CASE REPORT

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Drug-related pityriasis rubra pilaris with acantholysis

Pityriasis rubra pilaris sa akantalizom izazvana lekom

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Abstract

Introduction. Acantholysis is rarely reported histological feature of Pityriasis rubra pilaris (PRP), recently recognized as having diagnostic specificity for differentiating PRP from psoriasis. **Case report.** Adult male patient one week after the introduction of simvastatin had experienced pruritic erythemo-squamous eruption on head and upper trunk that in a month progressed to erythrodermia, with islands of sparing. Histological picture combined pemphigus-like acantholysis with alternating hyper- and parakeratosis, follicular plugs and dermal inflammation, and confirmed the clinical diagnosis of classic adult type 1 PRP. Acitretin therapy resulted in a resolution of skin disease. Patch test with simvastatin was negative, scratch test was positive, and it was estimated that potential risk of oral challenge with simvastatin outweighed actual need for it. Drug triggering PRP episode is the most likely explanation for temporal relation between the start of simvastatin treatment and skin eruption. **Conclusion.** In management of rare inflammatory skin disease, such as PRP, we have to carefully observe and evaluate not only diagnostic features but possible external influences on its course also.

Key words:
pityriasis rubra pilaris; simvastatin; diagnosis; drug therapy; treatment outcome.

Apstrakt

Uvod. Akantoliza je retko prikazivana histološka karakteristika *Pityriasis rubra pilaris* (PRP) čiji značaj u diferencijalnoj dijagnozi prema psorijazi je nedavno prepoznat. **Prikaz bolesnika.** Prikazali smo odraslog bolesnika sa eritemoskvamoznom erupcijom po glavi i gornjem delu trupa praćenom svrabom koji je počeo nedelju dana nakon uvođenja simvastatina. Tokom mesec dana razvila se eritrodermija sa ostrvcima pošteđene kože. Histološki nalaz suprabazalne akantolize sa naizmeničnim zonama hiperkeratoze i parakeratoze u epidermisu i inflamatornog infiltrata u dermisu potvrdio je kliničku dijagnozu klasičnog adultnog oblika PRP. Terapija acitretinom dovela je do izlečenja kožnih promena. Epikutani *patch* test sa simvastatinom bio je negativan, *scratch* test bio je pozitivan, a test ekspozicije nije urađen jer je procenjeno da u tom momentu nosi veliki rizik. Epizoda PRP pokrenuta lekom je najverovatnije objašnjenje za vremensku povezanost kožnih promena sa početkom uzimanja simvastatina. **Zaključak.** U lečenju retkih zapaljenskih oboljenja kože treba pažljivo da tumačimo značaj kako dijagnostičkih parametara, tako i mogućih spoljašnjih uticaja na tok oboljenja.

Ključne reči:
pitirijazis rubra pilaris; simvastatin; dijagnoza; lečenje lekovima; lečenje ishod.

Introduction

Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disease, with 6 distinct forms that differ in the age of onset, clinical features, behavior, and prognosis: adult-onset forms (classical and atypical), juvenile forms (classic, circumscribed and atypical), and human immunodeficiency virus-associated one. Pathogenesis, etiology and triggering factors of PRP are not well characterized, and dilemmas about the diagnosis, associated diseases or therapeutic approach are frequent. Psoriasis is one of the most important differential diagnostic considerations, more in clinical than histological aspects. Acantholysis is a rarely reported histological feature of PRP that is recently recognized to have diagnostic specificity for differentiating PRP from psoriasis.

Case report

A 61-year-old male patient, experienced pruritic erythematous scaling eruption on head and upper trunk one week after the introduction of simvastatin 10 mg daily (Simvor® tbl 10 mg, Ranbaxy lab). The patient had discontinued simvastatin in five days, pruritus subsided, but during the next month the eruption spread to erythrodermia with pal-

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moplantar keratoderma, eyelid ectropion and small sharply demarcated “islands of sparing” (Figure 1). The clinical diagnosis was classical adult PRP type 1. The past medical

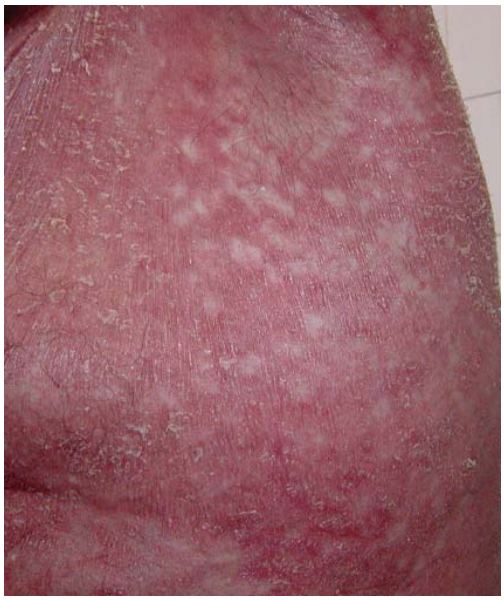

Fig. 1 – Erythrodermia with sharply demarcated islands of unaffected skin, typical adult form of Pityriasys rubra pilaris (PRP).

history of the patient was unremarkable: the patient did not currently use other medication, nor had reported any previous drug reaction. Apart from moderate hyperlipidemia, all the findings were within normal limits, including temperature, blood count and basic biochemistry profile, tests of thyroid function, autoimmune disorders, muscle enzymes, malignancy screening and direct skin immunofluorescence. Suprabasilar acantholysis suggestive for pemphigus vulgaris was the most prominent histological pattern in biopsy of recent papula (Figure 2), and features more usual for PRP (al-

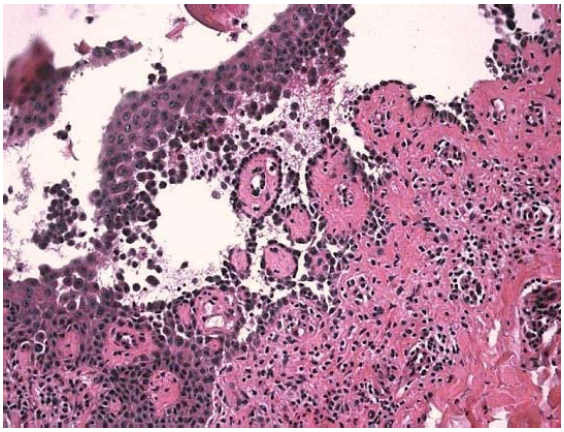

Fig. 2 – Skin histology: suprabasal acantholysis suggestive of pemphigus vulgaris (haematoxylin-eosin, original magnification × 200).

ternating hyper- and parakeratosis, dyskeratosis, follicular plugs, perivascular inflammation in upper dermis) were present in the biopsy of older plaque (Figure 3). Methylprednisolone therapy (initially 80 mg daily, tapered during 4 weeks) was without response. Acitretin, 35 mg daily brought a complete clearance in 3 months, following an inverse pattern of the initial cranio-caudal spread. It was discontinued after five months, without recurrence of PRP for the next 4 years. Nine months after clearance skin tests were performed with 2% simvastatin solution in water for injection; patch test was negative, scratch skin test was positive, revealed wheal along scratch line through simvastatin solution (Figure 4). Oral exposition test was not performed because it was estimated that a potential risk outweighed the actual need for simvastatin.

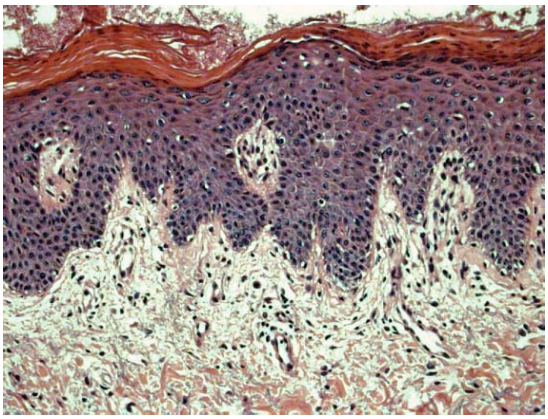

Fig. 3 – Skin histology: alternating hyper- and parakeratosis, dyskeratosis (haematoxylin-eosin, original magnification × 200).

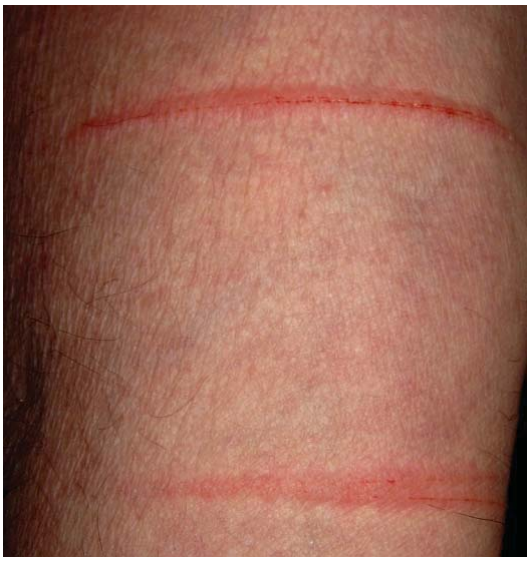

Fig. 4 – Positive scratch skin test with simvastatin: the upper line is a 3 mm wide wheal along the scratch line with aqueous simvastatin solution; the lower scratch line, surrounded with flare, represents negative control with water for injection.

Discussion

There is no single histological characteristic unique for PRP. The diagnosis combines several features (alternating hyper- and parakeratosis, follicular plugs, follicular lip parakeratosis, dermal perivascular infiltrate) and exclusion of

other differentials [1]. Early reports about acantholysis in PRP histology treated it as rare or incident finding [2, 3]. One large retrospective analysis of PRP histology detected small foci of acantholysis in about 70% of specimens [1]. Types of epidermal clefts in PRP were described as Darier-like, Hailey-Hailey-like, pemphigus-like, visible as solitary or combined patterns, or having features of epidermolytic hyperkeratosis [1–4]. With hypergranulosis and follicular plugs, acantholysis was of help in distinguishing histological findings favouring PRP towards others that are more psoriatic (capillary dilatations, hypogranulosis and epidermal pustules) [1]. Although the term acantholytic PRP was proposed for cases clinically and histologically suggestive of blistering disease, further reports of cases or case series are sparse and acantholysis is still a frequent cause of diagnostic dilemma [5]. All reported acantholytic PRP cases were typical adult erythrodermic form (type 1 PRP), but it is not conclusive whether acantholysis is a feature of solely type 1, or this form allows easier clinical recognition in spite of the unusual histology [1–5].

Intriguing is a relation between the start of new drug use and particular PRP episode, especially role of immediate hypersensitivity to simvastatin (as suggested by positive cutaneous scratch test), but can only be hypothesized. Oral challenge is the only way to sufficiently prove causal role of simvastatin, but due to severity of erythrodermia and positive skin tests, the risk of oral challenge was estimated to be unacceptable. Scratch test, when positive, is confirmatory test for immediate type hypersensitivity (urticaria – anaphylaxis), and presented case of PRP had no elements of such reaction pattern. Patch skin test when positive is confirmatory test for delayed type hypersensitivity (i.e. drug induced exanthemata), but patch test with simvastatin was negative in the presented patient, therefore excluding drug eruption with features of PRP. Drug triggering PRP is the most likely explanation for temporal association between the introduction of drug and occurrence of skin eruption, and quite long period of several months for clearance of PRP after drug discontinuation.

Pathogenesis of PRP is not resolved: apart from post-infectious forms of mostly juvenile and HIV-associated PRP, triggering events are not characterized also. Drug treatment as a trigger of PRP has only exceptionally rarely been evaluated. In the literature, one unique case of PRP induced with labetalol had been confirmed with oral challenge [6]. In the same period of the seventies of the 20th century beta blockers were recognized as triggers of psoriasis, skin disease that share some similarities with PRP. Later on drug-related PRP was hypothesized in few cases in the retrospective analysis, but were not evaluated by appropriate challenges in particular patients; incriminated drugs were anticonvulsants, antihistamines, diltiazem [1]. Aggravation of PRP has been described with topical imiquimod, suggesting that an imiquimod induced shift towards Th1 cytokine profile could be proinflammatory stimulus for PRP [7]. Statins have numerous pleiotropic (cholesterol-independent) effects on the immune system, and in clinical setting statins exert both anti- and proinflammatory properties. Cases of autoimmune diseases (lupus, dermatomyositis) closely related to statin treatments were described in the literature [8]. Also, cases of acquired ichtyosis caused by pravastatin treatment [9], or psoriasis relapsing upon treatment with different statins [10] suggest that statin effects on epidermal lipid homeostasis can have clinical implications in predisposed individuals.

Conclusion

Acantholysis is unexpected and underreported histological finding that should be recognized in diagnostic management of PRP. We should be careful to observe and to further investigate possible external influences on the entire course of rare inflammatory diseases, such as PRP. More extensive knowledge about the pathogenesis sequence of PRP is needed, to be able to estimate the role of external factors possibly influencing a cascade of skin inflammation and the course of PRP.

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