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.

Material 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
Background

Palmoplantar pustulosis (PPP) is a chronic inflammatory disease with poorly understood pathogenesis. The lesions are localized on the palms and soles, usually symmetrically. 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 commonly 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. The disease is classified by some authors as a variant of psoriasis, and by others as a separate condition. 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. 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 and other comorbidities. Thyroid dysfunction in PPP patients is observed more frequently than in the case of psoriasis.

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.

Material and methods

A total of 51 people suffering from PPP, who had been hospitalized in the Dermatology Department of the Medical University, Poland, took part in the study. The predominance of women among the participants 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 1 to 72 with the average value of 21.64. Nine (17.65%) PPP patients had 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 not influence the severity of PPP skin lesions (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 1 to 72 with the average value of 21.64. Nine (17.65%) PPP patients had 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 not influence the severity of PPP skin lesions (p = 0.03; 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...
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.

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**Table 1. Severity of PPP symptoms depending on concomitant treatment**

| Medicines                  | Use of medications | mild (ppPASI < 10) n (%) | moderate (ppPASI 10–19) n (%) | severe (ppPASI ≥ 20) n (%) | p-value |
|----------------------------|--------------------|--------------------------|-------------------------------|---------------------------|---------|
| 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%)                   |         |
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 (n = 51) | p-value |
|---------------------------------------------------|-----------------------------------------------------------------|---------|
|                                                   | mild (ppPASI < 10) n (%) | moderate (ppPASI 10–19) n (%) | severe (ppPASI ≥ 20) n (%) |
| Localization of skin lesions                      |                                  |                                  |                              |
| hands                                             | 2 (40%)                          | 3 (60%)                          | 0                             |
| feet                                              | 2 (20%)                          | 4 (40%)                          | 4 (40%)                       |
| hands and feet                                     | 5 (13.88%)                       | 11 (30.56%)                      | 20 (55.56%)                   |
| Age                                               |                                  |                                  |                               |
| <30 years                                          | 1 (33.3%)                        | 1 (33.3%)                        | 1 (33.3%)                     |
| 30–54 years                                       | 2 (10%)                          | 9 (45%)                          | 9 (45%)                       |
| ≥55 years                                         | 6 (21.4%)                        | 8 (28.6%)                        | 14 (50%)                      |
| Sex                                                |                                  |                                  |                               |
| women                                              | 7 (17.5%)                        | 15 (37.5%)                       | 18 (45%)                      |
| men                                                | 2 (18.2%)                        | 3 (27.3%)                        | 6 (54.5%)                     |
| The onset of the disease                          |                                  |                                  |                               |
| <30 years                                          | 3 (33.3%)                        | 2 (22.2%)                        | 4 (44.4%)                     |
| 30–55 years                                       | 3 (12%)                          | 11 (44%)                         | 11 (44%)                      |
| ≥55 years                                         | 3 (17.6%)                        | 7 (41.2%)                        | 7 (41.2%)                     |
| Duration of the disease                           |                                  |                                  |                               |
| <10 years                                          | 7 (17.9%)                        | 15 (38.5%)                       | 17 (43.6%)                    |
| 10–19 years                                       | 1 (14.3%)                        | 2 (28.6%)                        | 4 (57.1%)                     |
| ≥20 years                                         | 1 (20%)                          | 1 (20%)                          | 3 (60%)                       |
| Coexistence of cutaneous psoriasis                 |                                  |                                  |                               |
| PPP without psoriasis                             | 8 (21.6%)                        | 13 (35.1%)                       | 16 (43.2%)                    |
| PPP with psoriasis                                | 1 (2.4%)                         | 5 (35.7%)                        | 8 (57.1%)                     |
| Smoking                                           |                                  |                                  |                               |
| smoker                                            | 7 (14.9%)                        | 16 (34%)                         | 24 (51.1%)                    |
| non-smoker                                        | 2 (50%)                          | 2 (50%)                          | 0 (0%)                        |
| Pack-year score                                   |                                  |                                  |                               |
| <10                                                | 4 (50%)                          | 2 (25%)                          | 2 (25%)                       |
| 10–19                                              | 0 (0%)                           | 5 (41.7%)                        | 7 (58.3%)                     |
| ≥20                                                | 3 (11.1%)                        | 9 (33.3%)                        | 15 (55.6%)                    |
| Patch test                                        |                                  |                                  |                               |
| negative                                          | 6 (16.2%)                        | 13 (35.1%)                       | 18 (48.7%)                    |
| positive                                          | 3 (21.4%)                        | 5 (35.7%)                        | 6 (42.9%)                     |
| C. trachomatis infection                          |                                  |                                  |                               |
| yes                                               | 0 (0%)                           | 1 (50%)                          | 1 (50%)                       |
| no                                                | 9 (18.37%)                       | 17 (34.69%)                      | 23 (46.94%)                   |
| S. aureus colonization                             |                                  |                                  |                               |
| yes                                               | 1 (10%)                          | 3 (30%)                          | 6 (60%)                       |
| no                                                | 8 (19.51%)                       | 15 (36.59%)                      | 18 (43.9%)                    |
| BMI                                               |                                  |                                  |                               |
| normal                                            | 4 (19%)                          | 9 (42.9%)                        | 8 (38.1%)                     |
| overweight                                        | 2 (10.5%)                        | 8 (42.1%)                        | 9 (47.4%)                     |
| obese                                             | 3 (27.3%)                        | 1 (9.1%)                         | 7 (36.3%)                     |
| Metabolic syndrome                                |                                  |                                  |                               |
| present                                           | 7 (29.2%)                        | 9 (37.5%)                        | 8 (33.3%)                     |
| absent                                            | 2 (7.4%)                         | 9 (33.3%)                        | 16 (59.3%)                    |
| Thyroid disease                                   |                                  |                                  |                               |
| yes                                               | 4 (28.6%)                        | 3 (21.4%)                        | 7 (50%)                       |
| no                                                | 5 (13.5%)                        | 15 (40.5%)                       | 17 (46%)                      |
| Arthralgia                                        |                                  |                                  |                               |
| yes                                               | 6 (23.08%)                       | 10 (38.46%)                      | 10 (38.46%)                   |
| no                                                | 2 (8.33%)                        | 8 (33.33%)                       | 14 (58.33%)                   |

p-values are calculated using chi-square test.
Discussion

Palmoplantar pustulosis is a rare disease. In Western Europe, the incidence of this disease ranges from 0.01% to 0.05%, and in the Japanese population it is 0.12%. Palmoplantar pustulosis accounts for 20% of hand and foot skin diseases. 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%). Typically, PPP occurs in adults. The age of PPP patients varies from 21 to 50 years; however some authors pointed out a higher mean age (56.7 years).

Most of our patients, as in other publications, suffered from skin lesions located 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. Cigarette smoke contains over 4000 chemicals, 300 of which are carcinogens or have pro-inflammatory activities. 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. 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 palm 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. 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. 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.

Contact hypersensitivity may coexist with PPP, or may have an impact on the course of the disease. 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. 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. The etiopathogenic relationship of PPP and Helicobacter pylori infection has been observed as well. 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.

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. 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. Immuno- logical 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. 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. 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. 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 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, periostal hyperplasia and osteitis) syndrome, pustular osteomyelitis (PAO), and Sonozaki syndrome. 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 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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