levothyroxine	no	6 (15.4%)	15 (38.5%)	18 (46.1%)	0.61
	yes	3 (25%)	3 (25%)	6 (50%)	

mild-to-moderate lesions. Severe course of the disease with ppPASI > 20 was observed only in smokers. The mean pack-year score among patients with PPP was 21.36. Significantly higher severity of PPP was observed in patients with a higher pack-year score (p = 0.03).

Concomitant contact hypersensitivity

Contact hypersensitivity was found in 14 (27.5%) patients. The most common allergen was nickel. An allergy to this metal was present in 7 (14.73%) patients. Four (7.84%) patients were allergic to preservatives used in cosmetics and topical medications. Two patients reacted to KATHON™ CG, 2 to thiomersal and 3 to: sterol alcohols from lanolin, cobalt hydrochloride, p-tert-butylphenol-formaldehyde resins, a mixture of parabens, a mixture of carbon derivatives, potassium dichromate, and a thiuram mix. There was no correlation between the severity of PPP skin lesions and the presence of contact allergy (p = 0.89).

Co-infections

Chlamydia trachomatis urethritis was found in only 2 (3.92%) patients, and *S. aureus* colonization of the nasal vestibule was found in 10 (19.61%) patients. There was no statistically significant correlation between the severity of PPP and the coexistence of chlamydia infection or *S. aureus* colonization.

Treatment of comorbidities

Due to comorbidities, 33 (64.71%) of the studied patients were taking medications. Severe PPP with ppPASI ≥ 20 was observed in 8 of 10 patients treated with β-blockers and in 6 of 7 patients treated with angiotensin-converting-enzyme (ACE) inhibitors. However, there was no correlation between the severity of PPP and treatment with these medications, although the p-value was low (0.06). On the other hand, significantly lower intensity of PPP lesions was observed in patients treated with ibuprofen (p < 0.01). Only 4 patients were treated with ibuprofen, but 3 of them had mild disease (Table 2).

BMI and metabolic syndrome

Patients' BMI ranged from 17.18 to 48.33, with mean value of 26.82. Twenty-one (41.18%) patients had normal weight, 19 (37.25%) were overweight and 11 (21.57%) were obese. Despite the fact that over half of obese patients had severe disease (ppPASI ≥ 20), no correlation was found between the severity of skin lesions and their BMI (p = 0.3). A total of 24 patients had metabolic syndrome that did not correlate with the PPP severity.

Thyroid disease and arthralgia

Of all 51 of the studied patients, 14 (27.45%) had thyroid disease or had a history of thyroid disease. Twenty-six patients (50.98%) complained of arthralgia. However, these conditions did not correlate with the severity of PPP.

Table 2. Severity of PPP symptoms depending on lesions location, demographic factors, duration of the disease, smoking, concomitant diseases, bacterial factors, and coexistence of metabolic syndrome

Factors potentially influencing the severity of PPP	Number of patients with different intensity of skin lesions in the course of PPP PPP (n = 51)			p-value
	mild (ppPASI < 10) n (%)	moderate (ppPASI 10–19) n (%)	severe (ppPASI ≥ 20) n (%)	
Localization of skin lesions hands feet hands and feet	 2 (40%) 2 (20%) 5 (13.88%)	 3 (60%) 4 (40%) 11 (30.56%)	 0 4 (40%) 20 (55.56%)	0.21
Age <30 years 30–54 years ≥55 years	 1 (33.3%) 2 (10%) 6 (21.4%)	 1 (33.3%) 9 (45%) 8 (28.6%)	 1 (33.3%) 9 (45%) 14 (50%)	0.66
Sex women men	 7 (17.5%) 2 (18.2%)	 15 (37.5%) 3 (27.3%)	 18 (45%) 6 (54.5%)	0.81
The onset of the disease <30 years 30–55 years ≥55 years	 3 (33.3%) 3 (12%) 3 (17.6%)	 2 (22.2%) 11 (44%) 7 (41.2%)	 4 (44.4%) 11 (44%) 7 (41.2%)	0.63
Duration of the disease <10 years 10–19 years ≥20 years	 7 (17.9%) 1 (14.3%) 1 (20%)	 15 (38.5%) 2 (28.6%) 1 (20%)	 17 (43.6%) 4 (57.1%) 3 (60%)	0.91
Coexistence of cutaneous psoriasis PPP without psoriasis PPP with psoriasis	 8 (21.6%) 1 (7.4%)	 13 (35.1%) 5 (35.7%)	 16 (43.2%) 8 (57.1%)	0.44
Smoking smoker non-smoker	 7 (14.9%) 2 (50%)	 16 (34%) 2 (50%)	 24 (51.1%) 0 (0%)	0.09
Pack-year score <10 10–19 ≥20	 4 (50%) 0 (0%) 3 (11.1%)	 2 (25%) 5 (41.7%) 9 (33.3%)	 2 (25%) 7 (58.3%) 15 (55.6%)	0.03
Patch test negative positive	 6 (16.2%) 3 (21.4%)	 13 (35.1%) 5 (35.7%)	 18 (48.7%) 6 (42.9%)	0.89
C. trachomatis infection yes no	 0 (0%) 9 (18.37%)	 1 (50%) 17 (34.69%)	 1 (50%) 23 (46.94%)	0.75
S. aureus colonization yes no	 1 (10%) 8 (19.51%)	 3 (30%) 15 (36.59%)	 6 (60%) 18 (43.9%)	0.62
BMI normal overweight obese	 4 (19%) 2 (10.5%) 3 (27.3%)	 9 (42.9%) 8 (42.1%) 1 (9.1%)	 8 (38.1%) 9 (47.4%) 7 (63.6%)	0.3
Metabolic syndrome present absent	 7 (29.2%) 2 (7.4%)	 9 (37.5%) 9 (33.3%)	 8 (33.3%) 16 (59.3%)	0.07
Thyroid disease yes no	 4 (28.6%) 5 (13.5%)	 3 (21.4%) 15 (40.5%)	 7 (50%) 17 (46%)	0.3
Arthralgia yes no	 6 (23.08%) 2 (8.33%)	 10 (38.46%) 8 (33.33%)	 10 (38.46%) 14 (58.33%)	0.17

Discussion

Palmoplantar pustulosis is a rare disease. In Western Europe, the incidence of this disease ranges from 0.01% to 0.05%,[1] and in the Japanese population it is 0.12%.[6] Palmoplantar pustulosis accounts for 20% of hand and foot skin diseases.[19] The etiopathogenesis of the disease is not fully understood. In the literature, PPP is classified as a subtype of psoriasis or a separate disease entity. In our study, about 1/3 of patients with PPP had comorbid psoriasis, which is slightly more than data from other studies (about 20%).[1] Typically, PPP occurs in adults. The age of PPP patients varies from 21 to 50 years[1]; however some authors pointed a higher mean age (56.7 years).[6]

Most of our patients, as in other publications,[20] suffered from skin lesions located both on hands and feet. Among our patients, the disease onset was between 18 and 74 years of age (mean: 47.1 years). The duration of the disease was 1–45 years (mean: 7.14 years).

Clinical studies and case reports indicate that certain genetic, environmental and infectious factors affect the onset and/or the exacerbation of PPP. Recently, the pathogenic relationship between PPP and cigarette smoking was analyzed in the literature.[10] Cigarette smoke contains over 4000 chemicals, 300 of which are carcinogens or have pro-inflammatory activities.[21] Hagforsen et al. documented the relationship between smoking and the occurrence of PPPs, and found that this addiction increases the risk of developing PPP seventy-fold.[22] In our study, we found a statistically significant correlation between the severity of skin lesions and pack-year score. The relationship between the severity of PPP skin lesions and cigarette smoking has not been published before. The mechanism of smoking impact on the PPP symptoms has not been precisely established. Characteristic locations of the lesions on the palmar and plantar region support the theory that sweat glands and acetylcholine receptors (AChR) play the role in the PPP pathogenesis. There are 2 main types of acetylcholine receptor receptors: nicotinic (nAChR) and muscarinic (mAChR), which are found on keratinocytes and on sweat gland cells. The increased expression of alpha7 nAChR which controls homeostasis and terminal differentiation of epidermal cells was observed on the sweat glands and in the epidermis of patients with PPP compared to healthy individuals.[22–24] These receptors show greater affinity for nicotine than for acetylcholine. New theory explains that nicotine-stimulated nAChR play a role in the PPP pathogenesis by leading to the accumulation of neutrophils and eosinophils in the epidermis.[25,26] Additionally, peripheral arterial disease caused by smoking may probably trigger PPP. This idea is supported by the case report of a patient with Leriche syndrome. Symptoms of PPP improved after smoking cessation and authors observed complete cure of skin lesions after vascular surgery and improved arterial circulation.[27]

Contact hypersensitivity may coexist with PPP, or may have an impact on the course of the disease.[28] In our study, 27.5% of patients had positive result of patch tests. Nickel was the most common allergen. In the literature, even higher percentage of PPP patients with coexisting contact hypersensitivity (39–60%) has been reported.[8,11] The most common contact allergens in these patients were: nickel, balsam of Peru and a mixture of fragrances. More frequent use of jewellery and cosmetics may promote the PPP occurrence in women. Furthermore, patients with PPP, due to the chronic disease, use topical medications and cosmetics for a long time and contact allergy to creams and ointments ingredients can exacerbate skin symptoms. Therefore, patch tests should be performed in patients with no reaction to topical therapy or if disease worsening during topical treatment is observed.

The relationship between focal bacterial infections and the severity of skin lesions in PPP has recently been discussed in the literature. Tonsillectomy or treatment of any bacterial infections led to significant improvement or cure of PPP in some patients.[29,30] The etiopathogenetic relationship of PPP and *Helicobacter pylori* infection has been observed as well.[31,32] No relationship between the appearance or exacerbation of PPP skin lesions with bacterial infections or symptoms of gastric ulcer was observed in our study. However, 26 (51%) of study participants suffered from tooth caries. According to the literature, odontogenic and other infections may exacerbate skin lesions in the course of PPP.[29,30,33,34]

Pustular skin lesions are also observed in the course of reactive arthritis caused by chlamydia infection. Isolated PPP caused by *C. trachomatis* was considered recently and higher level of chlamydial antibodies in PPP patients in comparison to healthy people was documented.[35] Nevertheless, only 2 (3.92%) of our patients had chlamydia infection. In recent years, the colonization of skin and mucous membranes by *S. aureus* in patients with psoriasis has been carefully examined. Immunological processes triggered by bacterial antigens probably play a role in the course of this disease. Keratinocytes stimulated by bacterial antigens produce antimicrobial proteins (e.g., protein S-100) that contribute to local inflammation. Elevated levels of these proteins have been shown in psoriatic lesions. Studies on the colonization of the skin and nasal vestibule in people with psoriasis were performed, but their results are ambiguous. A higher and similar percentage of psoriatic patients with *S. aureus* colonization in the atrium of the nasal vestibule in comparison to control was documented.[36] So far, colonization of the nasal vestibule by *S. aureus* in PPP patients has not been studied. In our study, bacteria were found in 10 (19.61%) patients. In 6 patients, we observed severe PPP (ppPASI ≥ 20); however, there was no correlation between staphylococcal colonization and PPP severity.

The correlation between PPP and treatment of comorbidities should be also taken under consideration. A significant percentage of patients with PPP described in the literature

were simultaneously treated for concomitant diseases.[14] However, the influence of drugs on the course of the disease has not been observed. In our study, most of the studied patients receiving medications for high blood pressure suffered from severe PPP. In the group of 10 patients treated with β-blockers, 8 (80%) had severe PPP. Similarly, 7 patients treated with ACE inhibitors presented severe skin lesions with ppPASI ≥ 20. No relationship was observed between the occurrence or exacerbation of PPP lesions and starting treatment for hypertension. Only 1 person claimed that the PPP lesions began after introducing a new drug (amlodipine) and improved a few weeks after discontinuation of this calcium channel blocker. Stanford et al. described the occurrence of PPP following the initiation of β-blockers.[37] On the other hand, statistically significant lower severity of skin lesions was observed in patients taking ibuprofen ($p < 0.01$). Anti-inflammatory activity of this medication could have a beneficial effect on the severity of PPP symptoms. This positive impact of ibuprofen in PPP requires further verification due to a small group of patients taking this drug in our study.

A numerous publications of increased prevalence of the metabolic syndrome in patients with psoriasis, as well as more severe course of psoriasis in patients with this condition[38] encouraged us to study the coexistence of PPP and the metabolic syndrome. Among our patients, 47.1% had the metabolic syndrome and the PPP course was more severe in these patients ($p = 0.07$).

Inflammatory and pustular lesions located on the hands and feet are very characteristic for PPP, but these lesions are also observed in chronic inflammatory disorders such as SAPHO (synovitis, acne, hands and feet pustulosis, periosteal hyperplasia and osteitis) syndrome, pustular osteomyelitis (PAO), and Sonozaki syndrome.[39] None of our patients had SAPHO, PAO or Sonozaki syndrome. However, 26 participants (50.98%) reported arthralgia, but no correlation was observed between the severity of PPP skin lesions of and joint pain.

Conclusions

Cigarette smoking has been shown to affect the PPP course. As this is a modifiable factor, patients with PPP should be advised to quit smoking. As the research results show, a positive effect of ibuprofen on skin lesions in the course of PPP and the use of ibuprofen in the therapy should be considered, but it requires further studies on a larger number of patients.

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References

1. Khandpur S, Singhal V, Sharma V. Palmoplantar involvement in psoriasis: A clinical study. *Indian J Dermatol Venereol Leprol*. 2011;77(5):625. doi:10.4103/0378-6323.84071
2. Yamamoto T. Extra-palmoplantar lesions associated with palmoplantar pustulosis. *J Eur Acad Dermatol Venereol*. 2009;23(11):1227–1232. doi:10.1111/j.1468-3083.2009.03296.x
3. Ammoury A, El Sayed F, Dhaybi R, Bazex J. Palmoplantar pustulosis should not be considered as a variant of psoriasis. *J Eur Acad Dermatol Venereol*. 2008;22(3):392–393. doi:10.1111/j.1468-3083.2007.02344.x
4. Misiak-Galazka M, Wolska H, Rudnicka L. Is palmoplantar pustulosis simply a variant of psoriasis or a distinct entity? *J Eur Acad Dermatol Venereol*. 2017;31(7):e342–e343. doi:10.1111/jdv.14136
5. Misiak-Galazka M, Wolska H, Rudnicka L. What do we know about palmoplantar pustulosis? *J Eur Acad Dermatol Venereol*. 2017;31(1):38–44. doi:10.1111/jdv.13846
6. Kubota K, Kamijima Y, Sato T, et al. Epidemiology of psoriasis and palmoplantar pustulosis: A nationwide study using the Japanese national claims database. *BMJ Open*. 2015;5(1):1–9. doi:10.1136/bmjopen-2014-006450
7. Kumar B, Saraswat A, Kaur I. Palmoplantar lesions in psoriasis: A study of 3065 patients. *Acta Derm Venereol*. 2002;82(3):192–195. doi:10.1080/00015550260132488
8. Caca-Biljanovska N, V'lckova-Laskoska M, Balabanova-Stefanova M, Grivceva-Panovska V. Frequency of delayed-type hypersensitivity to contact allergens in palmo-plantar psoriasis. *Prilozi*. 2005;26(2):131–141. https://pubmed.ncbi.nlm.nih.gov/16400235/
9. De Waal AC, Van de Kerkhof PCM. Pustulosis palmoplantaris is a disease distinct from psoriasis. *J Dermatolog Treat*. 2011;22(2):102–105. doi:10.3109/09546631003636817
10. Hagforsen E, Awder M, Lefvert AK, Nordlind K, Michaëlsson G. Palmoplantar pustulosis: An autoimmune disease precipitated by smoking? *Acta Derm Venereol*. 2002;82(5):341–346. doi:10.1080/00015550232062406 9
11. Yiannias JA, Winkelmann RK, Connolly SM. Contact sensitivities in palmar plantar pustulosis (acropustulosis). *Contact Dermatitis*. 1998;39(3):108–111. doi:10.1111/j.1600-0536.1998.tb05857.x
12. Hayashi S, Shimaoka Y, Hamasaki Y, Hatamochi A. Palmoplantar pustulosis and pustulotic arthro-osteitis treatment with potassium iodide and tetracycline, a novel remedy with an old drug: A review of 25 patients. *Int J Dermatol*. 2017;56(8):889–893. doi:10.1111/ijd.13608
13. Becher G, Jamieson L, Leman J. Palmoplantar pustulosis: A retrospective review of comorbid conditions. *J Eur Acad Dermatol Venereol*. 2015;29(9):1854–1856. doi:10.1111/jdv.12545
14. Hiraiwa T, Yamamoto T. Comorbidities of Japanese patients with palmoplantar pustulosis: A report from a single center. *Int J Dermatol*. 2018;57(7):e40–e41. doi:10.1111/ijd.14023
15. Misiak-Galazka M, Zozula J, Rudnicka L. Palmoplantar pustulosis: Recent advances in etiopathogenesis and emerging treatments. *Am J Clin Dermatol*. 2020;21(3):355–370. doi:10.1007/s40257-020-00503-5.
16. Pontikides N, Krassas GE. Influence of cigarette smoking on thyroid function, goiter formation and autoimmune thyroid disorders. *Hormones*. 2002;1(2):91–98. doi:10.14310/horm.2002.1156
17. Rosen K, Lindstedt G, Mobacken H, Nystrom E. Thyroid function in patients with pustulosis palmoplantaris. *J Am Acad Dermatol*. 1988;19(6):1009–1016. doi:10.1016/s0190-9622(88)70265-0
18. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644
19. Hongal AA, Rajashekhar N, Gejje S. Palmoplantar dermatoses: – A clinical study of 300 cases. *J Clin Diagn Res*. 2016;10(8):4–7. doi:10.7860/JCDR/2016/20818.8364
20. Pettey AA, Balkrishnan R, Rapp SR, Fleischer AB, Feldman SR. Patients with palmoplantar psoriasis have more physical disability and discomfort than patients with other forms of psoriasis: Implications for clinical practice. *J Am Acad Dermatol*. 2003;49(2):271–275. doi:10.1067/s0190-9622(03)01479-8

21. Miot HA, Miot LD, Lopes PS, Haddad GR, Marques SA. Association between palmoplantar pustulosis and cigarette smoking in Brazil: A case-control study. *J Eur Acad Dermatol Venereol.* 2009;23(10): 1173–1177. doi:10.1111/j.1468-3083.2009.03282.x
22. Hagforsen E, Michaëlsson K, Lundgren E, 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(3):225–232. doi:10.1080/00015550510026587
23. Hagforsen E, Hedstrand H, Nyberg F, Michaëlsson G. Novel findings of Langerhans cells and interleukin-17 expression in relation to the acrosyringium and pustule in palmoplantar pustulosis. *Br J Dermatol.* 2010;163(3):572–579. doi:10.1111/j.1365-2133.2010.09819.x
24. Hagforsen E, Michaëlsson G, Stridsberg M. Normal and PPP-affected palmoplantar sweat gland express neuroendocrine markers chromogranins and synaptophysin differently. *Arch Dermatol Res.* 2010; 302(9):685–693. doi:10.1007/s00403-010-1070-3
25. Hagforsen E, Awder M, Lefvert AK, Nordlind K, Michaëlsson G. Palmoplantar pustulosis: An autoimmune disease precipitated by smoking? *Act Derm Venereol.* 2002;82(5):341–346. doi:10.1080/000155502320624069
26. Hagforsen E. Palmoplantar pustulosis. Pathogenetic studies with special reference to the role of nicotine. Acta Universitatis Upsaliensis. Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 2001. https://www.diva-portal.org/smash/record.jsf?pid=diva2%3A167253&dswid=mainwindow. Acceesed May 29, 2017.
27. Murao K, Minato M, Kubo Y. Improvement of palmoplantar pustulosis lesions after angioplasty for Leriche syndrome. *Australas J Dermatol.* 2013;54(3):e80–81. doi:10.1111/j.1440-0960.2012.00940.x
28. Ito T, Mori T, Fujiyama T, Tokura Y. Dramatic exacerbation of palmoplantar pustulosis following strongly positive nickel patch testing. *Int J Dermatol.* 2014;53(5):327–329. doi:10.1111/ijd.12242
29. Takahara M, Hirata Y, Nagato T, et al. Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro-osteitis: A retrospective subjective and objective quantitative analysis of 138 patients. *J Dermatol.* 2018;45(7):812–823. doi:10.1111/1346-8138.14348
30. Yamamoto T. Triggering role of focal infection in the induction of extra-palmoplantar lesions and pustulotic arthro-osteitis associated with palmoplantar pustulosis. *Adv Otorhinolaryngol.* 2011;72: 89–92. doi:10.1159/000324620
31. Martin Hübner A, Tenbaum SP. Complete remission of palmoplantar psoriasis through *Helicobacter pylori* eradication: A case report. *Clin Exp Dermatol.* 2008;33(3):339–240. doi:10.1111/j.1365-2230.2007.02634.x
32. Sáez-Rodríguez M, Noda-Cabrera A, García-Bustínduy M, et al. Palmoplantar pustulosis associated with gastric *Helicobacter pylori* infection. *Clin Exp Dermatol.* 2002;27(8):720. doi:10.1046/j.1365-2230.2002.01102_6.x
33. Kouno M, Nishiyama A, Minabe M, et al. Retrospective analysis of the clinical response of palmoplantar pustulosis after dental infection control and dental metal removal. *J Dermatol.* 2017;44(6):695–698. doi:10.1111/1346-8138.13751
34. Kikuchi N, Yamamoto T. Dental infection as a triggering factor in palmoplantar pustulosis. *Acta Derm Venereol.* 2013;93(6):721–722. doi:10.2340/00015555-1552
35. Jansen CT, Hollmén, Pajarre R, Terho P. Antichlamydial antibodies in chronic palmoplantar pustulosis. *Acta Derm Venereol.* 1980;60(3): 263–266.
36. Ng CY, Huang YH, Chu CF, Wu TC, Liu SH. Risks for *Staphylococcus aureus* colonization in psoriasis patients: A systematic review and meta-analysis. *Br J Dermatol.* 2017;177(4):967–977. doi:10.1111/bjd.15366
37. Stanford CW, Kollipara R, Melookaran AM, Hall JC. Palmoplantar pustular psoriasis following initiation of a beta-blocker: Disease control with low-dose methotrexate. *Cutis.* 2014;94:153–155.
38. 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(4):654–662. doi:10.1016/j.jaad.2012.08.015
39. Brzezińska-Wcisło L, Bergler-Czop B, Lis-Święty A. Sonozaki syndrome: Case report and review of literature. *Rheumatol Int.* 2012;32(2): 473–477. doi:10.1007/s00296-009-1335-3