PITYRIASIS RUBRA PILARIS - FOUR CLINICAL CASES

VIRGIL PĂTRAȘCU* , LILIANA GABRIELA GEOLOAICA*

Summary

Introduction. *Pityriasis rubra pilaris (PRP) is a chronic papulo-squamous disease of unknown etiology, characterized by the appearance of scaly, red-orange plaques, palmo-plantar keratoderma and keratotic follicular papules. The acquired forms are the majority and develop in the 5-6 decades of life, and the familial forms (autosomal dominant transmission) usually appear in childhood.*

Clinical cases. *We present 4 cases, two with PRP classic adult type and two pediatric cases, of which one boy with PRP circumscribed juvenile type, respectively the other case with the classic juvenile form.*

Discussions. *The etiopathogenesis of PRP remains unknown, the following hypotheses have been proposed: abnormal metabolism of vitamin A in the skin; the association with autoimmune diseases, cancers or infections, especially HIV. The involvement of the genetic factor is supported by the presence of mutations at the CARD 14 gene level in PRP type V. The diagnosis is clinically suspected and confirmed based on the histopathological aspect, which is suggestive for the diagnosis of PRP, without being specific. There is no consensus regarding treatment, but to date, systemic retinoids appear to be the most effective therapeutic agents. More recently there is interest in biological therapy. Familial forms, whose onset is usually in childhood, have a less favorable prognosis and can evolve throughout life.*

Conclusions. *Pityriasis rubra pilaris is a rare condition, complex from a social and psychological point of view, which can be found in adults and children of both sexes. Recognizing the skin manifestations of PRP allows the rapid initiation of treatment to limit the evolution of the disease and prevent complications.*

Key words: *pityriasis rubra pilaris; etiopathogenesis; treatment; prognosis.*

Received: 09.01.2023 *Accepted: 13.02.2023*

Introduction

Pityriasis rubra pilaris (PRP) is a chronic papulo-squamous disease of unknown etiology, characterized by the appearance of scaly, red-orange plaques, palmo-plantar keratoderma and keratotic follicular papules.

It was reported as a disease for the first time by Tarral in 1828, which Devergie called „pityriasis pilaris", in 1856. Besnier named it PRP in 1889 when he described several cases.[1]

It occurs equally in men and women, regardless of ethnicity. It is more common in Europeans. In the USA, the incidence is 1/5000, and in India one case is found in 50000 inhabitants. In South Africa and Southeast Asia pityriasis rubra pilaris is even rarer.

The acquired forms are the majority and develop in the 5-6 decades of life, and the familial forms (autosomal dominant transmission) usually appear in childhood.[2]

We present 4 cases, *two with PRP classic adult type and two pediatric cases*, of which one boy with PRP circumscribed juvenile type, respectively the other case with the classic juvenile form.

Clinical case 1

A 51-year-old man requested a dermatological consultation for an erythematous-scaly

* Department of Dermatology, Emergency County Hospital, Craiova, University of Medicine and Pharmacy of Craiova, Romania.

eruption, with fine scales, disseminated on the face (Fig. 1), trunk (Fig. 2) and for round, erythematous-scaly plaques, with thick, well-defined scales located on the lower limbs. It also shows scaly plaques on the scalp.

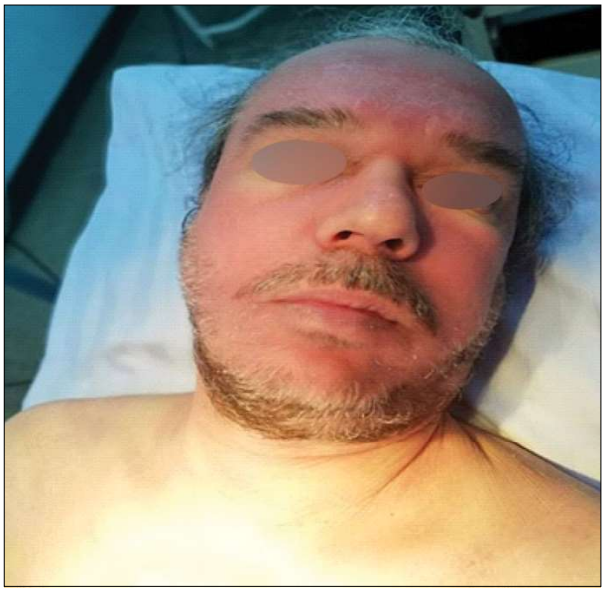

Figure 1 - Erythematous-scaly eruption (clinical case 1)

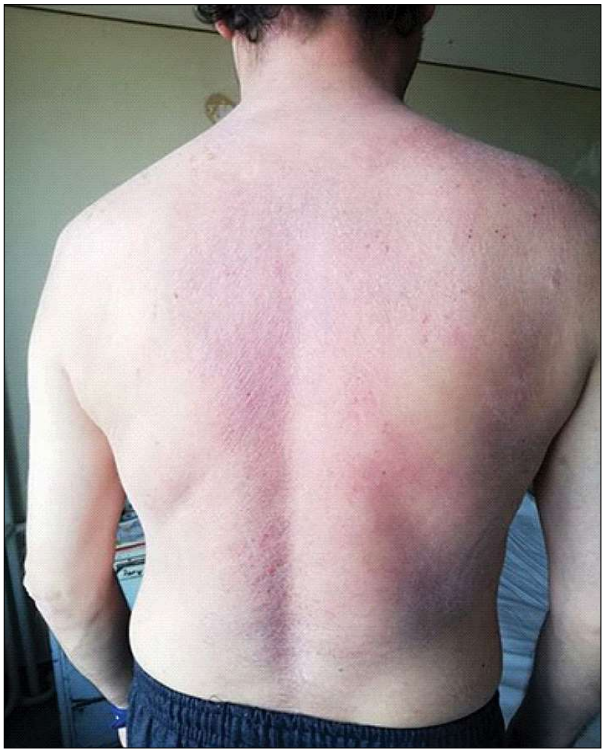

Figure 2 - Erythematous-scaly eruption (clinical case 1)

The lesions started on the face, 3 months ago. The patient underwent treatment with Medrol 16 mg/day for 10 days and local topicals, without favorable evolution. The lesions on the trunk and limbs started one month ago.

Past medical history: Cholecystectomy (10 years ago), primary hypertension grd. II and dyslipidemia for one year. Objective examination: Phototype II, normal weight (BMI 21.5).

Pulmonary X-ray: nothing active, heart without changes in diameters.

Abdominal-pelvic ultrasound: liver with left lobe 9.8 cm, right lobe 16.2 cm steatotic, diffusely inhomogeneous, without localized processes, with posterior attenuation. Cholecystectomy. The rest of the devices are within normal limits.

Paraclinical investigations revealed the presence of dyslipidemia and a mild increase in liver transaminases. The test for HIV infection was negative.

We performed biopsy from some lesions at the level of the right genial, right subclavian and at the level of the left knee. The histopathological examination revealed: epidermis with moderate acanthosis and foci of parakeratosis, foci of hyper and agranulosis; in the papillary dermis ectatized capillaries and discrete perifollicular and perivascular inflammatory infiltrate.

Based on the clinical examination and the histopathological examination, we made the diagnosis of ***classical Pityriasis rubra pilaris of the adult.***

We instituted systemic treatment with methotrexate 10 mg/ml pre-filled syringe one ampoule/week and folic acid 5mg/week, hepatoprotective, and local emollients and dermatocorticoids from class III activity. The evolution was favorable, with the disappearance of the rash after two months of therapy.

Clinical case 2

A 60-year-old man was hospitalized in December 2022 for an almost generalized rash consisting of erythematous-scaly plaques with fine, slightly infiltrated, pruritic scales interspersed with areas of healthy skin. The face is erythemato-squamous, infiltrated and with bilateral ectropion, and the tongue has a cerebriform appearance (Fig. 3). There are also follicular hyperkeratotic papules on the trunk,

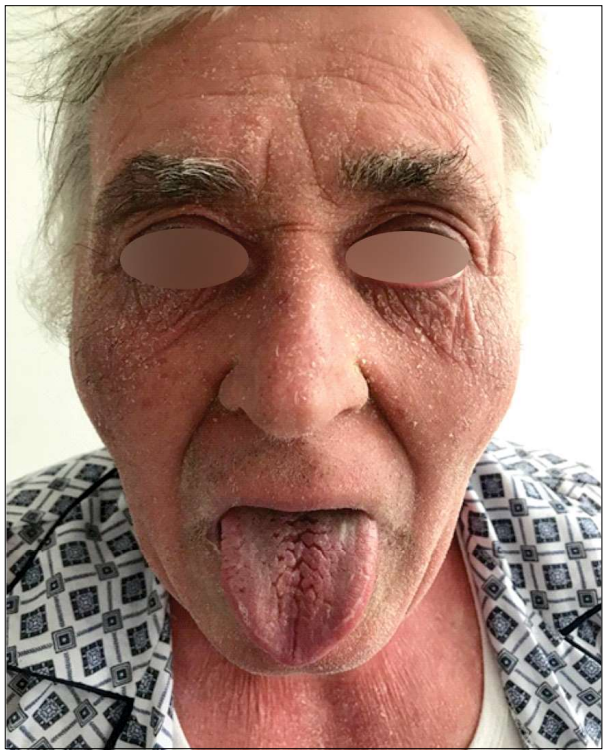

Figure 3 - Cerebriform tongue, ectropion, erythematous-squamous facies, infiltrated (clinical case 2)

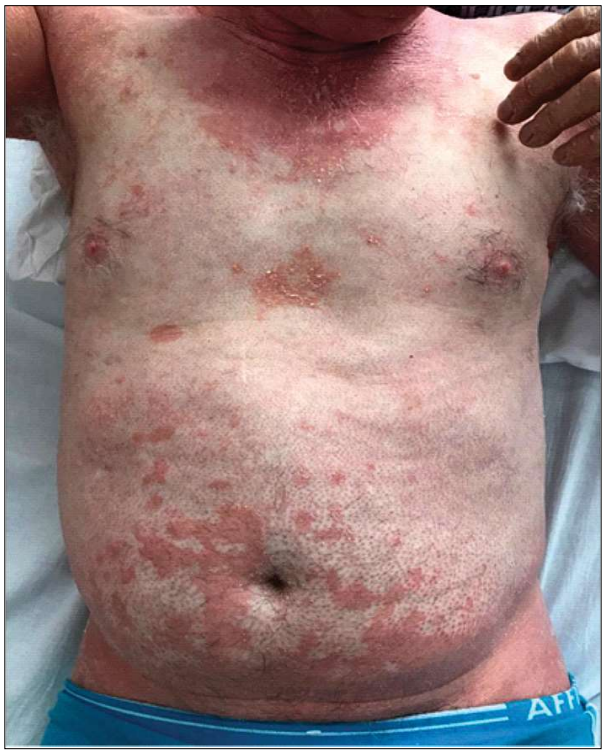

Figure 4 - Erythematous-scaly plaques, associated with areas of depigmented skin (vitiligo); follicular keratotic papules (clinical case 2)

rough to the touch and depigmented areas due to vitiligo (Fig. 4), erythematous-scaly plaques separated from normal skin (Fig. 5) and palmoplantar xanthochromic hyperkeratosis (Fig. 6). The nails are thickened, matte, with hyperkeratosis of the nail bed (Fig.7).

The condition started in May 2022, in the upper limbs, after the oral administration of an non-steroidal anti-inflammatory, later spreading to the whole body.

Past medical history: Vitiligo (since 1997), Chronic gastritis, Type II diabetes since 2022.

Psysical examination: Phototype III, normal weight, tongue with cerebriform appearance, ectropion at the level of the eyelids, dull, thickened nails.

Laboratory tests: Complete blood count, urea, creatinine, uric acid, ALT, AST, total bilirubin, blood glucose, Alkaline phosphatase, total proteins, atg HBs, anti-HCVantibodies, anti-HIV antibodies, ASO titer, urine summary examination were within limits rule

Lung X-ray: nothing active. Diffuse pulmonary fibrosis. Cord within limits.

Abdominal-pelvic ultrasound: liver with left lobe 8.8 cm, right lobe 14 cm, without localized processes. Absent surgical cholecystitis. Spleen 9.6 cm normal. Pancreas not palpable (pronounced abdominal flatulence). Prostate moderately hypertrophied 4.2/5.1 cm, with calcifications in the parenchyma. No fluid in the peritoneal cavity.

Ophthalmological exam: Superficial punctate keratopathy. Dry eye syndrome. Ectropion.

We biopsied 2 skin fragments from the flank and left arm. *The histopathological examination* revealed: epidermis with parakeratosis, the presence of red blood cells between keratin lamellae, irregular acanthosis, alternating with areas of atrophy, spongiosis. In the dermis, infiltrated with perivascular and perifollicular lymphoid cells with aspects of exocytosis, extravasated red blood cells, capillaries with stasis.

Based on the clinical examination and the histopathological examination, we made the

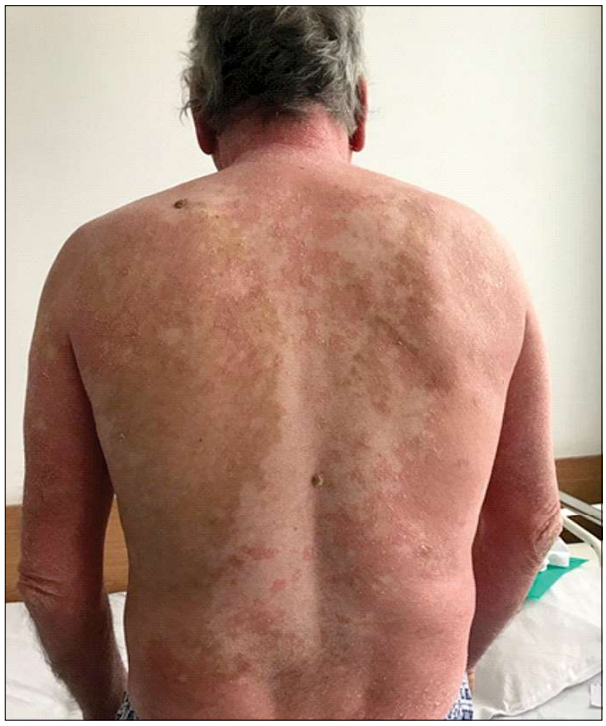

Figure 5 - Erythematous-scaly plaques, associated with areas of healthy skin (clinical case 2)

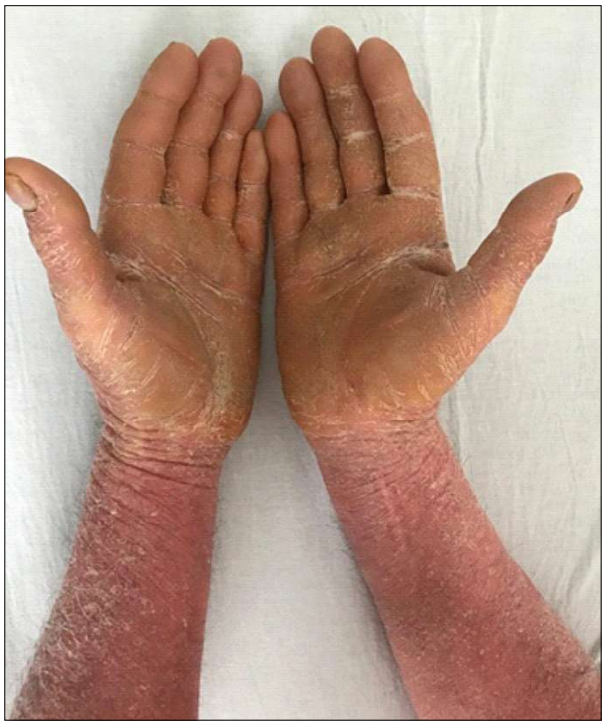

Figure 6 - Palmo-plantar xanthochromic hyperkeratosis (clinical case 2)

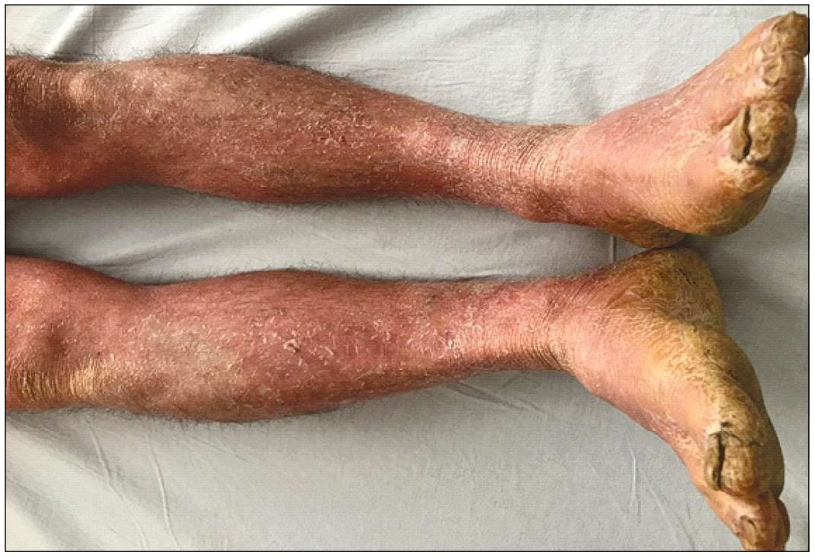

Figure 7 - Thickened, matted nails with hyperkeratosis of the nail bed (case 2)

diagnosis of ***classical Pityriasis rubra pilaris of the adult.***

The patient underwent antibiotic treatment (Tavanic 500 mg 1 cp/day), antihistamine, Lordestin 5 mg 1 cp/day, Methotrexate 15 mg/ml once/week, Folic acid 5 mg/week 72 h after Methotrexate administration, protective liver, creams with keratolytics in dermatocorticoids and emollients (A-derma exomega, Cerave, Lipikar). The evolution was favorable.

Clinical case 3

A 12-year-old boy was hospitalized for circumscribed, keratotic follicular plaques, rough

to palpation, located at the level of the knees bilaterally (Fig. 8). The disease started 2 years ago, after an episode of streptococcal pharyngotonsillitis.

Past medical history: not significant.

Laboratory tests: ESR, fibrinogen, C-reactive protein, ASO titer increased. The HIV test was negative.

Pharyngeal exudate: beta-hemolytic streptococcus present.

The *histopathological examination* (Fig. 9) revealed: epidermis with orthokeratosis, with formation of infundibular keratosis plugs, foci of hypogranulosis, discrete spongiosis. In the papillary dermis ectatized capillaries and discrete perifollicular lymphocytic infiltrate.

Based on the clinical examination and the histopathological examination, we made the diagnosis of ***Pityriasis rubra pilaris circumscribed juvenile form***.

He was treated with Cefuroxime 500 mg every 12 hours, 7 days, Vitamin A 50000 IU/day, 15 days, Daivobet ointment, Diprosalic ointment, Xerolys 10, with the disappearance of the lesions after 3 weeks.

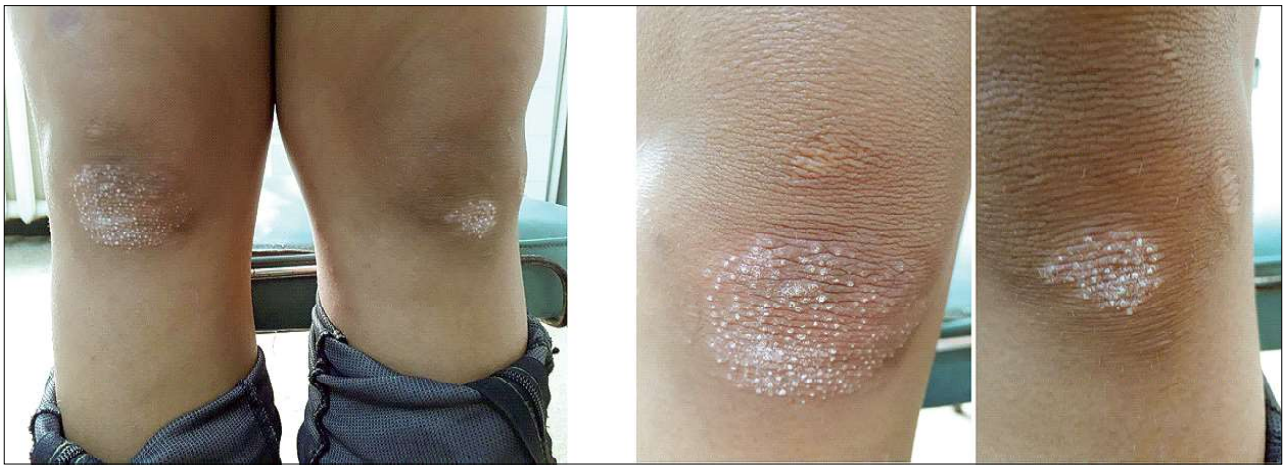

Figure 8 - Circumscribed keratotic follicular plaques (clinical case 3)

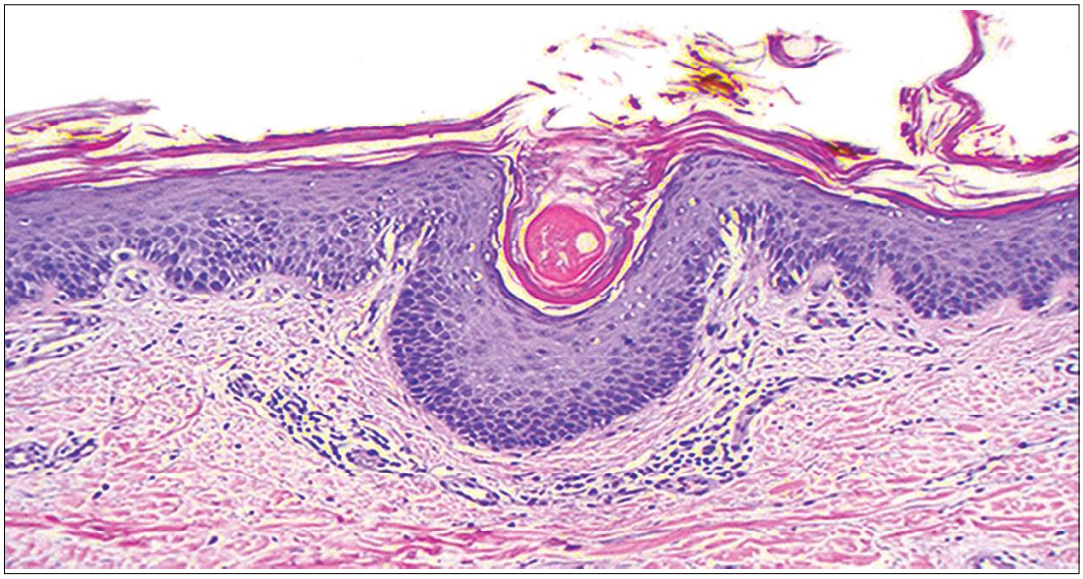

Figure 9 - PRP, histopathological aspect (clinical case 3)

Clinical case 4

A 6-year-old girl was hospitalized for round-oval, red-orange, scaly, well-defined, slightly itchy plaques, located on the extension areas of the upper limbs, lower limbs (Fig. 10, 11) and buttocks, with hyperkeratotic follicular papules. At the level of the plants, they show erythematous, hyperkeratotic plaques, with crusts and painful cracks (Fig. 12). The first lesions appeared on the calves, 3 years ago.

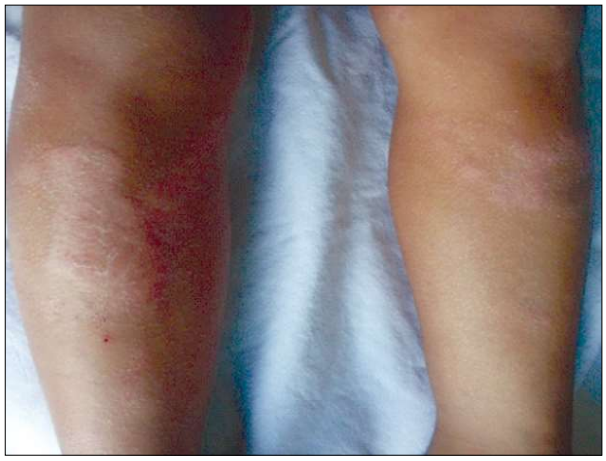

Figure 10 - Round-oval, red-orange, scaly plaques (clinical case 4)

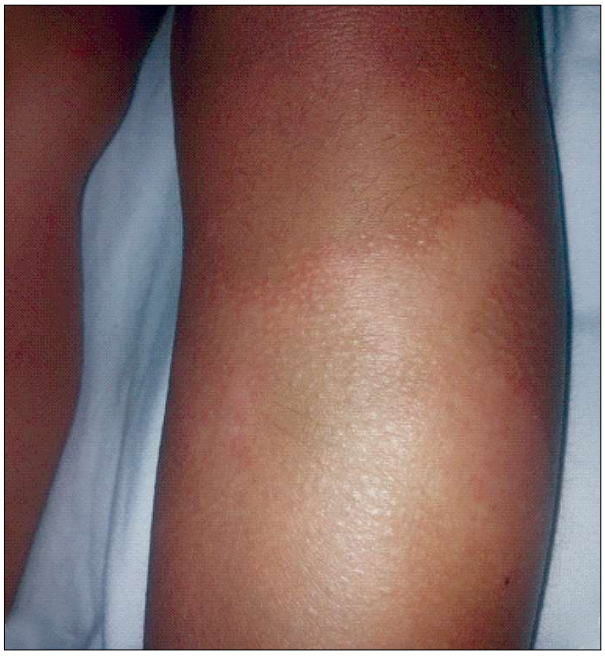

Figure 11 - Round-oval, red-orange, squamous plaque and keratotic follicular papules (clinical case 4)

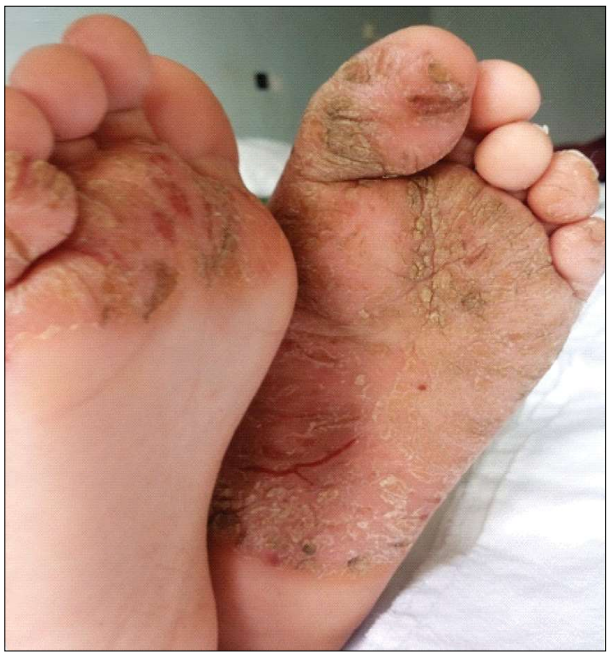

Figure 12 - Erythematous, hyperkeratotic plaques with crusts and painful fissures at plantar level (clinical case 4)

Past medical history: not significant.

Psysical examination: Reduced subcutaneous tissue, underweight (BMI 17.5).

Laboratory analyses: Normal blood count, urine examination shows frequent leukocytes, rare flora, increased ASO titer (400 IU/ml), normal pharyngeal exudate, and the urine culture was negative. HIV infection was ruled out following specific tests.

For the *histopathological examination*, we collected two skin fragments, one from the interfacial region, the other from the left plantar, showing epidermis with moderate acanthosis, ortho-parakeratosis and discrete spongiosis, in the papillary dermis with chronic perivascular and perifollicular inflammatory infiltrate; for the II skin fragment, the microscopic appearance was: epidermis with extensive area of para-keratosis, hypogranulosis, moderate spongiosis, and in the papillary dermis chronic inflammatory infiltrate.

Based on the clinical examination and the histopathological examination, we made the diagnosis of ***Pityriasis rubra pilaris, the classic juvenile form***.

The patient underwent treatment with Daivobet gel, Elocom ointment, Neotigason 10 mg, 1 cps/day, Moldamin 600,000 IU/week IM. The evolution was favorable after 8 weeks of treatment.

Discussions

The etiopathogenesis of PRP remains unknown, and the following hypotheses have been proposed:

- abnormal metabolism of vitamin A in the skin;
- association with autoimmune diseases: hypothyroidism, myasthenia gravis, celiac disease, autoimmune thyroiditis, vitiligo, collagenosis, etc.;
- malignancies: renal carcinoma, Merkel cell carcinoma, epidermoid carcinoma, adenocarcinomas, hepatocellular, bronchogenic, laryngeal carcinoma, liver metastases etc.;
- infections, especially HIV;
- genetics, mutations in the CARD 14 gene in cases of PRP type V (juvenile atypical form).

Baran et al. found increased p53 protein expression in the skin of patients with PRP.[3]

Another biochemical marker is defective synthesis of retinol-binding protein RBP, a protein specific for vitamin A transport.[4]

Also, PRP has been observed after various infections. Two children developed PRP shortly after streptococcal infection, which resolved spontaneously within a few months. Superantigens derived from bacteria may play a causative role in triggering PRP in children. An abnormal response to antigenic stimuli could be the cause. Other infectious agents discussed are: cytomegalovirus and varicella-zoster virus.[5]

Several cases of PRP have been described in patients with HIV infection, some with PRP as the first manifestation of infection.[6]

Follicular inflammation secondary to HIV infection of the hair bulb was noted by Misery et al.[7]

Shvili noted increased suppressor T cell activity with impaired T helper cell functions in a 6-year-old child with PRP.[8]

Circumscribed juvenile PRP was described in 2 patients with Down syndrome, one of whom had vitiligo. Another patient with Down syndrome developed PRP type III at 15 years of age.[9]

Cutaneous malignancies have also been found to be more aggressive when associated with PRP.[10]

PRP has been described in association with autoimmune diseases: SLE, dermatomyositis or seronegative arthropathies, celiac disease, diabetes, autoimmune thyroiditis, vitiligo. Another association is with autoimmune hypothyroidism. Specific treatment allowed rapid remission of PRP. Thyroid hormone deficiency inhibits the conversion of carotene to vitamin A, and a disorder in the metabolism of this vitamin has been suggested in PRP, which could explain the association of PRP with hypothyroidism.[11,12]

Clinical aspects

PRP was classified into 6 types (Table I), including hereditary and acquired forms. The classic description with follicular hyperkeratosis is associated with type 1 PRP. Follicular keratotic papules may coalesce to form erythematous, salmon-colored plaques that develop fine scales.[13]

Distribution throughout the body is possible, and pruritus is often present.

PRP can erythrodermize with a variable frequency.

In adults, PRP typically begins on the face and scalp and extends caudally, while in children, it usually begins in the lower half of the body, a situation also present in our cases.

A characteristic feature is the islands of intact skin.

The eruption can involve the oral mucosa. The changes consist of white or pale blue spots and lines and erythematous lesions covered with white streaks that may also affect the tongue. The lesions may be confused with lichen planus, and patients may complain of pain and irritation of the tongue.[14]

The palms and soles become hyperkeratotic and may take on an orange tint. Painful fissures may develop.

Dermopathic lymphadenopathy may be present if the affected surface is very large. The scaling is rather fine, (pithirasiiform) on the face and scalp and thicker on the lower half of the body. Follicular hyperkeratosis is often present, particularly on the dorsal surfaces of the hands and fingers.

Table I. Classification of Pityriasis rubra pilaris, according to Griffith, 1980 [13]

Classification	Age of onset (%)	Clinical manifestations	Prognosis
Type I, classic adult	- adult (55%)	- acute onset; features are classic, including erythroderma with islands of healthy skin, palmoplantar keratoderma, and follicular hyperkeratosis	- spontaneous remission in 80% of cases in 3 years
Type II, atypical of the adult	- adult (5%)	- ichthyosiform scales and areas of eczematized dermatitis and alopecia. Palmo- plantar keratoderma may be present	- chronic evolution
Type III, classic juvenile	- children 5-10 years old (10%)	- similar to type I	- usually remission after a year
Type IV, circumscribed juvenile	- children 3-10 years old (25%)	- well-defined areas of follicular hyperkeratosis, erythema at the level of the knees and elbows; children in prepuberty	- unclear
Type V, juvenile atypical	- children aged up to 4 years (5%)	- follicular hyperkeratosis, mainly. Family PRP	- chronic evolution
Type VI, associated with HIV	- variable	- similar to type I, prominent follicular plugs or lichen spinulosus type lesions. Patients may present conglomerate acne and hidradenitis suppurativa	- variable

The nails can be thickened, with a rough surface, discolored yellow-brown, with distal deformations.

In the case of prolonged erythroderma, ectropion may develop. Other ocular complications are peripheral ulcerative keratitis, corneal perforation and dry eye syndrome.[15]

Positive diagnosis

The diagnosis is clinically suspected and confirmed based on the histopathological aspect that highlights:

- epidermis with acanthosis, orthokeratosis alternating with parakeratosis in both directions, vertical and horizontal;
- focal or confluent hypergranulosis as well as thick suprapapillary plates and wide networks;
- the hair follicles are dilated and have a keratin plug;
- superficial perivascular and perifollicular infiltrate with lymphocytes often present in the underlying dermis.[16]

We mention that the histopathological appearance is suggestive for the diagnosis of PRP, without being specific. It differs according to the stage of the disease and may be different from one patient to another.

Differential diagnosis

PRP is often confused with psoriasis. From a histopathological point of view, PMN leukocytes and Munro microabscesses are absent in PRP. In psoriasis, the granular layer is often absent.

Erythrodermized PRP must be differentiated from other erythrodermized dermatoses: psoriasis, seborrheic dermatitis, eczema, lichen planus, follicular ichthyosis, T-cell lymphoma.

Other differential diagnoses are Darier's disease, pemphigus foliaceus, Grover's disease, epidermal nevus.[17]

In children, in whom PRP can occur after bacterial infections, the following must be excluded: scarlet fever, Kawasaki disease, atopic dermatitis etc.[18]

Treatment

PRP is often resistant to both topical and systemic therapies. Because spontaneous remission of PRP is possible, assessing the effectiveness of any therapy is difficult, especially since there are no randomized trials.

Topical treatment is usually used in combination with systemic treatment, to reduce the adverse effects of the latter. Emollients with urea 5-10%, salicylic acid 1-3%, dermatocorticoids, topical retinoids 0.05-0.1%, calcipotriol, pimecrolimus 1% are used.

Gregoriou successfully treated a young man with PRP located on the scalp and face with pimecrolimus 1% cream.[19]

A 12-year-old girl with PRP type IV, resistant to dermatocorticoids and pimecrolimus cream, had complete remission with 0.1% tazarotene gel applied for 6 weeks.[20]

Systemic treatment in children: acitretin 0.5 mg/kg/day (3-5 months) with or without exposure to UVB; isotretinoin 0.5-1 mg/kg/day (>12 years). In severe cases resistant to retinoids, methotrexate, cyclosporine, azathioprine (age over 10 years) or TNF alpha inhibitors (Infliximab, Etanercept, Adalimumab) are used.

Systemic treatment in adults

First-line treatment: retinoids (isotretinoin 1 mg/kg/day; acitretin; alitretinoin), with clinical improvement after 4-6 months of treatment; methotrexate (5-30 mg/week).

Second-line treatment: ciclosporin (less than 5 mg/kg/day); acitretin + UVA; Re-PUVA; fumaric acid; IG IV 2g/kg for 3 days; TNF alpha inhibitors; stanozolol (2 mg/day); azathioprine (50-200 mg/day); antiretroviral therapy in type VI (the form associated with HIV infection).[20] More recently, other biologic therapies such as anti IL 12/23 and anti IL 17 appear interesting.

To date, systemic retinoids appear to be the most effective therapeutic agents. Other treatments used have been described with variable success rates.

Isotretinoin and etetrinate (has been withdrawn from the market!) are synthetic derivatives of vitamin A that modulate the growth and differentiation of epithelial tissues. From a histological point of view, a decrease in hyperkeratosis occurs during therapy. Increased doses of vitamin A do not appear to be beneficial in PRP type I.[21]

In a study that included adults and minors with PRP, isotretinoin (1-2 mg/kg/day) was used for an average of 122 days. All 34 patients who remained on treatment for 12-16 weeks had significant improvement in their lesions.[22]

In a retrospective study of 18 patients treated with isotretinoin, etretinate, or both, the results suggested that etretinate is superior in the treatment of adult-type PRP, with the recommended dose being 0.5 mg/kg/day for 3-6 months.[[23]

Patients with erythrodermized PRP should be monitored for electrolyte abnormalities, hypoalbuminemia, secondary bacterial skin infections, and possible septicemia. Familial forms, whose onset is usually in childhood, have a less favorable prognosis and can evolve throughout life.[24]

Conclusions

Pityriasis rubra pilaris is a rare condition, complex from a social and psychological point of view, which can be found in adults and children of both sexes.

Recognizing the skin manifestations of PRP allows the rapid initiation of treatment to limit the evolution of the disease and prevent complications.

Bibliography

1. Besnier E. Observation pour servir a l`histoire clinique du Pityriasis rubra pilaire. *Ann Dermatol Syphiligr* (Paris) 1889;10(ser 2):454-464
2. Annette Klein, Michael Landthaler and Sigrid Karrer. Pityriasis Rubra Pilaris A Review of Diagnosis and Treatment. *Am J Clin Dermatol* 2010; 11 (3): 157-170
3. Baran W, Szepietowski JC, Szybejko-Machaj G. Enhanced expression of p53 in pityriasis rubra pilaris. *Acta Derm Venereol* 2006; 86: 276-277

4. Finzi AF, Altomare G, Bergamaschini L, et al. Pityriasis rubra pilaris and retinol-binding protein. *Br J Dermatol* 1981; 104: 253-256
5. Mohrenschlager M, Abeck D. Further clinical evidence for involvement of bacterial superantigens in juvenile pityriasis rubra pilaris (PRP): report of two cases. Pediatr Dermatol 2002; 19: 569
6. De D, Dogra S, Narang T, et al. Pityriasis rubra pilaris in a HIV-positive patient (type 6 PRP). Skinmed 2008; 7: 47-50
7. Misery L, Faure M, Claudy A. Pityriasis rubra pilaris and human immunodeficiency virus infection: type 6 pityriasis rubra pilaris? *Br J Dermatol* 1996; 135: 1008-1009
8. Shvili D, David M, Mimouni M. Childhood-onset pityriasis rubra pilaris with immunologic abnormalities. *Pediatr Dermatol* 1987; 4: 21-23
9. Hazini AR, Rongioletti F, Rebora A. Pityriasis rubra pilaris and vitiligo in Down's syndrome. *Clin Exp Dermatol* 1988; 13: 334-335
10. Sa´nchez-Regan˜a M, Lo´pez-Gil F, Salleras M, et al. Pityriasis rubra pilaris as the initial manifestation of internal neoplasia. *Clin Exp Dermato*l 1995; 20: 436-438
11. Conaghan PG, Sommer S, McGonagle D, et al. The relationship between pityriasis rubra pilaris and inflammatory arthritis. *Arthritis Rheum* 1999; 42:1998-2001
12. Orlandini V, Cogrel O, Doutre MS, et al. Pityriasis rubra pilaris and hypothyroidism: efficacy of thyroid hormone replacement therapy in skin recovery. *Br J Dermatol* 2007; 156: 606-607
13. Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol* 1980;5(1):105-112
14. Griffiths WAD. Pityriasis rubra pilaris: an historical approach. 2. Clinical features. *Clin Exp Dermatol* 1976; I: 37-50
15. Paranjothy B, Shunmugam M, MacKenzie J, et al. Peripheral ulcerative keratitis in pityriasis rubra pilaris. *Eye* 2007; 21: 1001-1002
16. Martinez Calixto LE, Suresh L, Matsumura E, et al. Oral pityriasis rubra pilaris. Oral Sur Oral Med Oral Pathol Oral Radiol Endod 2006; 101: 604-607
17. Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. *J Cutan Pathol* 1997; 24: 416-424
18. Betloch I, Ramo´n R, Silvestre J-F, et al. Acute juvenile pityriasis rubra pilaris: a superantigen mediated disease? *Pediatr Dermatol* 2001; 18: 411-414
19. Gregoriou S, Argyriou G, Christofidou E, et al. Treatment of pityriasis rubra pilaris with pimecrolimus cream 1%. *J Drugs Dermatol* 2007; 6: 340-342
20. Karimian-Teherani D, Parissa M, Tanew A. Response of juvenile circumscribed pityriasis rubra pilaris to topical tazarotene treatment. *Pediatr Dermatol* 2008; 25: 125-6
21. Karneva L, Lauharanta J, Niemi K-M, et al. Ultrastructure of pityriasis rubra pilaris with observations during retinoid (etretinate) treatment. *Br J Dermatol* 1983; 108: 653-663
22. Goldsmith LA, Weinrich AE, Shupack J. Pityriasis rubra pilaris response to 13-cis-retinoic acid (isotretinoin). *J Am Acad Dermatol* 1982; 6: 710-715
23. Borok M, Lowe NJ. Pityriasis rubra pilaris: further observations of systemic retinoid therapy. *J Am Acad Dermatol* 1990; 22: 792-795.
24. Virgil Pătrașcu. Boli dermatologice și infecții sexual-transmisibile, ediția a V-a, editura Sitech, Craiova, 2020, Vol. I: 402-3

Conflict of interest
NONE DECLARED

Correspondance address: Prof. univ.dr. Virgil Pătrașcu
University of Medicine and Pharmacy of Craiova
Petru Rares Street, No 2-4, 200345, Craiova, Romania,
E-mail: vm.patrascu@gmail.com