HHS Public Access

Author manuscript

Pediatr Dermatol. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Pediatr Dermatol. 2021 September ; 38(5): 1237–1242. doi:10.1111/pde.14779.

CARD14-associated papulosquamous eruption (CAPE) in pediatric patients: Three additional cases and review of the literature

Cindy P. Frare, MD[1], **Alli J. Blumstein, BS**[2], **Amy S. Paller, MD**[2], **Lia Pieretti, MD**[3], **Keith A. Choate, MD, PhD**[4], **Anne M. Bowcock, PhD**[5], **Margarita Larralde, MD, PhD**[1,6]

[1]Department of Dermatology, Hospital Alemán, Buenos Aires, Argentina

[2]Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[3]Dr Úraga Private Center for Skin Diseases, Guayaquil, Ecuador

[4]Department of Genetics, Yale University School of Medicine, New Haven, CT, USA

[5]Dermatology, Oncological Sciences and Genetics & Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[6]Department of Pediatric Dermatology, Ramos Mejía Hospital, Buenos Aires, Argentina

Abstract

CARD14-associated papulosquamous eruption (CAPE) is a proposed term that encompasses features ranging from psoriasis to pityriasis rubra pilaris (PRP) in association with *CARD14* mutations. The early onset of the disease, prominent facial involvement, family history of an autosomal dominant trait, and poor response to conventional treatment are characteristics of CAPE that distinguish it from classical psoriasis and PRP. We describe the clinical features, family history, and response to therapy in three unrelated children with CAPE and compare these characteristics with those of previously described pediatric patients. Testing for *CARD14* mutations in children with early onset of features of psoriasis or pityriasis rubra pilaris and resistance to conventional therapy should be considered.

Keywords

CARD14; child; pityriasis rubra pilaris; psoriasis; ustekinumab

1 | INTRODUCTION

Activating mutations in *CARD14*, encoding caspase recruitment domain family, member 14, manifest clinically in a variety of presentations, most often pityriasis rubra pilaris

Correspondence Dr Margarita Larralde, Department of Dermatology, Hospital Alemán, Pueyrredón 1640, Ciudad de Buenos Aires 1118, Argentina. doctoralarralde@gmail.com.

CONFLICT OF INTEREST

KAC and ASP have received honoraria from Janssen.

(PRP) or plaque psoriasis, but less commonly pustular psoriasis, erythrodermic psoriasis, or acute generalized exanthematous pustulosis. Patients with *CARD14* mutations can be distinguished from more common forms of psoriasis and acquired PRP by the early age of onset (primarily before 1 year of age), prominent facial involvement (cheeks, chin and ears), frequent family history of psoriasis or PRP, and limited response to conventional topical and systemic therapies for psoriasis or PRP. Increases in *CARD14* expression have been shown to activate the IL-23/Th17 pathway, and best responses have been described with ustekinumab.[1]

2 | CASE REPORTS

2.1 | Patient 1

A 12-month-old Caucasian girl developed an erythematous, desquamative diaper dermatitis at 10 months of age that slowly progressed to involve the entire body. Physical examination showed confluent erythema and scale in the diaper area, trunk, buttocks, axillae, and neck, with scattered scaly, erythematous plaques on the upper and lower limbs, scalp, and face (Figure 1). No palmoplantar involvement, islands of sparing, or follicular papules were present. She did not have ectropion or nail changes. Family history revealed a maternal aunt who suffered from mild-to-moderate plaque psoriasis, but her mother was unaffected. Skin biopsy revealed psoriasiform dermatitis with regular acanthosis, elongation of rete ridges, and a diminished granular layer.

Twice daily application of hydrocortisone 1% cream for one week to affected area led to a partial reduction in scales and erythema. However, she continued with several flares during three months with minimal response to more potent topical corticosteroids. Genomic DNA was extracted from blood lymphocytes and revealed heterozygous mutation in *CARD14* (c.1604A>G, p. Gln535Arg).

2.2 | Patient 2

A 7-year-old Caucasian boy had a history of a recurrent pruritus and desquamative dermatitis that started on his cheeks at 3 months of age. It was initially diagnosed as atopic dermatitis. Physical examination revealed well-demarcated orange-red scaling plaques and follicular papules on the trunk and limbs with distinct islands of sparing. He also had thick scaly plaques on the scalp, forehead, malar region, philtrum, and chin with sparing of the infralabial region (Figure 2). Bilateral ectropion, palmoplantar keratoderma, and scleroderma-like changes in the hands were also noted. Nail changes were not observed. He had a family history of a maternal grandfather with psoriasis, but his mother was unaffected. Histopathological evaluation of biopsy sections revealed epidermal acanthosis, alternating orthokeratosis and parakeratosis, both vertically and horizontally, as well as follicular dilation. The dermis displayed superficial perivascular lymphocytic infiltrate.

Pityriasis rubra pilaris type V was diagnosed, and isotretinoin was initiated at a dosage of 0.5–1 mg/kg/d. Mometasone 0.1% cream was applied twice daily to affected areas for the first month and then daily for the more erythematous plaques. However, only partial clinical improvement was noted after three months and the isotretinoin was stopped.

He showed a partial response after eight months to a trial of methotrexate (0.4 mg/kg/wk), but subsequently progressed to erythroderma, with 80% body surface area (BSA) affected during a viral infection, despite the continued methotrexate. Given the inadequate response to conventional treatments, *CARD14* analysis was performed on DNA extracted from blood lymphocytes and showed a heterozygous *CARD14* variant c.365T>C (p. Met119Thr).

Ustekinumab, 2 mg/kg (45 mg), was injected subcutaneously at weeks 0, 4, and 12. After the first month, there was rapid improvement noted, with a reduction in total BSA from 80% to 20%. Methotrexate was discontinued without worsening. At the third month of treatment, he had a flare, so the frequency of ustekinumab was increased to every eight weeks, resulting in further reduction of total BSA to 11%. He continued another four months of treatment without adverse events, despite the higher and more frequent dosing.

2.3 | Patient 3

A 5-year-old Caucasian boy developed a desquamative dermatitis at 6 months of age that progressed to well-demarcated erythematous scaly plaques on the cheeks, chin, ears, buttocks, arms, lateral aspects of the thighs, and legs. Follicular prominence was noted in plaques on the legs (Figures 3 and 4). Palmoplantar involvement, ectropion, and nail changes were absent. His mother had psoriasis from 8 years of age; his maternal uncle and maternal grandfather also had plaque psoriasis. Lesional erythema, scale, and associated pruritus were improved satisfactorily with a regimen of once daily alclometasone 0.05% ointment for facial lesions and mometasone 0.1% cream for non-facial sites, as well as daily calcipotriene 0.005% ointment. However, minimal improvement was noted with persistent plaques at all sites of involvement. The patient, as well as all affected family members, was tested for *CARD14* mutations using DNA extracted from blood lymphocytes, and all family members affected by psoriasis had a heterozygous *CARD14* deletion (c.437_439del (p.146_147del) in exon 4). This deletion of AAG from the codons of two contiguous amino acids retains the first amino acid (Lys at position 146) but effectively cuts out the Glu at 147. The resultant CARD14 protein has an altered conformation, promoting formation of the CARD14-containing complex that activates NF-κB.

3 | DISCUSSION

We have described the clinical characteristics of three children with autosomal dominant-activating mutations in *CARD14* and reviewed the 31 previously reported pediatric patients (Table 1).[1–7] The mean age of disease onset overall was 12.4 months versus 6 months of age for our cases. All three of our patients had a positive family history of psoriasis in extended family members. However, only one had an affected first-degree family member (Patient #3), and in this family with several more distant affected members, perfect genotype-phenotype concordance was found (the *CARD14* variant found only in those affected by psoriasis and wild-type *CARD14* in unaffected family members). The other family members of Patients #1 and #2 were not tested for a *CARD14* mutation, making it unclear whether the family exhibited incomplete penetrance in a parent or the affected child had a de novo mutation.

In the 31 previously reported cases, clinical features typical of PRP such as follicular papules were observed in 45%, islands of sparing in 42%, palmoplantar keratoderma in 68%, and sclerodermatous changes of the hands in 6%.[1–7] One of our three patients presented these manifestations, and two of them only had follicular papules. Biopsy samples of previously reported cases have shown alternating orthokeratosis and parakeratosis with follicular plugging in patients with clinical manifestations of PRP and regular acanthosis with elongated rete ridges in patients with features of psoriasis. One of our biopsies was typical of PRP, and the other showed a psoriasiform dermatitis, reflecting the clinical features of the patients, as previously described for CAPE.[8] As described in 93% of the 31 previously described patients, all of our patients had facial involvement that occurred early as symmetric, well-demarcated pink-red plaques involving the cheeks, chin, and ears with sparing of the infralabial region.[1] Ectropion developed in more severe cases (6% of previous reports and one of ours). Truncal involvement was present in 64% of previous cases and two of our cases.

At least partial recalcitrance to conventional treatment (local and oral steroids, oral retinoids, methotrexate, and cyclosporine) is a key finding. Patient 1 had a partial response with topical steroid application, which the family deemed satisfactory. Minimal to partial responses have been described with antagonists of tumor necrosis factor-α (TNF-α).[1,2] Notably, 7 of 8 patients treated with ustekinumab had near complete to complete response, four of them at a dosage of 0.75 mg/kg-1.1 mg/kg every 12 weeks, one at a dosage of 1.2 mg/kg every 8 weeks,[1] and two at a dosage of 2 mg/kg every 8 weeks.[2] Our patient had a near-complete response at a dosage of 2 mg/kg every 8 weeks. Patients with CAPE may require higher dose and more frequent dosing of ustekinumab to achieve clinical remission than children taking ustekinumab for psoriasis without a *CARD14* variant.

Better understanding of the pathogenesis of monogenic skin disorders has led to repurposing of medications used for common diseases, such as psoriasis. *CARD14* activates NF-kB and MAPK signaling pathways, leading to recruitment and differentiation of inflammatory cells with increased production of IL-23 by dendritic cells and of IL-17 and IL-22 by T cells.[9] Given the activation of this IL-23/Th17 pathway with *CARD14* mutations, a better therapeutic response to ustekinumab versus TNF-α inhibition or broad immunosuppressants is not surprising. Furthermore, recognition that lesional skin in PRP shows activation of the IL-23/Th17 pathway, even without CARD14 mutation,[10–14] has led to successful intervention with ustekinumab[15,16] and the IL-17 pathway inhibitors secukinumab,[17,18] ixekizumab,[19] and brodalumab.[20] Despite the positive experience with targeted biologics in children with CAPE, long-term potential efficacy and risks are unknown.

Herein, we describe three pediatric patients with CAPE, and each has overlapping features of psoriasis and PRP. We suggest performing genetic testing on patients with onset during infancy, a positive family history, typical facial compromise, or poor response to traditional therapy. Considering the often refractory response to many conventional therapies, detection of a *CARD14* mutation should prompt providers to choose inhibitors of IL-12/23, IL-23, or IL-17, rather than inhibitors of the TNF-α pathway.

Funding information

This work was supported by the Foundation for Ichthyosis and Related Skin Types and the National Institutes of Health (R01 AR068392 to KAC and R01 AR050266 to AMB)

REFERENCES

1. Craiglow BG, Boyden LM, Hu R, et al. CARD14-associated papulosquamous eruption: a spectrum including features of psoriasis and pityriasis rubra pilaris. J Am Acad Dermatol. 2018;79(3):487–494. [PubMed: 29477734]
2. Signa S, Campione E, Rusmini M, et al. Whole exome sequencing approach to childhood onset familial erythrodermic psoriasis unravels a novel mutation of CARD14 requiring unusual high doses of ustekinumab. Pediatr Rheumatol Online J. 2019;17(1):38. [PubMed: 31286971]
3. Chiramel MJ, Sathishkumar D, Edison ES, George R. Two cases of CARD14-associated papulosquamous eruption from India. Pediatr Dermatol. 2020;37(4):692–694. [PubMed: 32323375]
4. Takeichi T, Terawaki S, Kubota Y, et al. A patient with CARD14-associated papulosquamous eruptions showing atopic dermatitis-like features. J Eur Acad Dermatol Venereol. 2021;35(1):e58–e59. 10.1111/jdv.16799. [published online ahead of print, Jul 3, 2020]. [PubMed: 32619277]
5. Takeichi T, Sugiura K, Nomura T, et al. Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. JAMA Dermatol. 2017;153(1):66–70. [PubMed: 27760266]
6. Fuchs-Telem D, Sarig O, van Steensel MA, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. Am J Hum Genet. 2012;91(1):163–170. [PubMed: 22703878]
7. Wu T, Banerjee S, Deng J, et al. Familial pityriasis rubra pilaris in a Chinese family caused by a novel mutation in CARD14 gene. Indian J Dermatol Venereol Leprol. 2020;86(1):81–84. [PubMed: 31755479]
8. Ring NG, Craiglow BG, Panse G, et al. Histopathologic findings characteristic of CARD14-associated papulosquamous eruption. J Cutan Pathol. 2020;47(5):425–430. [PubMed: 31849081]
9. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. Am J Hum Genet. 2012;90(5):784–795. [PubMed: 22521418]
10. Eytan O, Sarig O, Sprecher E, van Steensel MA. Clinical response to ustekinumab in familial pityriasis rubra pilaris caused by a novel mutation in CARD14. Br J Dermatol. 2014;171(2):420–422. [PubMed: 24641799]
11. Napolitano M, Lembo L, Fania L, Abeni D, Didona D, Didona B. Ustekinumab treatment of pityriasis rubra pilaris: a report of five cases. J Dermatol. 2018;45(2):202–206. [PubMed: 29080273]
12. Lwin SM, Hsu CK, Liu L, Huang HY, Levell NJ, McGrath JA. Beneficial effect of ustekinumab in familial pityriasis rubra pilaris with a new missense mutation in CARD14. Br J Dermatol. 2018;178(4):969–972. [PubMed: 28301045]
13. Nieto-Benito LM, Baniandrés-Rodríguez O, Moreno-Torres A, Hernández-Martín A, Torrelo-Fernández A, Campos-Domínguez M. Clinical response to ustekinumab in CARD14-associated papulosquamous eruption (CAPE) with a new missense mutation in CARD14: a case report and systematic review. J Eur Acad Dermatol Venereol. 2020;34(11):e728–e730. [PubMed: 32349169]
14. Feldmeyer L, Mylonas A, Demaria O, et al. Interleukin 23-helper T cell 17 axis as a treatment target for pityriasis rubra pilaris. JAMA Dermatol. 2017;153(4):304–308.
15. Min MS, Shroff A, Rose S, Lebwohl M, Guttman-Yassky E. Ustekinumab as therapy for psoriasis in a 2-year-old girl. J Eur Acad Dermatol Venereol. 2016;30(11):109–110.
16. Bonomo L, Raja A, Tan K, Guttman-Yassky E. Successful treatment of juvenile pityriasis rubra pilaris with ustekinumab in a 7-year-old girl. JAAD Case Rep. 2018;4(2):206–210. [PubMed: 29892668]
17. Liang JY, Ye RX, Tian X, Zhang SQ, Zhang XB. Secukinumab Monotherapy successfully treated severe refractory type V (atypical juvenile) pityriasis rubra pilaris: a case report and literature review. Dermatol Ther. 2020;33(6):e14097. [PubMed: 32725719]
18. Cole D, Mohammad T, Lim H. Rapid response of pityriasis rubra pilaris with psoriasis overlap to secukinumab. Br J Dermatol. 2019;181(6):1331–1332. [PubMed: 31260082]

19. Hanfstingl K, Pekar-Lukacs A, Motz R, Guenova E, Hoetzenecker W. Successful treatment of pityriasis rubra pilaris with ixekizumab. Case Rep Dermatol. 2018;10(2):97–100. 10.1159/000488902 [PubMed: 29867429]

20. De Felice C, Graceffa D, Morrone A, Bonifati C. Familial pityriasis rubra pilaris successfully treated with brodalumab. Int J Dermatol. 2020;59(7):885–887. [PubMed: 32202311]

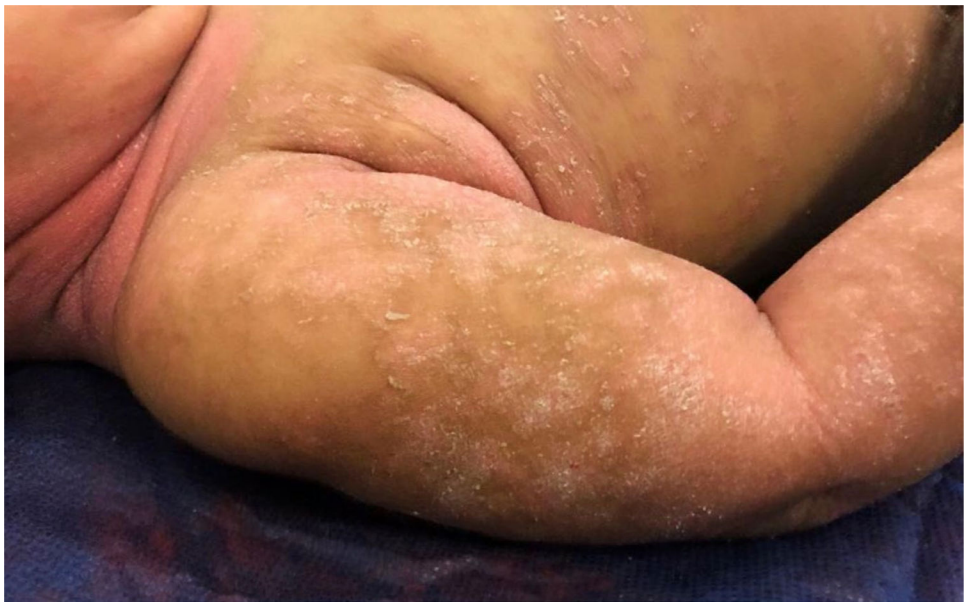

FIGURE 1.
Patient 1: Erythematous plaques with fine scaling on the upper limbs and neck

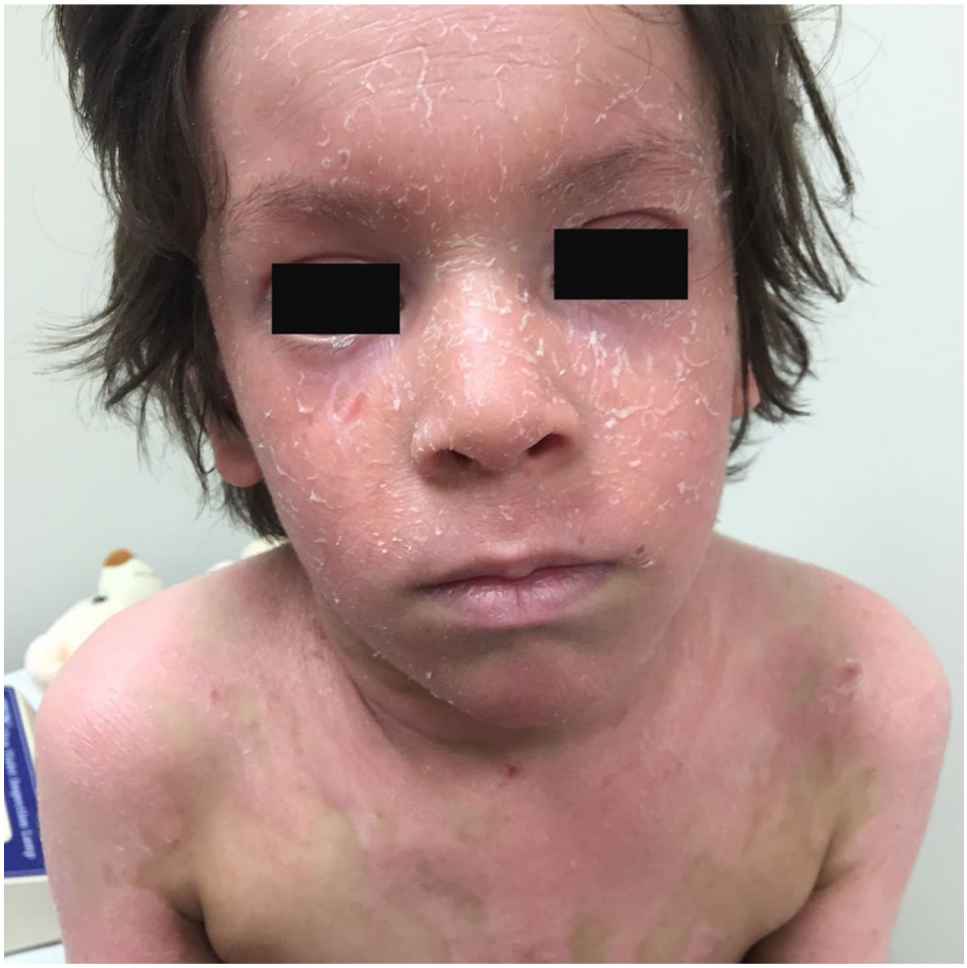

FIGURE 2.
Patient 2: Thick scaly plaques on the face and trunk with distinct islands of sparing

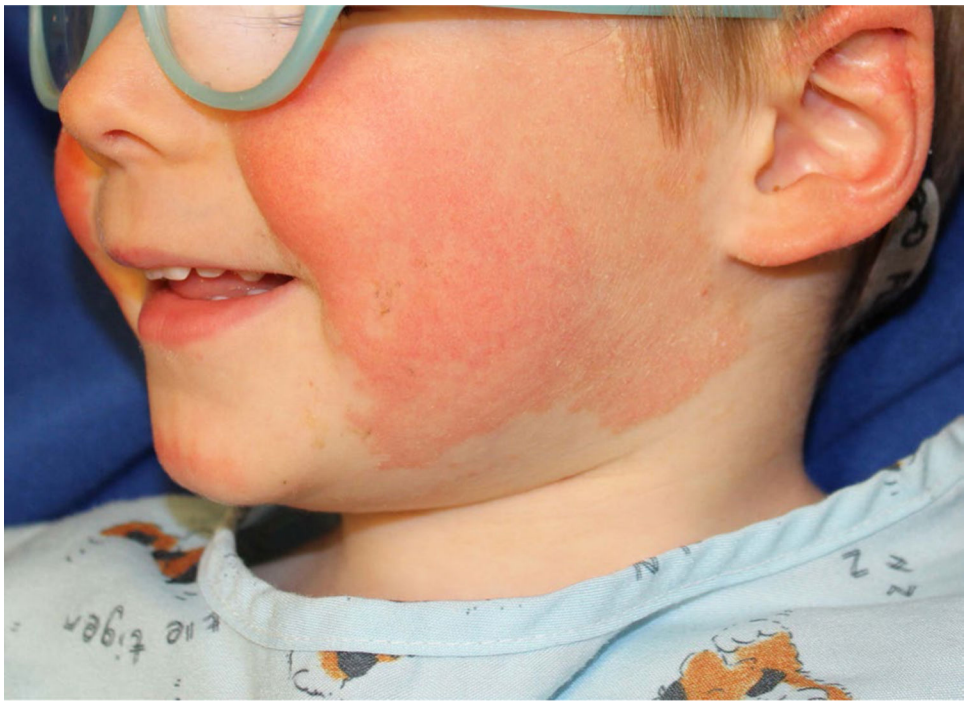

FIGURE 3.
Patient 3: Well-demarcated erythematous scaly plaques on the cheeks, chin, and ears

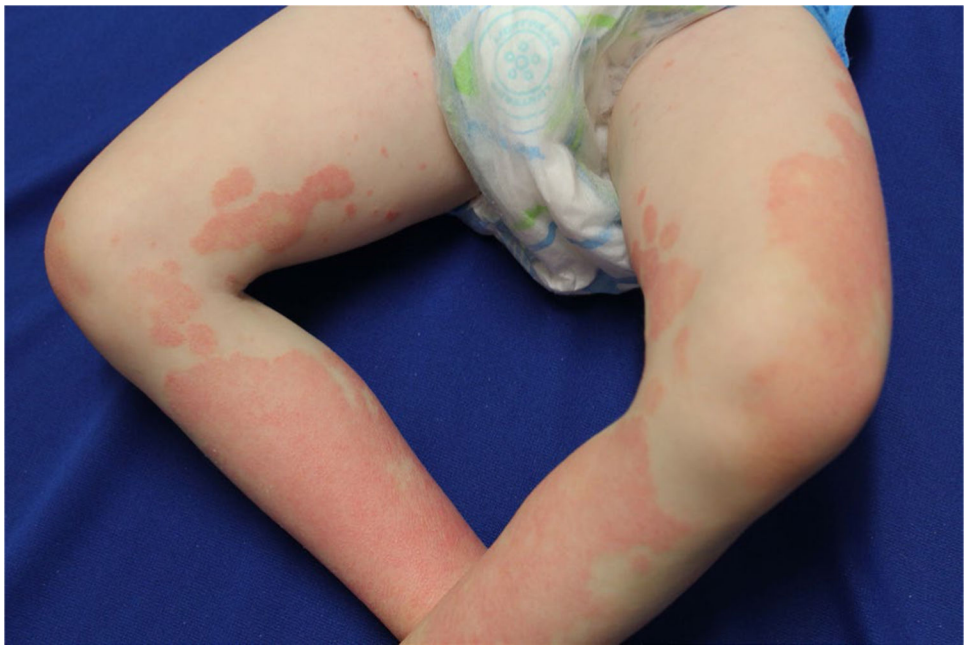

FIGURE 4.
Patient 3: Symmetric patches on lateral thighs and legs

TABLE 1

Pediatric patients with *CARD14*-associated papulosquamous eruption (CAPE)

Characteristics	Craiglow BG et al[1]	Signa S et al[2]	Chiramel MJ et al[3]	Takeichi T, Terawaki S, et al[4]	Takeichi T, Sugiura K, et al[5]	Fuchs-Telem D et al[6]	Wu T, et al[7]	Frare C et al
Patients (N)	15	2 (twins)	2 (siblings)	1	2	8	1	3
Mean Age of Onset	1.1 y (13 had onset at ≤1 y; a 2 y/o and an 8 y/o)	9 mo	17 mo	Infancy	1 m	14 mo	24 mo	6 mo
Clinical Features (N; % of patients)								
Facial involvement	14	2	2	1	2	8	0	3
Trunk involvement	13	2	2	1	2	0	0	2
Follicular papules	6	0	0	0	0	8	0	2
Island of sparing	5	0	0	0	0	8	0	1
PPK	12	0	0	0	0	8	1	1
Sclerodermatous changes of the hands	2	0	0	0	0	0	0	1
Nail changes	0	2	2	0	0	3	0	0
Ectropion	0	1	1	0	0	0	0	1
Histopathology	NA	Parakeratotic cornified layer and epidermis with marked elongation of rete ridges and hypogranulosis, Inflammatory cells and dilatation of blood vessels in the dermis (N = 2)	Chronic psoriasiform dermatitis with suprapapillary thinning and hypogranulosis (N = 1)	Hyperkeratosis, parakeratosis, acanthosis and slight spongiosis; neutrophilic infiltration in the stratum corneum, lymphocytic infiltration in the dermis	Hyperkeratosis, parakeratosis and acanthosis and lymphocytic infiltration in the dermis (N = 1) Hyperkeratosis, parakeratosis, follicular dilation filled with keratin and lymphocytic infiltration in the upper dermis (N = 1)	Alternating orthokeratosis and parakeratosis, follicular plugging, mild lymphocytic infiltration in the upper dermis (N = 8)	Hyperkeratosis, acanthosis and lymphocytic infiltration in the dermis	Regular acanthosis, elongation of rete ridges and hypogranulosis (N = 1) Alternating orthokeratosis and parakeratosis, follicular dilation, perivascular lymphocytic infiltration in the dermis (N = 1)
Treatment and Response	Ustekinumab (N = 6) (5)-NC; (1)-MP Ixekizumab (N = 1)-MP Etanercept (N = 9) (1)-NC; (7)-MP; (1)-W Adalimumab (N =	Ustekinumab (N = 2)-C Etanercept (N = 2)-MP Cyclosporine (N = 2)-MP Retinoids (N = 2)-MP	Cyclosporine (N = 1)-MP Acitretin(N = 1)-MP Local steroids, coal tar, calcipotriene (N = 1)-MP	Systemic steroids (N = 1)-NC	NA	NA	NA	Ustekinumab (N = 1)-NC Methotrexate (N = 1)-MP Isotretinoin (N = 1)-MP Local steroids and

Characteristics	Craiglow BG et al[1]	Signa S et al[2]	Chiramel MJ et al[3]	Takeichi T, Terawaki S, et al[4]	Takeichi T, Sugiura K, et al[5]	Fuchs-Telem D et al[6]	Wu T, et al[7]	Frare C et al
	1)-MP Methotrexate (N = 10) (1)-NC; (9)-MP Cyclosporine (N = 2)-MP Acitretin (N = 5) (4)-MP; (1)-W Isotretinoin (N = 4) (1)-NC; (3)-MP	Local and systemic steroids (N = 2)-MP						calcipotriene (N = 2)-MP
Family History[a] of PRP, PsO or PsA	Positive (N = 10) None (N = 5)	Positive	None	NA	None (N = 1) NA (N = 1)	Positive (N = 6) None (N = 2)	Positive	Positive (N = 3)

Abbreviations: C, complete; MP, minimal/partial; N, number of patients; NA, not available; NC, near complete; PRP, pityriasis rubra pilaris; PsA, psoriatic arthritis; PsO, psoriasis; W, worse.

[a]Family history: Parents, siblings, or extended family member affected (grandparents, aunts, uncles, cousins); None: no affected family member.