42 Metal Allergy and Palmoplantar Pustulosis

Paolo D. Pigatto and Gianpaolo Guzzi

42.1 Introduction

Palmoplantar pustulosis (PPP) is characterized by a chronic eruption of sterile pustules on the palms and soles. The disease affects mainly middle-aged and older women, but is also frequent in men [1]. The most characteristic associations are between PPP and smoking, thyroid gland dysfunction [2, 3], autoimmune comorbidities, and abnormal calcium homeostasis [1, 4]. Numerous consecutive studies have confirmed these associations [1, 4].

Skin lesions are predominantly localized to the palms and soles, but can spread to the lateral hands and feet. The primary lesions are sterile pustules on an erythematous and desquamative background. The lesions are sometimes painful and may negatively influence the affected patients' quality of life and even result in a job change if there is significant occupational irritant or mechanic exposure. Aside from this, psoriasis vulgaris and eczema-like lesions may also be found on other parts of the body [1, 5]. Nail lesions (similar to those observed in psoriasis vulgaris) are often present as well, and the most common are nail pitting, onycholysis, subungual pustules, and dystrophy [5, 6]. The differential diagnosis includes acrodermatitis continua of Hallopeau, palmoplantar pustular psoriasis, irritant contact dermatitis, pompholyx, and fungal infections [7].

42.2 Etiology

The etiology of PPP has remained a mystery, although past studies have suggested a possible association with psoriasis. PPP presents with genetic, histopathologic, and clinical features that are not present in psoriasis; however, the common coexistence of psoriasis vulgaris and/or positive family history for psoriasis indicates at least a close relationship between PPP and psoriasis, and, at present, there is insufficient data to exclude PPP from the psoriasis group. Notably, there is also evidence that PPP is driven by leukocyte infiltration with associated pustular lesions caused and/or exacerbated by metal exposure [8]. In a recent study, positive patch test reactions to several metals were found in patients with PPP [9]; patients with PPP are therefore not a homogeneous group. There are at least two major clinical subtypes of the disease: one subtype with a chronic course resistant to treatment and a second subtype characterized by flares of skin lesions and long periods of remission. The disease usually has a chronic and relapsing course and is resistant to treatment.

P.D. Pigatto (✉)
Department of Biomedical, Surgical and Dental Sciences, Unit of Dermatology, IRCCS Galeazzi Hospital, University of Milan, Milan, Italy
e-mail: paolo.pigatto@unimi.it

G. Guzzi
Italian Association for Metals and Biocompatibility Research – A.I.R.M.E.B, Milan, Italy

J.K. Chen, J.P. Thyssen (eds.), *Metal Allergy*, https://doi.org/10.1007/978-3-319-58503-1_42

42.3 Epidemiology and Associations

There are several descriptions of palmoplantar pustulosis in patients of different populations. The most precise data come from Swedish and Japanese studies, as well as Spanish studies [1, 4, 9–11].

Ericsson et al. [1] described patients with PPP in the Swedish population. The study group included 59 patients, 88% of whom were women. The onset of disease occurred between 15 and 66 years of age, with the peak between 30 and 50 years. A total of 50/59 (84.75%) patients had rapid remission of their disease (maximum 1 year), and nine (15.25%) had at least one remission after 1–6 years. Of 59 patients, 56 (94.92%) were active smokers and 8 (13.56%) patients had a history of thyroid gland dysfunction. Abnormal levels of at least one thyroid test were found in 17/39 (43.59%) cases. In addition, antigliadin IgA antibodies were found in 10/39 (25.64%) patients with PPP [1]. These results were confirmed in another study [10]. Antigliadin IgA antibodies were found in 17.9% of cases, and tissue transglutaminase antibodies were found in 9.6% of cases. Moreover, 7/123 (5.69%) patients suffered from celiac disease [10]. It was shown that patients with elevated antigliadin IgA antibodies and tissue transglutaminase values who adhered to the gluten-free diet experienced clearance or marked improvement of skin lesions. Improvement was slow and usually occurred within a few months or years. However, three patients with severe PPP without antigliadin IgA antibodies or tissue transglutaminase antibodies did not improve on the gluten-free diet [10]. The mechanism for the beneficial effect of the gluten-free diet on PPP is unknown. Tissue transglutaminase is expressed in the endothelium of the gut and in the basal layer of the epidermis. It could be speculated that the gluten-free diet decreases the expression of tissue transglutaminase, which may lead to decreased activation and proliferation of inflammatory cells in the dermis [10]. However, in another study in German patients by Weisenseel et al., the association between PPP and gluten sensitivity was not confirmed [11].

It also has been shown that in women with PPP, the calcium level was increased and parathyroid hormone level decreased in comparison with a control group [12]. Another study confirmed abnormalities in calcium homoeostasis in PPP and showed increased serum calcium values, decreased parathyroid hormone level, and low 1,25-hydroxyvitamin D3 values compared with a control group [13]. Interestingly, PPP was not shown to be associated with abnormalities in bone mineral density or osteoporosis [14]. The mechanisms and clinical significance of these high serum calcium levels are unknown [11, 14]. The results were not confirmed in other populations. Hagforsen et al. [12] suggested that patients with PPP are at higher risk of developing Type 2 diabetes (OR 8.7).

Japanese patients with PPP differed from Swedish ones. Akiyama et al. [9] studied a group of 469 patients. The onset of disease was between 9 and 80 years of age, with the peak at 43.3 in women and 44 in men. Interestingly, only 266/469 (56.72%) were women. Similarly, in another study, the percentage of women oscillated around 50% [10]. Akiyama et al. found that 138/469 (29.42%) patients reported psoriasis vulgaris lesions in other locations [9]. Chronic infections, with tonsillitis being the most common, were found in 173/469 (36.89%) patients. In Japanese publications, the role of tonsillitis was underlined as a causative factor for immunological processes leading to skin lesions. Many studies confirmed that tonsillectomy may have caused an improvement in skin lesions or even remission in some patients with PPP [15, 16]. Kubota et al. recently conducted an epidemiological study of psoriasis and PPP in the Japanese population using a national database [11]. They found that the national prevalence of PPP was 0.12% (95% CI, 0.12–0.12%). Interestingly, in patients with PPP, about two-thirds were female (male-to-female ratio, 0.53), and the average age was 55.5 years [11]. Japanese authors also tried to establish a causal connection between PPP and smoking. In one study, 74.7% of male patients smoked over 20 cigarettes per day in comparison with 37.2% of healthy individuals [9].

Patients with PPP may develop Sonozaki syndrome (pustulotic arthro-osteitis, PAO) [17]. It is characterized by a nonerosive aseptic arthritis of the mono- or oligo-arthritic type. The most characteristic feature is sternoclavicular involvement, but the disease can affect the spinal column and peripheral joints as well [17]. The majority of cases were described in Japan. In one study, 70/469 (14.9%) patients had PPP and concomitant PAO symptoms [9]; whereas in another study, 4.2% of patients presented with PAO alone [11].

As far as the Spanish population is concerned, Gimenez-Garcia et al. demonstrated a higher prevalence of tobacco use and thyroid gland dysfunction in a Spanish group of 17 PPP patients, as well as predominance of the disease among women [4]. Moreover, 7/17 patients reported a personal history of repetitive tonsillitis, which is a frequent finding in Japanese patients [4, 9].

Recently, Scottish authors carried out a retrospective study of comorbidities associated with PPP [17]. The main characteristics of the patients supported the existing literature [1, 4]: 78.1% of patients were women and 79.4% were tobacco smokers. The median age of onset was 47 years (range 18–74). It was also shown that 49.3% patients with PPP presented with dyslipidemia, 38.3% presented with hypertension, and 24.6% with ischemic heart disease [16].

Arthralgia and arthritis are common problems in patients with PPP. In one study, arthralgia was reported in 42.37% of patients; [1] in another study, psoriatic arthropathy was present in nine patients (12.3%) [16]. As described above, an association has been found with PPP and Sonozaki syndrome, as well as SAPHO (synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis) syndrome [9, 11, 16–18]. The differences between various populations of patients with PPP are intriguing and probably result from differences in genetic background [6].

42.4 Palmoplantar Pustulosis and Metal Allergy

Skin lesions caused and/or exacerbated by metals are well known. For example, various types of metal alloys are used in prosthodontic replacements for dental applications and, although these metallic materials are biocompatible, metal allergies have occurred. Documented presumed metal allergies from dental restorations include reactions to nickel, iron, cobalt, and zinc (Fig. 42.1).

The relation between PPP and metal allergy has been reported primarily in the Japanese population. Yanagi et al. [19] described a case of PPP presumed to be secondary to zinc allergy on the basis of clinical history, positive patch test reaction to zinc, characteristic histology, and positive

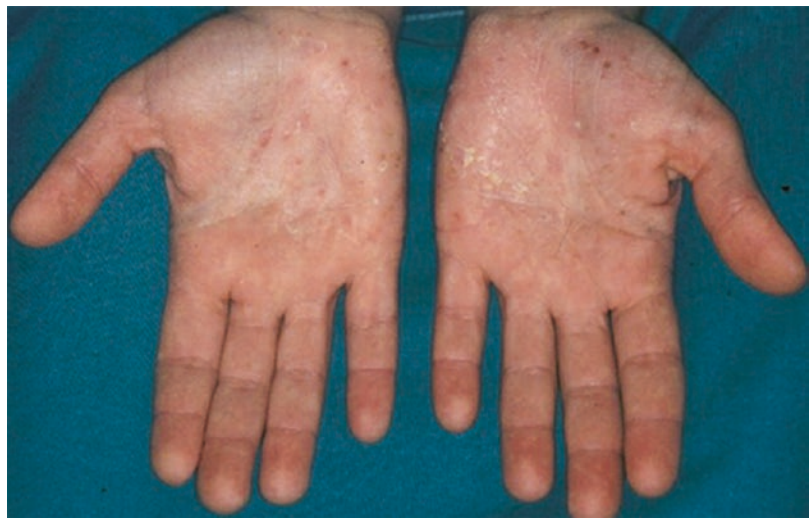

Fig. 42.1 Palmoplantar pustulosis, histologically confirmed, likely caused by cobalt contained in dental amalgam fillings

drug lymphocyte stimulating test (DLST) index. Histologically, identical pustules were found to be induced by zinc patch testing, and a complete remission was achieved by removal of zinc dental restorations.

Cobalt is present in cobalt chromium alloys and has also been implicated in PPP. For example, Song et al. [20] reported an unusual case of PPP on the hands and feet of a 58-year-old male patient caused by a cobalt allergy. The patient developed PPP, characterized by redness, pustules, vesicles, and scaly erythema on his hands and feet, 1 month after having cobalt chromium alloy cast crowns placed on his molar teeth. Skin manifestations persisted for 1 year. He underwent standard patch testing, which showed a strong positive reaction to cobalt chloride. After the crowns were removed, the skin manifestations disappeared in 3 weeks. In this case, there was a strong relationship between the appearance of PPP and metal exposure, as well as improvement after removal of the oral metal.

Two cases of PPP were reported from China that resolved after removal of oral metallic material [21]. Both patients were patch test positive to nickel and one also to cobalt. Both patients showed no recurrence of clinical findings or symptoms during a 1-year follow-up. A case of PPP dramatically exacerbated by a strongly positive patch test reaction to nickel has also been reported [22].

In North America, 9 of 15 patients with PPP who had undergone patch testing showed positive results, including to nickel and mercury, which were of unclear clinical relevance. The authors suggested that it might be prudent to routinely patch test PPP patients since the rate of patch test positivity was higher than would be expected in the general population [23]. In another study, 8 of 22 PPP patients had positive patch test results to one or more of 16 tested metals, with 6 of the 8 reacting to more than 2 metals. Positive results were seen to iridium, nickel, aluminum, palladium, selenium, iron, gold, chromium, zinc, silver, platinum, chromium, copper, zinc, and manganese. Replacement of dental metal with resin in these patients resulted in the remission of PPP [24].

In four patients with PPP in whom blood mercury levels were elevated, a seafood-free diet and chelation with a lowering of blood mercury levels and a clearing of the disease was reported [25]. As mentioned above, an increased occurrence of PPP in patients with psoriasis has been noted, as well as some histopathologic similarities, and it is interesting to speculate that mercury could have been a cause of the PPP in psoriatic patients because mercury was used extensively, both topically and parenterally, in the treatment of psoriasis in the first half of the twentieth century.

Nakamura et al. [8] evaluated the significance of leukotriene (LT) B in the formation of pustules of PPP in metal allergic patients. Pustular and plasma levels of LTB were measured prior to and 48 h after metal patch testing, and the mean levels of LTB in both plasma and pustules 48 hours after patch testing were significantly higher than before testing. Positive metal patch test reactions were detected in all seven PPP patients, to nickel, cobalt, platinum, tin, iron, and palladium. Palmoplantar pustules worsened 48 h after metal patch testing in all patients. The authors concluded that metals may play a role in the pathogenesis of PPP by contributing to the induction of high LTB concentrations in the pustules.

42.5 Conclusions

PPP is associated with moderate-to-severe discomfort and disability and is difficult to treat, often requiring the use of immunosuppressive agents. The etiology of PPP has remained unclear, and past studies have suggested a possible association with psoriasis, or an allergic reaction to metals such as zinc, cobalt, nickel, mercury, and others.

References

1. Eriksson MO, Hagforsen E, Lundin IP, et al. Palmoplantar pustulosis: a clinical and immunohistological study. Br J Dermatol. 1998;138:390–8.
2. O'Doherty CJ, MacIntyre C. Palmoplantar pustulosis and smoking. Br Med J (Clin Res Ed). 1985;291:861–4.
3. Rosen K, Lindstedt G, Mobacken H, et al. Thyroid function in patients with pustulosis palmoplantaris. J Am Acad Dermatol. 1988;19:1009–16.

4. 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.
5. Yamamoto T. Extra-palmoplantar lesions associated with palmoplantar pustulosis. J Eur Acad Dermatol Venereol. 2009;23:1227–32.
6. Burden AD, Kemmett D. The spectrum of nail involvement in palmoplantar pustulosis. Br J Dermatol. 1996;134:1079–82.
7. Coenraads PJ. Handeczema. N EnglJ Med. 2012;367:1829–37.
8. Nakamura K, Imakado S, Takizawa M, Adachi M, Sugaya M, Wakugawa M, et al. Exacerbation of pustulosis palmaris et plantaris after topical application of metals accompanied by elevated levels of leukotriene B4 in pustules. J Am Acad Dermatol. 2000;42:1021–5.
9. Song H, Yin W, Ma Q. Allergic palmoplantar pustulosis caused by cobalt in cast dental crowns: a case report. Oral Surg Oral Med Oral Pathol Oral Radiology Endod. 2011;111(6):e8–10.
10. Michaelsson G, Kristjansson G, Pihl Lundin I, et al. 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.
11. Weisenseel P, Kuznetsov AV, Ruzicka T, et al. Palmoplantar pustulosis is not inevitably associated with antigliadin antibodies. Br J Dermatol. 2007;156:1399–400.
12. Hagforsen E, Michaelsson 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;85:225–32.
13. Hagforsen E, Pihl-Lundin I, Michaelsson K, et al. Calcium homeostasis and body composition in patients with palmoplantar pustulosis: a case-control study. Br J Dermatol. 2012;166:74–81.
14. Akiyama T, Seishima M, Watanabe H, et al. The relationships of onset and exacerbation of pustulosis palmaris et plantaris to smoking and focal infections. J Dermatol. 1995;22:930–4.
15. Takahara M. Clinical outcome of tonsillectomy for palmoplantar pustulosis and etiological relationship between palmoplantar pustulosis and tonsils. Adv Otorhinolaryngol. 2011;72:86–8.
16. Becher G, Jamieson L, Leman J. Palmoplantar pustulosis–a retrospective review of comorbid conditions. J Eur Acad Dermatol Venereol. 2015;29:1854–6.
17. Sonozaki H, Mitsui H, Miyanaga Y, et al. Clinical features of 53 cases with pustulotic arthro-osteitis. Ann Rheum Dis. 1981;40:547–53.
18. Zhao Z, Li Y, Zhao H, et al. Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome with review of the relevant published work. J Dermatol. 2011;38:155–9.
19. Yanagi T, Shimizu T, Abe R, Shimizu H. Zinc dental fillings and palmoplantar pustulosis. Lancet. 2005;366(9490):1050.
20. Song H, Yin W, Ma Q. Allergic palmoplantar pustulosis caused by cobalt in cast dental crowns: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111:e8–e10.
21. 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(3):e93–6. https://doi.org/10.1111/ajd.12366. Epub 2015 Jun 16
22. 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):e327–9. https://doi.org/10.1111/ijd.12242.
23. Yiannias JA, Winkelmann RK, Connolly SM. Contact sensitivities in palmar plantar pustulosis (acropustulosis). Contact Dermat. 1998;39:108–11.
24. Kosugi M, Ishihara K, Okuda K. Implication of responses to bacterial heat shock proteins, chronic microbial infections, and dental metal allergy in patients with pustulosis palmaris et plantaris. Bull Tokyo Dent Coll. 2003;44(3):149–58.
25. Dantzig P. The role of mercury in pustulosis palmaris et plantaris. J Occup Environ Med. 2003;45:468–9.