

Pityriasis Rubra Pilaris: A Report of Two Cases and Literature Review

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Abstract

Pityriasis rubra pilaris (PRP) is an idiopathic inflammatory hyperproliferative chronic dermatosis characterized by: perifollicular coalescing papules with central keratotic acuminate plugs gradually submerged in sheets of erythema; perifollicular erythema with islands of unaffected skin; palmoplantar keratoderma; diffuse desquamation which typically spreads from the head down to the feet. The cause of the condition is unknown, but possible etiological factors include: vitamin A deficiency, trauma, infections, autoimmune mechanisms, and malignancies. Taking into account different age of onset, clinical course, morphology and prognosis, there are six different types of the disease: two in adults (classical and atypical); three in children (classical, circumscribed and atypical); one in individuals infected with human immunodeficiency virus.

This paper presents two male patients with clinical symptoms of classical PRP, 53 and 69 years of age at the onset of the disease, with rapid generalized involvement, typical erythematous perifollicular papules, islands of unaffected skin, palmoplantar hyperkeratosis with a waxy appearance and nail changes. The diagnosis was based on clinical findings and histopathologic analysis. Apart from topical therapy with emollients, corticosteroids and keratolytics, they received systemic retinoids and corticosteroids, which resulted in improvement of skin lesions.

It is extremely important to consider the possible triggering factors, establish the diagnosis as soon as possible and begin proper treatment.

Key words

Pityriasis Rubra Pilaris + diagnosis + classification + therapy; Diagnosis, Differential; Case Reports; Dermatologic Agents; Treatment Outcome; Review

Pityriasis rubra pilaris (PRP) (synonyms - lichen ruber pilaris, lichen ruber acuminatus, Devergie's disease) (1), is an idiopathic inflammatory hyperproliferative dermatosis which is characterized by: follicular hyperkeratotic papules grouped into broad erythematous patches with islands of unaffected skin, palmoplantar keratoderma, diffuse follicular squamous papules of the scalp, and often present progressive exfoliative erythroderma (2, 3, 4). The name of the disease comes from Latin words for: redness (Lat. rubra), desquamation (Lat. pityriasis) and follicular inflammation (Lat. pilaris). It was first

described in 1835 by Claudius Tarral, but he did not consider it to be a separate entity, but a variant of psoriasis (5). In 1856, Alphonse Devergie described "pityriasis pilaris" as a combination of follicular lesions and psoriasis palmaris, pityriasis capillitii and pityriasis rubra, naming Tarral's case as pityriasis pilaris (6), while in 1877 Richaud recognized it as a distinct entity (7). In 1889, Ernest Besnier named this condition - pityriasis rubra pilaris (8), whereas in 1910, De Beurmann first described the familial form of PRP (9).

The incidence of PRP is low: in the United States it has been reported to occur with 1: 3500 to 1 :

5000 patients presenting in dermatology clinics (10), in India, 1 case in every 500 new pediatric patients with a dermatologic disease (11). It occurs equally in male and female patients; in childhood, the male to female ratio is 3:2 (3). It affects members of all races, but it is less common in black people. Although PRP may occur at any age (10), it most commonly affects those in their first, second, fifth or sixth decades of life (1). Usually these are sporadic acquired forms, familial forms are rare, being rather transplacentally transmitted (1), than inherited in an autosomal dominant or autosomal recessive or X-linked fashion (3, 12).

Based on the age of onset, clinical course, morphology and prognosis, in 1980 Griffiths (13) classified PRP into five types: two adult types (classical and atypical) and three juvenile types (classic, circumscribed and atypical). In 1983, Larregue et al. (14) described a new variant, as a subtype of type III, acute or postinfection juvenile PRP (15). The characteristics of this type include: a) no familial

occurrence; b) begins at early childhood, after the first year of life; c) previous infectious episode; d) scarlatiniform erythema followed by the appearance of follicular papules; e) no laboratory abnormalities, except for those derived from the infectious process; f) clinical appearance similar to classic juvenile PRP; and g) acute course with good outcomes, although resolution may be slow, and no tendency toward recurrence.

In 1994, Piamphongsant and Akaraphant (16) analyzed 168 patients with PRP and proposed a new classification that distinguished the following 4 types of PRP based on clinical appearance: 1. salmon-colored or erythematous thick plaques on the palms and soles, which extend beyond the dorsopalmar and plantar junctions; 2. circumscribed scaly erythematous patches on the elbows and knees; 3. patches involving large areas of the trunk which are not generalized; 4. exfoliative erythroderma associated with diffuse follicular plugging. However, in practice, Griffiths classification is still actual, although in 1995 (17) sixth type was added: PRP associated with human immunodeficiency virus (HIV) infection, which differs from other types in terms of clinical course and poor prognosis (18).

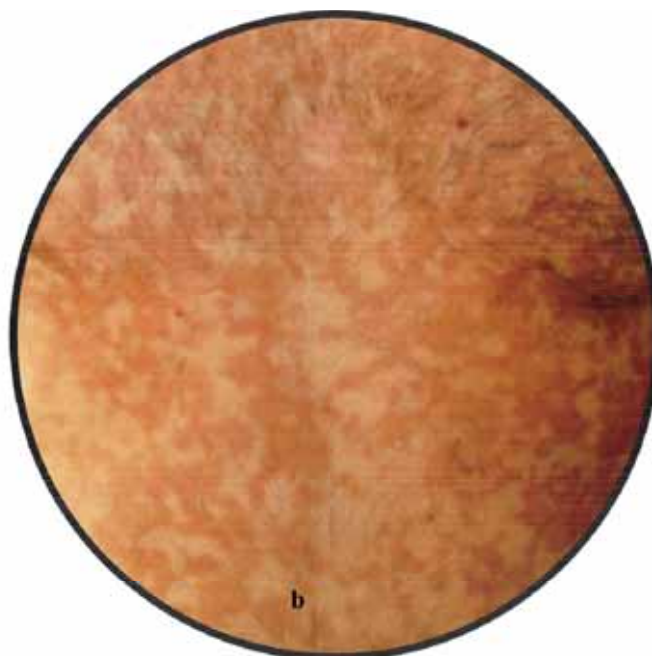


Figure 1. The skin of the abdomen: a) intense individual and coalescing erythematous plaques covered with thin whitish poorly adherent scales with well demarcated islands of unaffected skin; b) an enhanced detail



Figure 2. Palmar hyperkeratosis with a waxy appearance with shallow rhagades and a marked lamellar desquamation

Case reports

Patient 1. A 53-year-old farmer, with a diagnosis of erythroderma, was admitted due to skin changes that appeared 15 days earlier including redness and itching of the scalp, which soon spread to the whole body. His personal and family medical histories were unremarkable. The dermatological examination revealed: intense erythematous plaques on the whole body, especially on arms and legs, covered with thin whitish poorly adherent scales with well demarcated islands of unaffected skin (Figure 1); the skin of the face and scalp was erythematous with fine velvety desquamation; the hands and feet were edematous with palmoplantar hyperkeratosis and a waxy appearance, shallow rhagades and a marked lamellar desquamation mostly on the palms (Figure 2).

Laboratory test results

All relevant laboratory findings were within normal limits, except for slightly elevated cholesterol and triglyceride levels.

Histopathological analysis

Histopathological examination of the fully developed erythematous lesion showed a moderate to prominent orthokeratosis with alternating

parakeratosis, mild acanthosis with short and broad rete ridges; a nonspecific perivascular infiltrate in the papillary and subpapillary dermis composed predominantly of lymphocytes (Figure 3).

Therapy

The patient received a systemic corticosteroid therapy for 15 days and after initial improvement, acitretin was initiated at a dose of 75 mg per day, which was gradually reduced to 25 mg per day; topical treatment included corticosteroids, emollients and keratolytics. On discharge, the patient showed a significant improvement of skin lesions.

Patient 2. A 70-year-old retired male patient, diagnosed with erythroderma, was admitted due to skin changes that began 6 months earlier on his right cheek with redness, itching and subsequent scaling. The skin lesions then spread to the chest, abdomen, shoulders and back, with intense itching. Almost from the beginning, the disease also affected the palms, soles and nails, with painful thickening. A month before admission, the patient developed burning in the eyes and his eyelids were stuck together in the morning. He received outpatient treatment without

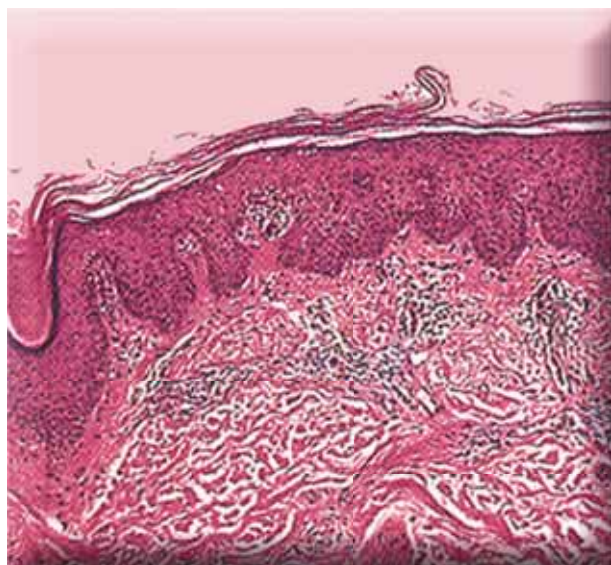


Figure 3. Fully developed erythematous lesion: moderate to prominent orthokeratosis with alternating parakeratosis in the epidermis, mild acanthosis with short and broad rete ridges; a nonspecific perivascular infiltrate in the papillary and subpapillary dermis composed predominantly of lymphocytes (HE stain, x 50)

significant improvement, and when the changes spread to the whole body, half a year after the onset of symptoms, he was referred to hospital for examination and treatment. Apart from elevated blood pressure, the patient's personal and family history were unremarkable; dermatological examination showed: pinhead-sized erythematous follicular papules on the chest and abdomen, single or coalescing, forming plaques with whitish pityriasisform scaling (Figure 4); red-orange lesions with diffuse thickening were found on the face, neck, back, arms and legs, covered with whitish scales with islets of healthy skin (Figure 5); the skin of both palms and soles was thickened, yellowish-brown with a wax appearance (Figure 6); the distal third parts of the nail plates of the fingers and toes were yellowish and thickened, with longitudinal ridging and subungual hyperkeratosis.

Laboratory test results

All relevant laboratory findings were within normal limits. After examination, the ophthalmologist diagnosed blepharoconjunctivitis, and 3% solution of boric acid eye drops was introduced, as well as chloramphenicol eye ointment.



Figure 4. Red-orange lesions with diffuse thickening on the legs, covered with whitish scales with islets of healthy skin



Figure 5. The skin of both palms and soles is thickened, yellowish-brown with a waxy appearance

Histopathological analysis

Histopathological examination of the areas corresponding to follicular papules showed: dilated infundibulum filled with orthokeratotic plug; the hairs were present, but reduced in volume (Figure 7); perifollicular parakeratosis; mild perifollicular lymphocytic infiltrate.

Therapy

The treatment was initiated with parenteral methylprednisolone (the initial dosage of 80 mg per day, with gradual reduction of the daily dose), and systemic antihistamines; topical treatment included corticosteroids, emollients and keratolytics. The patient was discharged in a much improved condition: reduced erythema, desquamation and infiltration of the skin, especially on the palms and soles.

Discussion and a Literature Review

PRP is rare heterogeneous dermatosis with unclear etiology and pathogenesis (19, 20). The skin lesions are the result of hyperproliferation of keratinocytes in the epidermis and inflammation in the dermis. In conjunction with the genetic background,

different infectious, endogenous and environmental triggers, such as vitamin A deficiency, autoimmune, neoplastic, and traumatic have been sought, but none has been conclusively associated with the disease (1, 21, 22). Thus, no positive correlation between vitamin A deficiency and PRP has been established, whereas beneficial effects of vitamin A in PRP therapy are compared with its therapeutic efficacy in the treatment of dermatoses with follicular and nonfollicular keratosis, where no vitamin A deficiency has been determined. The potential etiological role of inadequate vitamin A transport due to lack of retinol-binding protein requires further verification. According to the National Organization for Rare Disorders, PRP may develop due to abnormalities in the way the body processes vitamin A (22). In the literature, some cases of PRP were preceded by upper respiratory tract infections, in children usually triggered by streptococcal superantigen (15, 23), varicella virus (24), cytomegalovirus (21), Epstein Barr virus (19), vaccination against diphtheria-tetanus-polio, flu vaccination, and vaccination against measles, mumps and rubella (25, 26). Cases associated with HIV infection have also been reported

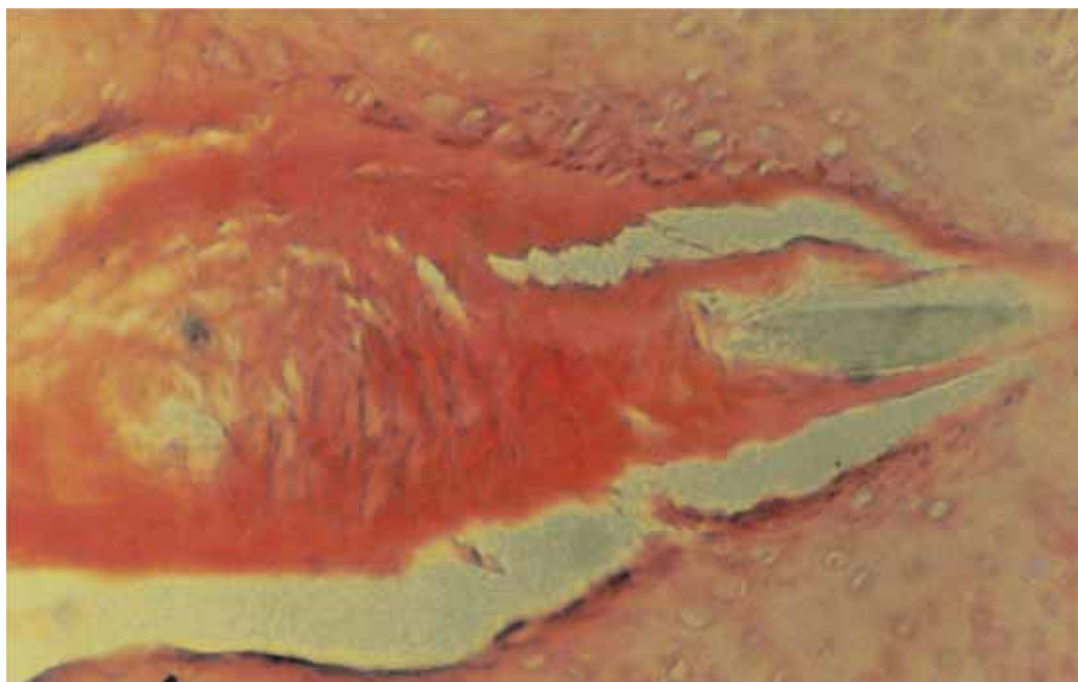


Figure 6. Areas corresponding to follicular papules show: dilated infundibulum filled with orthokeratotic plug; the hair is present, but reduced in volume (HE stain, x 400)

(17, 27). It seems that infections and other triggers act only as initiators of the aberrant cell-mediated immune response. The absence of prodromic symptoms in both our patients, as in most cases, cannot eliminate the possibility of an asymptomatic illness triggering PRP.

Besides acquired, sporadic cases, familial cases of PRP have been reported, most commonly with autosomal dominant inheritance (10). Mutations in the CARD14 gene on chromosome 17q25 (28), which encodes a group of interactive protein known as nuclear factor-kappa B (NF-kB), have been found in some families. NF-kB regulates the activity of multiple genes, including genes that control immune responses and inflammatory reactions; CARD14 gene mutations enhance the activation of NF-kB signaling pathway which causes an aberrant inflammatory response. The CARD14 protein is found in many of the body's tissues, but it is particularly abundant in the skin, where it appears to play important roles in regulating inflammatory reactions. Data obtained recently (28), demonstrate that autosomal-dominant PRP is allelic to familial psoriasis, which was recently shown to be caused also by mutations in CARD14 gene (29).

In PRP, skin, nails, mucous membranes, and eyes can be affected (10). The skin is typically

orange-red or salmon-colored with scaly plaques, with sharp borders, with islands of unaffected skin not exceeding 1.5 cm in diameter. The nails show a yellow-brown discoloration, subungual hyperkeratosis, nail-plate thickening, and splinter hemorrhages. Lesions of the mucous membranes include white plaques confined to the palate, bilateral gray-white plaques with a rough surface in the buccal mucosa and erythematous lesions, even erosions (30). Complications may involve the eyes: ectropion, blurred vision and dry eyes.

Griffith's classification (13), which is generally used, gives precise descriptions of the PRP types.

Type I is classic adult pityriasis rubra pilaris which accounts for 50 to 55% of all cases (4). The onset is acute, it is sporadic and there are no familial cases. PRP is characterized by cephalocaudal progression. Scarring alopecia may also develop (31). It has the best prognosis: about 80% of patients have remission in an average of 3 years. One reported case resolved spontaneously after 20 years (32).

Type II is atypical, accounting for 5% of patients. It is characterized by: marked desquamation, thin hair, increased palmoplantar keratosis, ichthyosiform lamellar scales, alopecia, incomplete erythroderma,

sometimes with psoriasiform appearance, but never progresses to psoriasis, and has no cephalocaudal spread. It has a long-term chronic course (11), and lasts several years (10).

Type III is a classic juvenile type, and accounts for 10% of all patients with PRP (3); it has the same clinical picture as Type I, but its onset is within the first 2 years of life and the course is more favorable in children compared with adults. Classical juvenile type may progress into circumscribed form. Initially, it may resemble other superantigen-mediated diseases: staphylococcal scalded skin syndrome (SSSS), scarlet fever, toxic shock syndrome, and Kawasaki disease. It is featured by raspberry tongue, shiny, chapped lips, flexural (particularly perineal) erythema followed by peeling, palmo-plantar erythema, and generalized rash, whereas usual lesions appear days or weeks later. Symptoms spontaneously resolve within 3 years or earlier (10). In 6% of patients self-limitation occurs in the first year, and in 90% in three years.

Type IV is circumscribed juvenile PRP and it occurs in prepubertal children or young adults. This form accounts for about 25% of all cases. It is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema of the knees and the elbows. Sometimes it is extremely difficult to distinguish it from psoriasis. The long-term outcome is unclear; it rarely progresses; it may resolve spontaneously, but may also be persistent and last for several years (33).

Type V is atypical juvenile generalized chronic PRP. Most familial PRP cases belong to this type (10). It accounts for 5% of patients with PRP, and it is characterized by diffuse ichthyosiform follicular lesions on the feet, with severe keratoderma, and sclerodermiform palmoplantar lesions, mostly without erythema.

Type VI is associated with HIV infection (17). It is characterized by follicular keratosis, acneiform, nodular and pustular lesions with elongated follicular plugs or lichen spinulosus-type lesions on the face and upper trunk, often with clear symptoms of immune deficiency (10). It significantly differs from other types of PRP; it is refractory to treatment and it has an increasing incidence (4).

The diagnosis of PRP is based on clinical and histological findings (10, 34). Our patients presented

with clinical symptoms of classical PRP at the age of 53 and 69, respectively. Although there are no specific laboratory markers for PRP, all relevant laboratory and other tests were performed to detect the potential trigger factors (10). The test results of both patients were within reference values. Although histological features are not pathognomonic in PRP, they are useful to rule out other possible papulosquamous and erythrodermic disorders (10). In classical adult type, histopathological changes are distinctive, and vary depending on the stage and localization of lesions from which the biopsy is taken (1). It is characterized by hyperkeratosis with alternating ortho- and parakeratosis, focal and confluent hypergranulosis, follicular plugging with perifollicular parakeratosis forming a shoulder effect, short and broad rete ridges, and sparse superficial dermal lymphocytic perivascular infiltration (35). Acantholysis has been reported as an additional histological finding, and together with hypergranulosis, follicular plugs, dilated, but not tortuous dermal capillaries and absence of epidermal pustules, it may help to distinguish pityriasis rubra pilaris from psoriasis (35). Unlike psoriasis, the acanthotic epidermis in PRP is not thinned above the dermal papillae (1). Histopathological findings in type IV, circumscribed PRP differ from those in classical: lamellar hyperkeratosis with unchanged or increased granular layer; marked follicular hyperkeratosis; scarce acanthosis; rare cell infiltration (1). The classical type I PRP was histologically confirmed in both of our patients.

In early stages, many diseases, including PRP, may have similar symptoms, so the differential diagnosis includes a series of dermatoses. In adults they are: contact dermatitis, scabies crustosa, cutaneous T-cell lymphoma, Darier's disease, dermatomyositis, eczema, erythroderma, lichen spinulosus, phrynoderma, psoriasis, pityriasis versicolor, pityriasis lichenoides chronica, pityriasis rosea, pityriasis rosea-like drug eruption, psoriasis, subacute cutaneous lupus erythematosus, sclerodermiform dermatitis, dermatitis seborrhoica, secondary syphilis. In children, differential diagnosis includes: eczema, erythroderma variabilis, Kawasaki disease, lichen spinulosus, nummular dermatitis, phrynoderma (36). Sometimes it is difficult to differentiate these lesions from psoriasis (37). Unlike psoriasis, PRP

has the following features: bimodal age of onset; general state of the patient is good, even in those with erythroderma; the presence of islets of unaffected skin is easy to distinguish from areas of uninvolved skin in psoriatic erythroderma if we bear in mind that "islands of unaffected skin" in PRP do not exceed 1.5 cm in diameter; the primary lesion is papule with a hair in its center with no inclination to peripheral growth and fusion due to skin infiltration, but due to an ongoing erythematosquamous process when diffuse erythroderma is formed; brick-red or carrot-orange color; absence of infiltrates, lichenification, large lamellar scales; absence of onycholysis; palmoplantar hyperkeratosis without infiltration, with yellow-orange discoloration; rare seronegative arthropathy; variable response to methotrexate; hormonal therapy, primarily with corticosteroids, has no favorable effects; pure response to UVB therapy (1, 38).

Regarding complications of PRP, we should rather consider them as various associations of uncertain significance (1). PRP has been reported to be associated with: photosensitivity, increased susceptibility to herpes simplex eye infection, ectropion and vision disorders (39). Our older patient presented with eye irritation and watering; an ophthalmologist was consulted, but the patient did not develop ectropion. PRP is also associated with poor quality of life, depression, insomnia, suicidal ideation (40). Particular attention should be paid to the side effects of drugs used in the treatment of PRP, primarily retinoids (41).

The therapy is very diverse, with different results; treatment of children with PRP should be done with special caution and in most cases include topical agents only. Topical therapy involves the use of different agents such as emollients and keratolytics, creams with urea and lactic acid, corticosteroids, vitamin D analogues (calcipotriol), retinoids, imiquimod 5% (20, 22, 42, 43, 44). In systemic therapy results are unpredictable, although retinoids are widely considered the first-line treatment in the erythrodermic phase; methotrexate has been effective as an alternative or adjunct to oral retinoids but generally is less efficacious in PRP than in psoriasis; success and failure have been reported with cyclosporine, as well as with corticosteroids, high doses of vitamin A, vitamin E, antihistamines, azathioprine, biological agents such as infliximab,

ustekinumab, adalimumab (18, 20, 22, 42, 44-47). Phototherapy (UVB, NB UVB, PUVA) can be effective as monotherapy, or combined with retinoids (48). Treatment of refractory juvenile PRP with synthetic retinoid-analogue bexarotene, has shown good therapeutic effects (49). Tumor necrosis factor alpha (TNF- α) inhibitors have been used with various success, but their long-term use may cause serious side effects (50, 51). Based on their experience and literature review, Muller et al., (46) found infliximab monotherapy as first-line treatment for adult-onset PRP (type I).

Our first patient was initially treated with systemic corticosteroids, but they were found ineffective. A systemic retinoid was initiated, as well as topical therapy with corticosteroids, emollients and keratolytics, and this treatment resulted in significant improvement. The second patient was treated with systemic corticosteroids with beneficial therapeutic effects.

Conclusion

We presented two adult males with classical clinical picture of type I PRP. The diagnosis was based on clinical appearance and histological findings, and both had a favorable response to treatment. It is of utmost importance to be familiar with potential triggers of the disease, make early diagnosis, and start proper treatment.

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Abbreviations

- PRP - pityriasis rubra pilaris
 HIV - human immunodeficiency virus
 NF-κB – nuclear factor-kappa B
 SSSS - staphylococcal scalded skin syndrome
 UVB - ultraviolet B
 NB UVB - narrow-band ultraviolet B
 PUVA - psoralen and ultraviolet A
 TNF-α - tumor necrosis factor alpha

Pityriasis rubra pilaris: prikaz dva slučaja i pregled literature

Sažetak

Uvod. *Pityriasis rubra pilaris* (PRP) (sinonimi *lichen ruber pilaris*, *lichen ruber acuminatus*, *Divergijeva (Devergie)* bolest jeste idiopatska inflamatorna i hiperproliferativna dermatoza koju karakterišu: folikularne hiperkeratotične papule grupisane u široke eritematozne plaže, između kojih se nalaze ostrvca neizmenjene kože, palmoplantarna keratodermija, difuzne skvame u kosmatom delu glave i, često, progresivna ekfolijativna eritrodermija.

Bolest se retko registruje u Americi – jedan oboleli na 3 500–5 000 novoregistrovanih slučajeva dermatoloških oboljenja među pacijentima koji se javljaju na pregled dermatologu. Kod odraslih bolest se javlja podjednako često kod oba pola, dok je kod dece češća kod dečaka (odnos dečaka prema devojčicama je 3 : 2). Obolevaju pripadnici svih rasa, nešto ređe crne rase. Iako se PRP može javiti u bilo kom periodu života, najčešće započinje u prvoj, drugoj, petoj ili šestoj dekadi. Najčešće su to sporadični stečeni slučajevi, dok je pojava PRP među pripadnicima iste porodice posledica najverovatnije transplacentarnog prenošenja, ređe autozomno dominantnog, autozomno recesivnog, ili nasleđivanja vezanog za X hromozom.

Zbog razlika u vremenu početka bolesti, kliničkom toku, morfologiji i prognozi, Griffiths (*Griffiths*)

je 1980. godine izvršio klasifikaciju PRP na pet tipova: dva tipa kod odraslih (klasični i atipični) i tri juvenilna tipa (klasični, cirkumskriptni i atipični). Larege (*Larregue*) i saradnici su 1983. godine opisali novu varijantu kao podtip tipa III, akutni ili postinfekcioni juvenilni PRP, što se retko navodi u literaturi. Karakteristike ovog tipa su: a) odsustvo porodičnog javljanja; b) početak u detinjstvu, posle prve godine života; c) prisustvo prethodne infekcije; d) skarlatiniformni eritem, sa kasnijom pojavom folikularnih papula; e) nema laboratorijskih abnormalnosti, sem onih u vezi sa infektivnim procesom; f) klinički sličan klasičnom juvenilnom tipu; g) akutni tok sa dobrom prognozom, mada rezolucija može biti spora, ali bez tendencije ponovnog javljanja.

Piamphongsant i *Akaraphant* su 1994. godine predložili novu klasifikaciju oboljenja na osnovu analize 168 pacijenata sa PRP koja razlikuje sledeća četiri tipa PRP na osnovu kliničkog izgleda promena: 1. eritematozni zadebljali plakovi na dlanovima i tabanima sa širenjem na dorzopalmarne i plantarne zglobove; 2. eritemoskvamozni plakovi na kolenima i laktovima; 3. eritemoskvamozni plakovi koji zahvataju široke areale na trupu, bez generalizacije; 4. ekfolijativna eritrodermija udružena sa difuznim

folikularnim čepovima. U praksi je međutim i dalje aktuelna podela Grifitsa na pet tipova, kojima je 1995. godine dodat i šesti tip: PRP udružen sa infekcijom virusom humane imunodeficijencije (HIV) koji se od ostalih tipova razlikuje po kliničkoj slici i lošijoj prognozi.

Prikaz slučaja. Slučaj 1. Bolesnik mušog pola, starosti 53 godine, po zanimanju zemljoradnik, sa uputnom dijagnozom eritrodermije, primljen je na bolničko lečenje zbog promena na koži, koje su počele 15 dana ranije sa crvenilom i svrabom na kosmatom delu glave, a ubrzo su se proširile na čitavo telo. Lična i porodična anamneza bile su bez osobenosti; dermatološki pregled je otkrio: na koži čitavog tela, naročito ruku i nogu, pojedinačne i većim delom slivene intenzivno eritematozne plaže prekrivene tankim beličastim slabo adherentnim skvamama, sa ostrvcima neizmenjene kože između njih (Slika 1); na koži lica i kapilicijuma eritem sa sitnom brašnastom deskvamacijom; na šakama i stopalima edemi, palmoplantarna hiperkeratoza voštanog izgleda, sa plićim ragadama i krupnom lameloznom deskvamacijom, naročito izraženom na dlanovima (Slika 2). U laboratorijskim nalazima, osim lako povišenih nivoa holesterola i triglicerida u serumu, svi ostali relevantni laboratorijski nalazi bili su u granicama normale. Histopatološki pregled eritematozne lezije: u epidermisu umerena do jače izražena ortokeratoza i alternativna parakeratoza, blaga akantoza sa plitkim i širokim grebenima; u papilama i subpapilarno perivaskularno prisutan oskudan nespecifičan infiltrat sastavljen pretežno od limfocita (Slika 3). Posle sistemske kortikosteroidne terapije u prvih 15 dana, koja je dala početno poboljšanje, u terapiju je uključen acitretin u dozi od 75 mg dnevno, sa postepenim smanjivanjem na 25 mg dnevno; u lokalnoj terapiji primenjeni su kortikosteroidi, emolijensi i keratolitici. Bolesnik je otpušten na kućno lečenje znatno poboljšanog stanja kože.

Slučaj 2. Osoba muškog pola, stara 70 godina, po zanimanju penzioner, sa uputnom dijagnozom eritrodermije, primljen je na bolničko lečenje zbog promena na koži koje su počele 6 meseci ranije i to na koži desnog obraza u vidu crvenila i svraba, sa kasnijim perutanjem. Promene su zatim zahvatile kožu na grudima, trbuhu, ramenima i leđima, uz jak

osećaj svraba. Skoro od samog početka bolesti nastale su promene na dlanovima, tabanima i noktima u vidu zadebljanja i bolne osetljivosti. Mesec dana pred prijem u bolnicu, javio se osećaj pečenja u očima i „slepljenost“ očnih kapaka u jutarnjim časovima nakon buđenja. Lečen je ambulantno bez znatnijeg uspeha, a kada su se promene proširile na čitavo telo, pola godine od početka bolesti, upućen je na hospitalno ispitivanje i lečenje. Osim podatka o povišenom krvnom pritisku, lična i porodična anamneza bile su bez relevantnih osobenosti; dermatološki pregled je otkrio: na koži prednje strane grudnog koša i trbuha folikularne eritematozne papule veličine čiodine glave, pojedinačne i slivene, sa beličastim pitijaziformnim skvamama (Slika 4); na koži lica, vrata, leđa, ruku i nogu difuzno zadebljanje neravne površine crvenonaranđaste boje, prekriveno beličastim skvamama, sa ostrvcima zdrave kože (Slika 5); na koži oba dlana i tabana difuzno zadebljanje, žučkastosmeđe prebojeno – voštanog izgleda (Slika 6); u distalnim trećinama nokatnih ploča na prstima ruku i nogu žučkasobeličasto prebojena zadebljanja, sa uzdužnim grebenima i subungvalnom hiperkeratozom. Svi relevantni laboratorijski nalazi bili su u granicama normale. Histopatološki pregled folikularne papule: folikul dlake dilatiran, ispunjen ortokeratinskim čepom; dlaka je prisutna, ali redukovano volumena (Slika 7); perifolikularna parakeratoza; oskudni limfocitni perifolikularni infiltrat. Lečenje je započeto sa parenteralnom primenom metilprednizona, u početnoj dozi od 80 mg dnevno, uz postepeno smanjivanje dnevne doze, i sistemskom primenom antihistaminika; u lokalnoj terapiji primenjeni su kortikosteroidi, emolijensi i keratolitici; pregledom oftalmologa postavljena je dijagnoza blefarokonjunktivitisa, a lečenje je sprovedeno rastvorom borne kiseline 3%, u vidu kapi za oči i aplikacijom hloramfenikol masti za oči. Bolesnik je otpušten na kućno lečenje u znatno poboljšanom stanju: redukovano eritem, deskvamacija i infiltracija naročito kože na dlanovima i tabanima. Diskusija. *Pityriasis rubra pilaris* je retka u osnovi heterogena dermatoza sa nejasnom etiopatogeneom. Promene na koži su rezultat hiperproliferacije keratinocita u epidermisu i inflamacije u dermisu. Pored genetske predispozicije, različiti infektivni, endogeni i egzogeni ekološki faktori, npr.

nedostatak/disfunkcija A vitamina, autoimunski neoplazijski, traumatski činioci opisani su kao mogući pokretači PRP ali njihova uloga nije sa sigurnošću dokazana. Tako je dokazano odsustvo korelacije između deficijencije vitamina A i PRP, a potencijalni etiološki značaj neadekvatnog transporta vitamina A usled nedostatka retinol binding proteina, zahteva dalju proveru. Prema Nacionalnoj organizaciji za retke bolesti, PRP može nastati zbog abnormalnosti u načinu na koji telo procesira vitamin A. U literaturi su opisani slučajevi PRP, kojima je prethodila infekcija gornjih respiratornih puteva, kod dece najčešće izazvane streptokokom (sa superantigenom u ulozi pokretača), virusom varičele, citomegalovirusom, *Epstein Barr* virusom, posle difterija-tetanus-polio vakcinacije, vakcinacije protiv gripa, posle vakcinacije ROR (fr. *rougeole-oreillons-rubéole*) vakcinom protiv morbila, parotitisa i rubeole. Posebno su opisani slučajevi udruženi sa infekcijom HIV-om. Pretpostavlja se da infekcija kao i ostali nabrojani činioci imaju ulogu pokretača oboljenja tako što pokreću aberantni celularni imunski odgovor. Odsustvo prodromalnih simptoma kod oba naša pacijenta kao i kod većine ostalih slučajeva opisanih u literaturi, ne isključuju mogućnost postojanja asimptomatskog oboljenja u ulozi pokretača PRP.

Osим stečenih, sporadičnih slučajeva, opisano je i porodično javljanje PRP, sa najčešće autozomno dominantnim načinom nasleđivanja. Kod nekoliko porodica nađene su mutacije CARD 14 gena na hromozomu 17q25 koji reguliše aktivaciju *nuklearnog faktora kapa B* (NF-kB), a preko njega reguliše se aktivnost multiplih gena, uključujući gene koji kontrolišu imunske i inflamatorne reakcije. Mutacije CARD 14 gena dovode do prevelike aktivacije NF-kB signalnog puta što izaziva aberantni inflamatorni odgovor. Podaci dobijeni u skorije vreme pokazuju da je autozomno-dominantna PRP alelski povezana sa porodičnom psorijazom, koju takođe mogu izazvati mutacije u CARD14 genu.

Promenama na koži, na noktima, mukoznim membranama i očima može da se manifestuje PRP. Na koži su tipični narandžastocrveni ili crvenkasto prebojeni skvamozni plakovi sa oštrim ivicama, između kojih se nalaze ostrvca neizmenjene kože koja po većini ne prelaze 1,5 cm u dijametru. Na

noktima se može registrovati distalna žućkasto-smeđa diskoloracija, subungvalna hiperkeratoza, longitudinalne brazde, zadebljale nokatne ploče i hemoragije. Promene na mukoznim membranama su u vidu beličastih plakova, sivobelih papula ili plakova, eritema ili čak erozija na sluzokoži usta. Kao komplikacije na očima mogu nastati ektropion, nejasan vid i suvoća očiju.

Prema klasifikaciji Grifitsa koja je u opticaju i opšte korišćena, dati su preciznije opisi naznačenih tipova. Tip I je klasični tip koji se javlja kod odraslih i prisutan je kod 50% do 55% svih obolelih. Tip II je atipičan, javlja se u oko 5% pacijenata, praćen je izraženom deskvamacijom nekada psorijaziformnog izgleda, ali nikada ne prelazi u psorijazu. Tip III je klasični juvenilni tip; javlja se kod 10% od svih pacijenata sa PRP, ima istu kliničku sliku kao tip I, ali se javlja u prve dve godine života i ima povoljniji tok nego kod odraslih. U početku, klinički podseća na superantigenom izazvana oboljenja: šarlah, toksični šok sindrom i *Morbus Kawasaki*. Uobičajene karakteristike su malinast jezik, sjajne ispucale usne, fleksuralni (posebno perinealni) eritem koji prati ljuštenje, palmoplantarni eritem i generalizovani osip, dok se promene klasične PRP javljaju danima ili nedeljama kasnije. Tip IV je cirkumskriptni juvenilni tip koji se javlja kod prepubertetske dece i mlađih odraslih osoba. Nastaje kod 25% od svih bolesnika sa PRP. Karakterišu ga oštro ograničene skvamozne plaže folikularne hiperkeratoze i eritema na kolenima i laktovima. Tip V je atipična juvenilna generalizovana hronična forma. Najveći broj slučajeva PRP sa familijarnim javljanjem pripada ovom tipu. Nastaje kod 5% obolelih od PRP. Karakterišu ga difuzne folikularne lezije ihtioziformnog izgleda na nogama, sa značajnom keratodermijom, sklerodermiformnim promenama na palmarnim i plantarnim regijama i neretko eritem. Tip VI je udružen sa infekcijom HIV-om: promene su na licu i gornjem delu trupa u vidu folikularne keratoze, akneiformnih lezija nodularnih i pustuloznih, sa elongiranim folikularnim čepovima, lezijama sličnim lihen spinulozusu i često naglašenim znacima imunodeficijencije. Signifikantno se razlikuje od drugih tipova, refrakteran je na terapiju a incidencija mu je u porastu (4).

Dijagnoza PRP se postavlja na osnovu kliničkog

i patohistološkog nalaza. Kod naših pacijenata bolest je počela u 53. i 69. godini i manifestovala se kao klasični I tip PRP. Iako do sada nisu utvrđeni specifični laboratorijski markeri koji bi imali dijagnostički značaj, uradili smo sve relevantne laboratorijske i ostale analize radi otkrivanja/isključenja mogućih faktora okidača. Ni kod jednog od naša dva pacijenata nije bilo bitnih odstupanja od referalnih vrednosti relevantnih laboratorijskih analiza.

Histološke karakteristike nisu patognomonične u PRP, ali mogu da omoguće razlikovanje PRP od drugih papuloskvamoznih i eritematoznih dermatoza. Kod klasičnog tipa kod odraslih, patohistološke promene su upadljive, i razlikuju se prema stepenu bolesti i lokalizaciji promena sa kojih je uzeta biopsija. Karakteristična je hiperkeratoza sa naizmeničnom orto i parakeratozom, fokalna i konfluentna hipergranuloza, folikularni keratinski čepovi sa perifolikularnom parakeratozom, plitki a široki grebeni, limfocitna papilarna i subpapilarna infiltracija. Kao dodatna promena može se registrovati akantoliza, koja zajedno sa hipergranulozom, folikularnim čepovima, dilatiranim ali neizuvijanim dermalnim kapilarima i odsustvom epidermalnih pustula, omogućavaju diferencijalnu dijagnozu PRP u odnosu na psorijazu. Za razliku od psorijaze, akantotičan epidermis u PRP nije suprapilarno istanjen.

Za razliku od psorijaze PRP se odlikuje sledećim karakteristikama: doba javljanja je bimodalno; opšte stanje pacijenata je dobro, čak i kod eritrodermijskog oblika; prisustvo ostrvaca klinički nepromenjene kože čiji dijametar je manji od 1,5 cm; primarna lezija je papula iz čijeg centra izrasta dlaka i koja ne pokazuje tendenciju širenja putem infiltracije konfluiranja već putem eritemske deskvamacije; narandžasta boja se poredi sa bojom cigle, odnosno mrkve; odsustvo infiltrata, lihenifikacije, velikih lamelarnih skvama; odsustvo oniholize; palmoplantarna hiperkeratoza bez infiltracije, sa žućkastonarandžastom prebojenošću; seronegativna artropatija je retko prisutna; odgovor na metotreksat varijabilan; hormonska terapija, u prvom redu kortikosteroidima, ostaje bez željenog efekta; slab odgovor na UVB fototerapiju. Klasični tip I oboljenja potvrđen je patohistološki kod oba naša pacijenta.

Komplikacije kod PRP se mogu pre smatrati udruženim stanjima, komorbiditetima, a ne komplikacijama u užem slislu te reči. Opisani su slučajevi PRP udruženi sa povećanom predispozicijom za herpes simpleks infekciju oka, ektropion i smetnje sa vidom: kod našeg starijeg pacijenta manifestovali su se simptomi u vidu peckanja u očima i vlaženja, zbog čega je konsultovan oftalmolog, ali se nije razvio ektropion. Takođe može doći do znatnog pogoršanja kvaliteta života, sa depresijom, insomnijom, suicidalnim idejama. Posebno treba obratiti pažnju na neželjena dejstva lekova koji se primenjuju za lečenje PRP, u prvom redu retinoida

Terapija može biti veoma raznovrsna sa nepredvidim rezultatima; kod dece treba biti oprezan i uglavnom primenjivati lokalnu terapiju. Lokalna terapija podrazumeva primenu agenasa kao što su: emolijensi i keratolitici, kreme sa ureom i mlečnom kiselinom, kortikosteroidi, analozi D vitamina (kalcipotriol), retinoidi, imikvimod 5%. Krajnji efekat sistemske terapije je nepredvidiv iako se retinoidi smatraju lekovima prvog izbora za lečenje PRP naročito u eritrodermijskoj fazi oboljenja; metotreksat može predstavljati alternative ili dodatak retinoidima, ali je njegova efikasnost kod PRP manja nego kod psorijaze; uspešna/neuspešna se pokazala i primena ciklosporina, kortikosteroida, visokih doza vitamina A i D, antihistaminika, azatioprina, bioloških lekova kao što su infliksimab, ustekinumab, adalimumab. Fototerapija (UVB, NB UVB, PUVA) može dati rezultate kao monoterapija ili u kombinaciji sa retinoidima. Lečenjem refrakterne juvenilne PRP sa abeksarotenom, sintetskim retinoid-analogom, postignut je dobar terapijski efekat. Inhibitori tumorske nekroze faktor alfa (TNF- α) upotrebljeni su sa različitim uspehom, ali njihova dugotrajna upotreba može dovesti do značajnih sporednih efekata. Miler (*Müller*) i saradnici, na osnovu svojih iskustava i pregledane literature, zastupaju stav da je monoterapija infliksimabom prva linija lečenja PRP kod odraslih (I tip).

U prvom slučaju opisanom u ovom radu, posle početne primene sistemskih kortikosteroida koji nisu pružili željeni efekat, uključen je sistemski retinoid nakon čega je uz lokalnu terapiju kortikosteroidima, emolijensima i keratolicama došlo do značajnog poboljšanja; u drugom slučaju je povoljan terapijski

efekat postignut već nakon početne primene sistemskih kortikosteroida.

Zaključak. Prikazali smo dve odrasle muške osobe sa klasičnom kliničkom slikom PRP tip I, kod kojih je dijagnoza potvrđena na osnovu kliničkog izgleda i

patohistološkog nalaza i koje su povoljno reagovala na primenjenu terapiju. Izuzetno je važno poznavati mogućnost dejstva raznih mogućih okidača bolesti, na vreme postaviti dijagnozu i započeti adekvatno lečenje.

Ključne reči

Pityriasis rubra pilaris + dijagnoza + klasifikacija + terapija; Diferencijalna dijagnoza; Prikazi slučajeva; Dermatološki agensi; Ishod terapije; Pregled literature