ORIGINAL ARTICLE

The management and genetic background of pityriasis rubra pilaris: a single-centre experience

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Abstract

Background Pityriasis rubra pilaris (PRP) is a rare chronic inflammatory dermatosis with multifactorial aetiology. It is known that particular caspase recruitment domain family member 14 (*CARD14*) gene mutations are associated with familial PRP and certain forms of psoriasis. Additionally, few data are available about the role of *CARD14* gene variants in sporadic PRP. The clinical picture is variable for the different types of PRP, therefore choosing the adequate treatment is often difficult, furthermore there are no specific guidelines for therapy.

Objective Our aim was to survey the efficacy of the applied therapies and to screen the *CARD14* gene variants in our PRP patients.

Methods In this retrospective study, patients diagnosed with PRP between 2006 and 2016 at our clinic were involved. Besides the follow-up study of the treatments, the genetic analysis of *CARD14* gene was performed.

Results We analysed 19 patients, among whom 17 were diagnosed with type I, one with type III, and one with type V PRP. The majority of the patients were successfully treated with acitretin in combination with systemic corticosteroids, and the remaining patients were treated with other systemic therapies with diverse effects. The genetic screening of *CARD14* gene revealed two previously described mutations (rs114688446, rs117918077) and six polymorphisms (rs28674001, rs2066964, rs34367357, rs11653893, rs11652075, rs2289541). Ten of 19 patients carried different *CARD14* genetic variants either alone or in combination.

Conclusion Based on our experience, we propose that acitretin and an initial combination of short-term systemic corticosteroid therapy could be a successful treatment option for PRP. Although we identified several *CARD14* variants in almost half of our cases, we did not find a correlation between the therapeutic response and the genetic background. Our data support the previous observation that CARD14 genetic variants are not specific to PRP, although they may indicate chronic inflammation.

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Conflict of interest

All authors confirm that this manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. The manuscript has been read and approved by all authors. We declare no conflict of interests among the authors in financial or other relationship. Detailed investigation of patient 14 was carried out and published as a case report: Danis *et al.* Nuclear Factor κB Activation in a Type V Pityriasis Rubra Pilaris Patient Harboring Multiple CARD14 Variants, Front. Immunol 9:1564, 2018.

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Introduction

Pityriasis rubra pilaris (PRP) is a rare chronic inflammatory papulosquamous dermatosis of uncertain aetiology manifested by palmoplantar keratoderma, follicular hyperkeratotic papules and reddish-orange scaly plaques often with characteristic islands of sparing. The skin symptoms may often progressively worsen and become erythrodermic; nevertheless, a spontaneous remission may occur a few years after the onset of the disease.

Table 1 Classification of PRP, according to Griffiths

Type	Age at onset	Ratio (%)	Clinical manifestation
I	Adult	55	Red-orange plaques, follicular papules, erythroderma with 'napples claires', diffuse palmoplantar keratoderma, nail involvement
II	Adult	5	Ichtiosiform scaling on legs, eczematous dermatitis, nonscarring alopecia
III	5–10 years	10	Similar to type I
IV	3–10 years	25	Well demarcated areas with follicular hyperkeratosis on elbows and knees
V	0–4 years	5	Follicular hyperkeratosis, Familial PRP
VI	Variable	<5	Similar to type I, in HIV positive patients

According to Griffiths, PRP is classified into five forms: classic adult type, atypical adult type, classic juvenile type, circumscribed juvenile type and atypical juvenile type. Recently, HIV-associated form, as a sixth category has been added to this classification (Table 1).[1,2]

Most of PRP cases are sporadic. However, approximately 5% of the cases are familial and show autosomal dominant inheritance.[3] Previously, Fuchs-Telem and co-workers have revealed that familial PRP develops as a consequence of the activation of the NF-κB signalling pathway due to rare mutations of the caspase recruitment domain family member 14 (*CARD14*) gene.[4] Moreover, *CARD14* gene variants are implicated in sporadic PRP as well.[5–7] In addition, *CARD14* single nucleotide polymorphisms (SNP) and gain-of-function mutations have been reported in psoriasis.[8] Besides the genetic similarities, these erythematosquamous diseases share common phenotypical features that make the diagnosis often difficult.[9]

Since the treatment options in PRP are limited and there are no specific guidelines for the therapy, it is important to investigate the associated genetic background of PRP patients to establish genotype–phenotype correlations, which may lead to better therapeutic approaches. Here, we describe the efficacy of the applied therapy in our PRP patients, and the identified genetic variants of the *CARD14* gene.

Materials and methods

Patients

In this retrospective, non-controlled study, we analysed PRP patients at the University of Szeged Department of Dermatology and Allergology between 2006 and 2016. The definitive PRP diagnosis was based on the clinical and histopathologic information. Nineteen patients were diagnosed with PRP, and the classification of PRP was defined according to Griffiths (Table 1). The patients' demographic and clinical data were collected, and the therapeutic outcome was followed. This study was approved by the Human Investigation Review Board of the University of Szeged and carried out in compliance with the Declaration of Helsinki. All patients provided written informed consent.

Genetic investigations

Genetic analysis of the *CARD14* gene was performed using diagnostic formalin-fixed paraffin-embedded skin biopsies of patients that were available in our histological archive ($n = 12$) or blood samples of the patients ($n = 7$). The paraffin-embedded tissues were deparaffinized and genomic DNA was isolated using the BioRobot EZ1 DSP Workstation (QIAGEN; Hilden, Germany). The coding region of the *CARD14* gene and the flanking introns were amplified applying primer sequences displayed on UCSC Genome Browser (http://genome.ucsc.edu/) and DNA sequencing was performed on the amplification products. Direct sequencing was performed on an ABI 3100 sequencer and compared with the wild-type gene at the Ensembl Genome Browser (https://www.ensembl.org/). The indicated minor allele frequencies (MAFs) are according to Caucasian databases.

Results

Clinical background

During the 10-year follow-up, 19 PRP cases were diagnosed, whose clinical characteristics, demographic data and genetic variants are summarized in Table 2. The mean age of the patients at the time of their diagnosis was 55.16 (range, 8–73) years. Based on the literature, the disease occurs equally in both sexes,[10] nonetheless, we diagnosed 13 male and 6 female patients.

Seventeen patients had type I PRP; one patient had type III PRP. One patient was diagnosed with type V PRP; her family members (father, sisters, daughter and grandchild) had similar skin lesions and were diagnosed with psoriasis, moreover in her childhood this type V PRP patient was misdiagnosed with psoriasis. Similarly, Patient 15 with type I PRP was also misdiagnosed with psoriasis ten years prior to our PRP diagnosis. In these cases, both the clinical features as well as the histopathology indicated PRP.

The above mentioned observations are in line with the described difficulties in the differential diagnosis between psoriasis and PRP.[11] In 13 patients, the disease started with erythroderma.

Genetic screening of the CARD14 gene

All of the 19 patients were screened for *CARD14* gene variants. Nine of the patients showed wild-type *CARD14,* while in 10 patients several CARD14 genetic variants were identified alone or in combination, these variants are listed in Table 3. The genetic sequence analysis identified two *CARD14* mutations, both of them missense mutations and had already been described previously (rs114688446, rs117918077), marked with

Table 2 Clinical/demographic data of the patients, therapeutic outcomes and detected genetic variants

Patient No./ sex/type based on Griffiths	Age at onset	Family history	Erythroderma	*CARD14* variants	Therapy	Therapy response	Disease duration (months)	Additional information
1./female/I	62	NA	Yes	neg	SS+acitretin	Symptom-free	3	
2./male/I	61	neg	Yes	neg	SS+acitretin	Symptom-free	3	
3./male/I	32	neg	No	neg	SS+acitretin	Symptom-free	6	
4./male/I	73	neg	Yes	rs114688446† rs11652075	SS+acitretin	Symptom-free	9	
5./male/I	60	NA	Yes	rs2066964	SS+acitretin	Symptom-free	19	
6./male/I	56	neg	Yes	neg	SS+acitretin+ PUVA	Symptom-free	42	
7./male/I	73	neg	Yes	Rs34367357 rs28674001 rs11653893 rs11652075	SS+acitretin	Symptom-free	16 (ongoing)	Later relapses, maintenance therapy is necessary
8./male/I	68	neg	yes	rs2066964 rs28674001 rs11653893 rs11652075	SS+acitretin	Symptom-free	19 (ongoing)	Later relapses, maintenance therapy is necessary
9./male/I	67	NA	yes	rs2066964	Vitamin A, SS+azathiorin, SS+acitretin	Symptom-free	10	later CTCL, than he died
10./male/I	69	neg	yes	rs2066964	SS+PUVA, SS+MTX	Symptom-free	4	
11./male/I	66	neg	no	rs2289541 rs2066964 rs28674001 rs11653893 rs11652075	Acitretin	Symptom-free	7	later BP
12./female/I	55	NA	no	neg	Acitretin	Symptom-free	22	frequent relapses
13./female/III	8	neg	no	neg	Vitamin A	Almost symptom-free	5	
14./female/V	61	psoriasis	yes	rs117918077† rs2066964 rs28674001 rs11652075	Acitretin, ustekinumab	Improving symptoms	17 (ongoing)	
15./male/I	60	neg	yes	neg	PUVA, acitretin, MTX	Almost always symptomatic	132 (ongoing)	His previous diagnosis was psoriasis for 10 years
16./female/I	46	psoriasis	no	neg	vitamin A, acitretin, extracorporeal photochemotherapy	Almost always symptomatic	144 (ongoing)	
17./male/I	48	neg	yes	rs2066964	311 nm UVB	Symptomatic	2	Alcohol addiction, noncompliance, relapse, died
18./male/I	40	neg	no	neg	Acitretin	NA	NA	Noncompliance
19./female/I	43	neg	no	rs28674001 rs11653893 rs11652075	Topical steroid	NA	NA	Noncompliance

†Minor allele frequency <0.01.
SS, systemic corticosteroid; PUVA, psoralen+ultraviolet A; MTX, methotrexate.

an asterisk in Table 2. The rs114688446 and rs117918077 mutations of the *CARD14* gene were described previously not only in PRP, but in psoriasis as well. The association of the rare variant rs114688446 with psoriasis vulgaris and generalized pustular psoriasis was previously described in American cohorts with European ancestry and this rare variant is assumed as a potential modifier for disease onset.[8,12] Although there is a significant association between these mutations and papulosquamous diseases, their *in vitro* functional studies did not reveal any effect on NF-κB activation.[6,8] The *in silico* predicted effect of these two mutations on protein function is considered benign (Ensembl, NCBI/refSNP, VarSome, SIFT, PolyPhen2). In our previous functional study, we identified one of these mutations (rs117918077) and additional 3 *CARD14* variants (rs28674001,

Table 3 Detected CARD14 variants of the PRP patients

Variant ID	Variant cDNS	Variant prot	Function	MAF	Exon
rs114688446	c.599G/A	p.Ser200Asn	Missense	0.01	4
rs28674001	c.676-6G/A	–	Splice site	0.34	4–5
rs2066964	c.1641G/C	p.Arg547Ser	Missense	0.37	14
rs34367357	c.1753G/A	p.Val585Ile	Missense	0.08	15
rs117918077	c.2044C/T	p.Arg682Trp	Missense	0.01	17
rs11653893	c.2399-4A>G	–	Splice site	0.36	17–18
rs11652075	c.2458C/T	p.Arg820Trp	Missense	0.35	20
rs2289541	c.2648G/A	p.Arg883His	Missense	0.02	21

MAF, minor allele frequency (Reported MAF at www.ensembl.org).

rs2066964, rs11653893) in a type V PRP patient, who demonstrated increased NF-κB activation in skin biopsies, isolated keratinocytes and peripheral blood mononuclear cells (PBMCs). The higher inflammatory state cannot be explained exclusively by the *CARD14* variants, but the cumulative effect of these variants may contribute to the increased NF-κB activity.[13]

Besides the two mutations, further 6 *CARD14* polymorphisms were identified as follows: 4 missense (rs2066964, rs34367357, rs11652075, rs2289541) and 2 splice site variants (rs28674001, rs11653893). All of these SNPs have been described previously in psoriasis and/or in PRP in a number of cohorts.[6–8,14] The rs2066964 variant was identified with high frequency in sporadic PRP patients.[6,7] Eskin-Schwartz and co-workers investigated a family with CARD14-related psoriasis, and they found the rs2066964, rs11652075 and rs34367357 polymorphisms in severely affected individuals which suggest a possible association of these SNPs with the severity of the disease.[14] The common rs11652075 polymorphism has been associated with the development of psoriasis[8,15] and it was described in sporadic PRP patients as well.[6,7] As far as the function of these SNPs based on *in silico* analysis, all are considered benign (Ensembl, VarSome). Moreover, a previous study revealed that the rs2066964 polymorphism has no significant influence on NF-κB activation *in vitro*.[16] The *in vitro* function of the other 5 SNPs was not investigated yet.

Therapy and outcome

Spontaneous remission was not observed in our patients. In 6 patients, the therapy is still ongoing, 11 patients were treated successfully without reoccurrence of the symptoms during the follow-up. Two patients died of different causes irrespective of their PRP. The patients' treatment and disease outcomes are shown in Table 2. We determined the disease duration as the time period from the beginning of the therapy to the asymptomatic or nearly asymptomatic stage.

All patients received topical skin care therapy combined with systemic therapy; the topical treatment included corticosteroids, keratolytics and emollients. Based on our clinical experience and the available data, it is very likely that systemic therapy is necessary in most cases.

Eight patients received a combination of systemic corticosteroids and acitretin as first-line therapy. Five of them had a complete recovery within 8 ± 6.6 months and they have remained in remission (follow-up 64 ± 58.1 months). (Patient 6 who was initially treated with corticosteroid and acitretin cannot be compared to the similarly treated other group, because his corticosteroid therapy was abruptly discontinued). At the start of the steroid therapy – when patients displayed extensive inflammatory signs or erythroderma – they received systemic corticosteroids in a relatively low dose (0.5 mg/kg prednisolone). The steroid dose was gradually reduced according to their symptoms. At the same time, acitretin was started usually at a 10 mg/day dose, which later was increased to 20–25 mg, if necessary. Acitretin was usually continued until patients achieved complete remission (10.4 ± 6.8 months). Of the eight patients treated with this combined therapy, two relapsed when acitretin was discontinued after 16 and 19 months, and we reintroduced their previous therapy. Currently, both of them are given a maintenance dose of 5–10 mg prednisolone/day and 10–20 mg acitretin/day, and they are symptom-free. It is worth mentioning that these two patients had the highest number of genetic variants in this group.

Patient 9 first received different kinds of therapies before the combination of systemic corticosteroid and acitretin was introduced, and he became symptom-free. Following a six-month symptom-free period, he developed cutaneous T cell lymphoma (CTCL).

The other 10 patients were treated with several systemic therapies, such as acitretin in monotherapy, high dose vitamin A, methotrexate, azathioprine, PUVA, extracorporeal photochemotherapy and ustekinumab. Patient 11 was given acitretin monotherapy and responded well and became almost symptom-free in 7 months when, however, he developed bullous pemphigoid. Regarding his new disease, we supplemented his previous treatment with systemic steroid therapy. Our only familial PRP patient has been on ustekinumab therapy for 1.5 years, her symptoms improved but she is not symptom-free. In the remaining eight patients, the various other therapies did not seem to help, since two are either symptomatic or have frequent relapses. We have two patients in this group with no information on the course of their disease.

Conclusion

Due to the rare disease prevalence and the wide range of clinical manifestations, the diagnosis of PRP can be very difficult in certain cases: clinical findings can overlap with other skin diseases, therefore PRP is often misdiagnosed, mainly as psoriasis.[9,17] However, in most cases histopathology can help to distinguish these two erythematosquamous skin disorders from each other. Typical histological features of PRP include psoriasiform hyperplasia, follicular hyperkeratosis, perivascular lymphocytic infiltrate, and intact or thickened stratum granulosum. In contrast,

in psoriasis there are characteristic hypogranulosis and the presence of Munro microabscesses. However, the histologic spectrum of both PRP and psoriasis is varied and in atypical PRP, cases can overlap with psoriasis.[11,18] In addition, since there are no specific or uniformly effective therapy guidelines available in PRP, finding the successful treatment is also often challenging. Hence, the detailed understanding of the PRP pathogenesis, the associated genetic background and establishing genotype–phenotype association are essential, and may contribute to the investigation of new therapeutic approaches in PRP.

Recent studies demonstrated that familial PRP has been associated with *CARD14* mutations, which are also identified in familial psoriasis.[19] CARD14 protein is higher expressed in the skin than in any other organs.[20] CARD14 is a known activator of NF-κB signalling, which is involved in inflammatory disorders due to the regulation of proliferation, differentiation and apoptosis.[21] NF-κB may play a crucial role in the pathogenesis of psoriasis and is also implicated in PRP.[22] Takeichi and co-workers suggested that *CARD14* mutations as common genetic features may give an explanation to the clinicopathological similarities between PRP and psoriasis vulgaris.[23] Moreover, Craiglow and co-workers recommended a new term *CARD14-associated papulosquamous eruption* to characterize this spectrum of disease. They found that the clinical symptoms of the patients in this group are very similar independently of their diagnosis being either psoriasis or PRP.[9] In our familial PRP patient with CARD14 mutation, the overlap between psoriasis and PRP was strongly suspected. However, the other patient with CARD14 mutation presented typical reddish-orange scaly plaques and islands of sparing characteristic of PRP.

Previous studies showed that the occurrence of *CARD14* mutations in sporadic PRP is very low (0–12.5%).[6,7,24] In agreement with these data, we demonstrated *CARD14* mutation in 5.3% of our sporadic PRP cases. In this study, we showed already reported SNPs in 38.9% of our 18 sporadic PRP patients, all of which have been previously described in PRP and in psoriasis.[6,8,12,14,15] *In vitro* functional studies of rs114688446 and rs117918077 mutations and the rs2066964 SNP demonstrated no functional effects of these variants on NF-κB activity.[6,8] The other 5 *CARD14* gene variants have not been studied *in vitro* so far. The *in vitro* functional studies were performed separately with the variants, therefore, we cannot exclude the possible involvement of the combined presence of different variants in one patient.[13]

Unfortunately, there is not enough data to establish a generally accepted therapeutic guideline for PRP. Although an important part of the management is the topical therapy, most PRP patients need systemic therapy. Some reports recommended ultraviolet-B phototherapy for juvenile type IV PRP.[25] One of our adult patients received UVB phototherapy, however, he subsequently relapsed. Other studies suggested that topical retinoids or corticosteroids may be sufficient in some cases, mainly in localized forms of the disease.[26,27]

Due to the rarity of PRP, only case reports and case series are available regarding the therapeutic options in the literature. Most reported reviews consider oral retinoids as first-line therapy.[10,28] Some studies indicated that PUVA and re-PUVA (oral retinoid and phototherapy) are presumably good alternatives. There are also some data indicating good clinical response to methotrexate. Moreover, cyclosporine, extracorporeal photochemotherapy and fumaric acid may also be used efficiently.[10] These medications are particularly applied in refractory cases with diverse effects. Recently, biological therapies, such as TNF-alpha blocking agents, IL-23 and IL-17 inhibitors may also represent therapeutic options.[29,30] Ustekinumab acting on the NF-κB pathway may be effective in cases of PRP with a gain-of-function mutation in CARD14.[5]

Systemic corticosteroids are considered to be ineffective and not used in PRP and psoriasis in general. It is well documented that if steroid is used as a monotherapy, the withdrawal may trigger the exacerbation of the disease, as in psoriasis.[31,32] However, the use of systemic corticosteroids in adequate dosage and in combination with other systemic treatment is beneficial in most cases of acute or erythrodermic psoriasis.[33] Erythroderma can develop as a complication of PRP, however, the reported incidence in the literature shows high variability.[10] According to some authors, erythroderma is a very frequent complication of PRP.[34,35] Piamphongsan and co-workers identified only 4 children and 10 adults with exfoliative erythroderma among 168 investigated patients.[36] PRP progressed to exfoliative erythroderma in 68.4% of our patients, mainly at the beginning of the disease. The majority of our PRP patients with erythroderma received combined therapy with systemic corticosteroid and acitretin. Among our patients, this combination from the beginning of the therapy seemed to be the most useful treatment. It is important to note that patients did not present any side effects during this treatment. Steroids are known to inhibit the NF-κB pathway and if this pathway is important in PRP the beneficial steroid effect can be explained. It is also obvious that steroid therapy itself is not sufficient for treatment, suggesting that excess inflammation is only part of the pathomechanism. The good therapeutic effect of acitretin indicates that besides the abnormal immune regulation, keratinocyte proliferation and differentiation processes are also contributing to the pathomechanism.

The *CARD14* gene mutations and SNPs may partially explain the chronic inflammation in PRP; however, in accordance with the literature, they are not specific to PRP, they only indicate chronic inflammatory disorders, and that is why they can be detected in some psoriasis cases. However, the reported rare and common SNPs of *CARD14* in both diseases could explain the clinical and histopathological similarities between cases of PRP and psoriasis.

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