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Pityriasis rubra pilaris as a systemic disease

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Abstract Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disorder of unknown etiology, initially described in 1835. It is characterized by keratotic follicular papules, well-demarcated salmon-colored erythematous scaly plaques interspersed with distinct islands of uninvolved skin, and palmoplantar keratoderma. Is PRP a systemic disease? Skin is mainly affected in PRP. Despite its clinical heterogeneity, PRP could be associated with a variety of rheumatologic, infectious, neoplastic, and other extracutaneous manifestations. We accept the hypothesis of not only an association but also a causative relation between skin and systemic manifestations with possible common underlying pathomechanisms such as systemic immunologic processes and superantigen mimicry.

Introduction

Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disorder of unknown etiology, characterized by keratotic follicular papules, well-demarcated salmon-colored erythematous scaly plaques interspersed with distinct islands of uninvolved skin, and palmoplantar keratoderma; however, little is known of the concomitant extracutaneous manifestations of the disease.

Historic perspective

After its first description in a patient in 1835 by Claudius Tarral (1810-1886),[1] the disease was later characterized and named "pityriasis pilaris" by Marie-Guillaume-Alphonse Devergie (1798-1879) in 1856.[2] Ernest Henri Besnier (1831-1909) introduced the name "pityriasis rubra pilaris" in 1889.[3]

Epidemiology

No reliable data concerning incidence and prevalence have been reported. One English study reported that 1 in 5,000 new outpatient visits to a dermatologist is due to PRP,[4] whereas an Indian study suggested 1 in 50,000 visits to a dermatologist due to PRP.[5] There is no sexual or racial predilection reported. All ages, including children, are affected, with two common peaks: the first one in childhood (1-10 years of age) and the second one in adulthood (50-60 years of age).[6]

Although PRP has a sporadic occurrence in most cases, up to 6.5% of all PRP-affected individuals may have a positive

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family history.[7] Those rare familial cases demonstrate mostly an autosomal-dominant inheritance with an early age of onset, incomplete penetrance, and variable expression, but a few cases of presumed autosomal recessive inheritance have also been reported.

Etiology and pathogenesis

Little is known about the etiology and pathogenesis of PRP. In this condition, similar to psoriasis, the epidermis is in a hyperkinetic state with increased turnover of the follicular keratinocytes. In the past, a deficiency or a malfunction of vitamin A[8] or decreased serum level of retinol-binding protein, which is the carrier of vitamin A,[9] had been suggested to play a pathogenetic role in PRP, which bears some clinical similarities to phrynoderma—a cutaneous manifestation of vitamin A deficiency.

Accepted triggers of PRP are viral or bacterial infections. Some reports suggest that autoimmune diseases and neoplasia can trigger PRP.[10] These observations have led some authors to hypothesize that PRP is induced by an abnormal immune response toward various antigenic stimuli, such as infections, trauma, and malignancy.[11] Additional theories have been proposed, including an altered retinoid signaling pathway due to an immune disturbance[10] and the role of abnormal keratins, especially in cases demonstrating acantholytic dyskeratosis.[11]

In the familial form of the disease, there are heterozygous mutations in caspase recruitment domain family, member 14 (CARD14).[12] CARD14 is a known activator of nuclear factor kappa B signaling, a pathway that has been implicated in the pathology of inflammatory disorders.

Clinical manifestations

In 1980, William Andrew David Griffiths first divided PRP into the following five types based on clinical characteristics, age of onset, and prognosis:

- Classic adult type I
- Atypical adult type II
- Classic juvenile type III
- Circumscribed juvenile type IV
- Atypical juvenile type V[4]

More recently, the VI type, which is the HIV-associated form, was added.[13,14]

The majority of patients with PRP (55%) have type I PRP. This form, also called classic adult-onset PRP, usually begins on the upper half of the body and has a cephalocaudal progression. Pruritus or burning occurs in approximately 20% of patients.[10] Palmoplantar keratoderma of a prominent orange-yellow color typically appears within weeks or months. Nail involvement manifests most frequently as yellow-brown discoloration and thickening of the nail plate, subungual hyperkeratosis, and splinter hemorrhages. Onycholysis, nail pitting, and "oil drop" findings are not common and

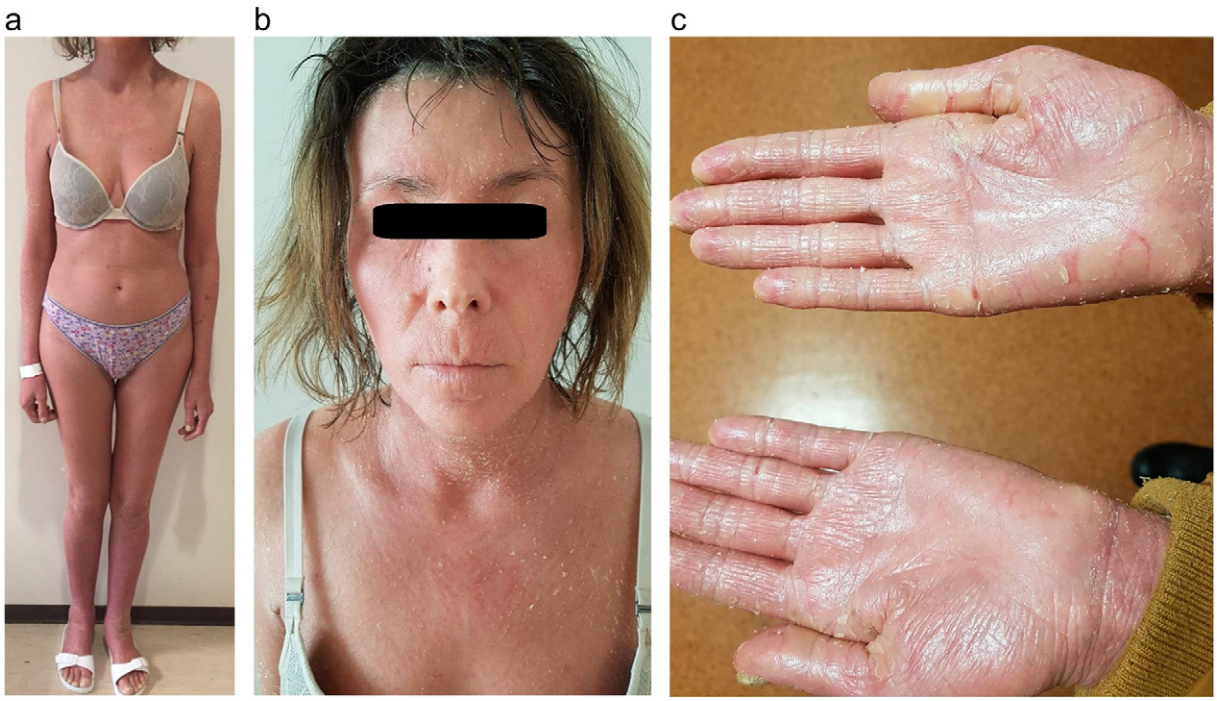

Fig. 1 Erythrodermic changes in a patient with adult classic type of pityriasis rubra pilaris **(a)**, facial efflorescences **(b)**, and orange thick hyperkeratosis and rhagades on the flexural aspects of the palms **(c)**.

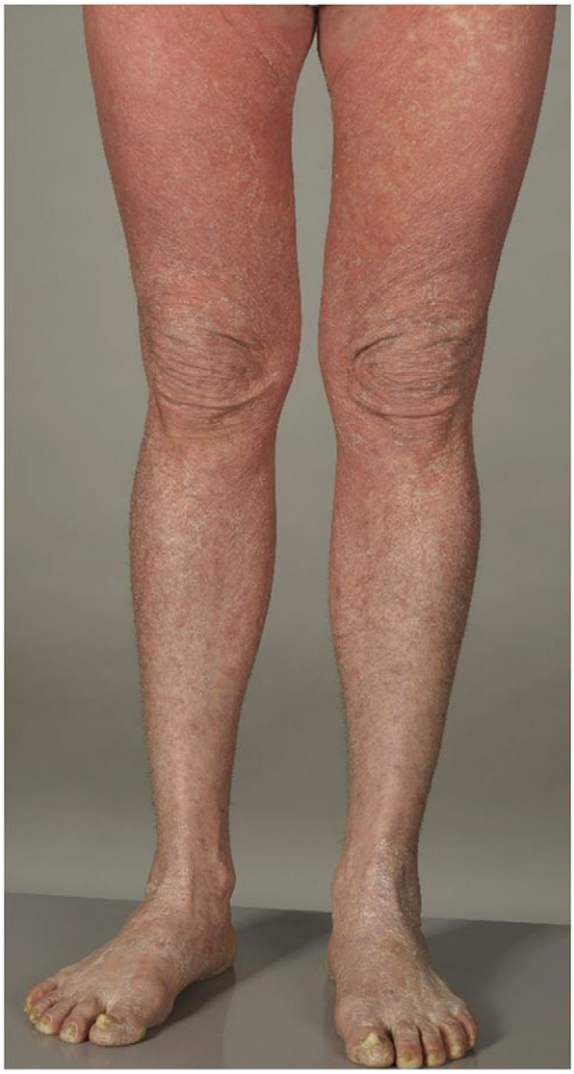

Fig. 2 Ichthyosiform dermatitis of the legs of a 63-year-old woman with type II pityriasis rubra pilaris.

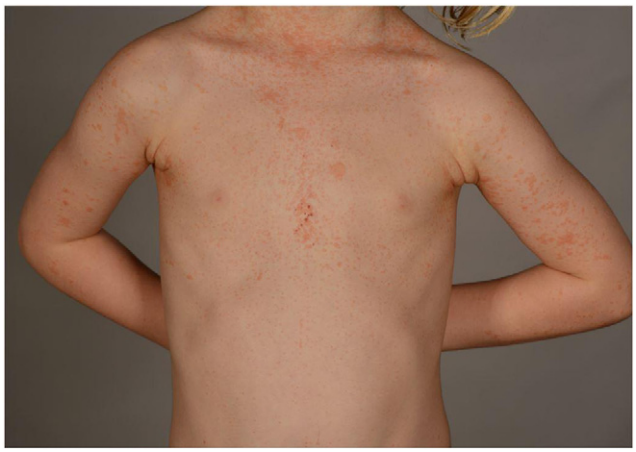

Fig. 3 Typical manifestations in a 4-year-old girl with type III pityriasis rubra pilaris.

differentiate the nail changes from these in psoriasis.[15] Rarely, there are oral mucous membrane changes, including diffuse hyperkeratosis or erythema with white streaks, resembling lichen planus.[16] Despite the quick progression of the disease in this form, which has erythroderma as a common complication, the prognosis is mostly good, with more than 80% of patients with type I PRP experiencing spontaneous resolution within 3 years. The clinical changes in classic adult form PRP are presented in Figure 1.

The atypical adult type II PRP, developed by 5% of the patients, does not follow a cephalocaudal progression. It often shows eczematous lesions, ichthyosiform dermatitis of the legs (Figure 2), and coarse palmoplantar keratosis, as well as alopecia. The course is usually chronic, and only about 20% of these patients show remission within 3 years.

The classic juvenile type III PRP affects children between 5 and 10 years of age and represents approximately 10% of all PRP cases. Its clinical manifestations are similar to those in type I adult-onset PRP (Figure 3), and it has an even better prognosis with frequent spontaneous resolution within 1 year.

Circumscribed juvenile type IV PRP is frequently seen in adolescence and represents 25% of all cases of PRP. It manifests as sharply demarcated erythema and follicular hyperkeratosis that is mostly limited to the knees and elbows. Palmoplantar involvement with keratoderma or dorsal involvement of hands and feet is also characteristic of this form. The course is usually chronic, with a 3-year remission rate of only 32%, and it can be punctuated by remissions and exacerbations.[17]

The atypical juvenile type V can be present at birth or develop in infancy and early childhood, representing 5% of all PRP cases. The majority of patients with hereditary PRP belong to this subtype and often have a chronic course. Type V PRP is characterized by follicular hyperkeratosis, ichthyosiform dermatitis, and sclerodermalike skin lesions on the hands and feet, whereas erythema is not prominent. Response to treatment is usually disappointing.

The HIV-related form VI is similar to type I, with a symmetrical, pruritic eruption composed of erythematous and keratotic follicular papules, but it has a more severe course and tends to be refractory to treatment. Prominent follicular plugging with formation of spicules is another typical finding in this form. Other follicular manifestations, such as acne conglobata, hidradenitis suppurativa, and lichen spinulosus, can be associated with HIV-related PRP.[18]

It is not always possible to assign every single case of PRP to a single type, because intermediate forms and transition from one type to another can occur.[19,20]

The diagnosis of PRP is primarily clinical, based on typical findings. Due to the variability in manifestations, a broad differential diagnosis has to be considered, including psoriasis, dermatitis, ichthyosis, generalized hypersensitivity reaction, erythrokeratoderma variabilis, T-cell lymphoma, seborrheic dermatitis, and even lichen planopilaris. Histopathologic confirmation is essential.

Histopathology

Histopathologic findings of PRP reveal a psoriasiform dermatitis with dry para hyperkeratosis (Figure 4). Although not pathognomonic, alternating orthokeratosis and parakeratosis in both vertical and horizontal directions forming a checkerboard pattern are considered to be an important clue for the diagnosis.[21] Prominent follicular keratosis with shoulder parakeratosis is another very useful clue. Other frequent findings are hypergranulosis, broad rete ridges, narrow dermal papillae, and a sparse superficial perivascular lymphocytic infiltrate. Thick, rather than thin, suprapapillary plates and lack of neutrorphils in the stratum corneum are helpful in distinguishing PRP from psoriasis.[11] Spongiosis and focal acantholytic dyskeratosis within the epidermis have been reported in a proportion of cases with PRP.[22]

Therapy

The relative rarity of PRP and the fact that it often resolves spontaneously make therapeutic studies difficult to conduct and interpret. Recently a proposal for a treatment algorithm in PRP has been published as a result of clinical experience, small case series and case reports, because no randomized controlled trials on PRP have been published.[23]

The management of PRP involves topical and systemic therapies, according to the extension and severity of the disease. In localized forms of PRP, topical therapy is the treatment of choice, and topical agents should also always be applied together with the systemic treatment in severe forms. Established regimens include medium- to high-potency topical corticosteroids, pimecrolimus, keratolytics, emollients, vitamin D derivatives (ie, calcipotriol), and topical retinoids (namely, tretinoin and tazarotene).

If topical treatment is not sufficient, systemic retinoids are the first-line choice among the systemic treatment options. Second-line systemic agents are methotrexate, cyclosporine, or azathioprine. If no marked clinical response is achieved after 12 weeks, switching to biologics should be considered. If no marked clinical response is achieved after 12 weeks, switching to biologics should be considered.

In addition to clinical and histologic similarities to psoriasis, upregulation of proinflammatory innate cytokines (including TNF, IL-12, and IL-23) and adaptive T-cell cytokines (especially the TH17 cytokines IL-17A and IL-22) may be upregulated.[24] This finding has provided a rationale for targeting TNF and the IL-23-TH17 pathway in the treatment of refractory PRP. A comprehensive review of experiences with these biologics has recently been published.[25]

A general recommendation for or against UV therapy in the treatment of PRP cannot be made. Improvement of the skin condition, as well as aggravation, has been reported. If phototherapy is beneficial in an individual patient, it should be considered as an additional therapeutic option.

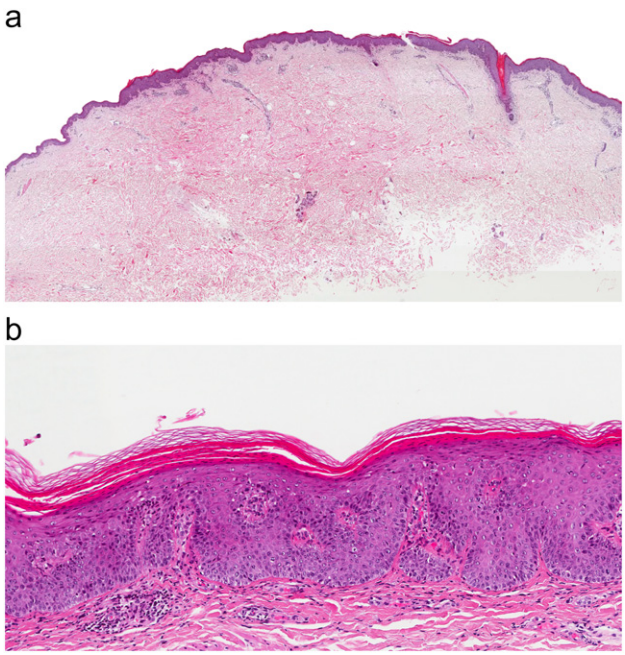

Fig. 4 Histology of pityriasis rubra pilaris (PRP). **(a)** HE, x 20: overview of PRP plaque. Normal skin could be seen on the left-hand side, while the PRP plaque shows hyperkeratosis, parakeratosis, acanthosis, and some dermal, predominantly lymphocytic, infiltration. Compact follicular hyperkeratosis is present on the right-hand side. **(b)** HE, x 200: alternating orthokeratosis and parakeratosis in both vertical and horizontal directions.

Systemic involvement in PRP

PRP is a rare disease; however, there are a number of reports on various associations of PRP with systemic diseases.

Paraneoplastic PRP

There is a report of a patient with fulminant form of PRP recalcitrant to systemic retinoid therapy and associated with cholangiocarcinoma.[26] On initial examination, the skin disease had been present for 10 days with rapid improvement after treatment with oral acitretin. Three months later, the patient experienced an exacerbation with exfoliative erythroderma and palmoplantar keratoderma. Acitretin was stopped, and oral methotrexate initiated. The fulminant and recalcitrant evolution of the skin disease prompted a paraneoplastic investigation. Cholangiocarcinoma was diagnosed. The eruption disappeared completely after 30 weeks of methotrexate therapy. At that time, methotrexate was stopped, and chemotherapy was started. At the 2-year

follow-up visit, the patient was still receiving chemotherapy without any cutaneous signs.

In 2013, a case of PRP in an 89-year-old woman was reported in association with adenocarcinoma of the colon.[27] The skin lesions disappeared 1 month after a right hemicolectomy. In another patient, there was complete resolution of PRP-associated bronchogenic carcinoma 6 months after radiotherapy.[28]

PRP has been associated with laryngeal carcinoma with complete resolution of the skin changes after surgical treatment of the neoplasm.[29] Apart from solid tumors, hematologic malignancy, as in acute undifferentiated leukemia, has been associated with PRP.[30] The mechanism by which cancer triggers PRP is unknown. It may involve secretion of functional peptides or hormones from the tumor or immune cross reaction between normal host cells and initially targeted tumor cells.[31]

Although it is unclear whether the coexistence of PRP and malignant comorbidities represents a true paraneoplastic syndrome, the sudden appearance of PRP, refractory to conventional systemic retinoid treatment, should raise the suspicion of an associated neoplasia.[26]

PRP and autoimmune disorders

An 11-year-old girl was clinically and histopathologically found to have PRP 1 year before developing muscle weakness and increasing fatigue. Elevated creatinine kinase levels, electromyographic changes, and a muscle biopsy confirmed the dermatomyositis in this patient.[32] PRP has also presented as subacute cutaneous lupus erythematosus.[33]

A large meta-analysis of 26 PRP cases has revealed 6 patients with autoimmune coexistent disorders.[11] In a report of two patients with PRP having an abnormal immunologic profile, the authors suggested that clinicians should be aware of an existing autoimmune disorder or abnormal immunologic markers in PRP patients.[34]

A 30-year-old man was reported to have PRP associated with autoimmune hypothyroidism.[11] A rapid and complete resolution of the skin lesions occurred after thyroid hormone replacement therapy. The suggested pathologic mechanism concerns a deficiency of thyroid hormone inhibiting the conversion of carotene into vitamin A, which could be responsible for the development of PRP.[35,36]

PRP and arthritis

A case report described an almost 8-year interval between the onset of PRP in young adult and development of seronegative, entheseal-based synovitis, suggesting screening for arthropathic complications in prolonged PRP cases.[37]

In a review of PRP associated with arthritis, five out of eight patients had seronegative arthritis, where one patient had a positive rheumatoid factor.[38] The status of the other two is unknown. It was speculated that, in the association of PRP with seronegative arthritis, the mechanism is the same as that for psoriatic arthritis, although the latter remains unclear.

PRP and infections

A 7-year-old girl developed juvenile PRP 10 days after varicella.[39] A 38-year-old woman developed classic PRP in association with a primary cytomegalovirus infection.[40] Another patient developed acute juvenile PRP after Kawasaki's disease, suggesting that PRP was a reactive exanthema to a superantigen.[41] Two children developed juvenile PRP after a group A beta-hemolytic streptococcal infection. It was speculated that this was superantigen-driven PRP.[42]

PRP and HIV

The accumulated data on the association of PRP with HIV infection has led to the separation of this association into a new distinctive type (type VI) in PRP classification.[13,14,43] PRP-VI or HIV-associated PRP is characterized by the presence of HIV infection, cutaneous lesions of PRP, and variable associations with acne conglobata, hidradenitis suppurativa, and lichen spinulosus. Triple antiretroviral therapy usually clears the PRP lesions, supporting the pathogenic role of HIV infection in PRP.[44]

Conclusions

In 80% of patients with PRP, spontaneous resolution occurs within 1 to 3 years.[45] Is PRP a systemic disease? Due to the rarity of PRP, a true association with systemic diseases is difficult to prove, and reporting data on the subject would be crucial for clarifying it. Until enough knowledge to draw conclusions is accumulated, it is suggested that a search for a systemic disease in cases of prolonged refractory PRP should be conducted.

A growing body of evidence suggests that PRP is often accompanied by a plethora of systemic diseases. This puts under debate the clinical relevance of administering laboratory investigations for the active screening of concomitant disorders. The question on the role of treating these comorbidities remains to be addressed in future controlled clinical trials.

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