Successful Treatment of Juvenile-onset Pityriasis Rubra Pilaris with Cyclosporine A: A Case Report and Review of Literature

Afsaneh Sadeghzadeh-Bazargan[1], Elnaz Pourgholi[2], Khatere Zahedi[2], Toktam Safari Giv[2], and Alireza Jafarzadeh[1]

[1]Iran University of Medical Sciences
[2]Shahid Beheshti University of Medical Sciences

March 22, 2024

Abstract

Pityriasis rubra pilaris (PRP) is a rare papulosquamous skin condition that affects both adults and the pediatric population. It is characterized by salmon-colored plaques with islands of sparing and palmoplantar hyperkeratosis. Currently, there are no established guidelines for PRP treatment, especially in pediatric patients. In this study, we presented an infant case of type III juvenile PRP successfully treated with a short-term, low-dose cyclosporine A (CsA). No recurrence occurred during the 3-month follow-up period after completing treatment. Additionally, we reviewed the use of CsA as an alternative treatment option for juvenile-onset PRP. The results of this study were consistent with previous findings for adult-onset PRP. Therefore, this study further supports using CsA as an alternative option for treating juvenile-onset PRP.

Keywords: pityriasis rubra pilaris, drug therapy, cyclosporine A, therapeutic use, juvenile PRP

Introduction

Pityriasis rubra pilaris (PRP) is a rare familial and acquired papulosquamous disease. It is characterized by salmon-colored plaques with islands of sparing and palmoplantar hyperkeratosis. This condition can affect both adults and the pediatric population. [1]Usually, it has a cephalocaudal progression, and the palms and soles show a waxy yellow-orange keratoderma. [1] PRP's pathogenesis is not well understood. Still, there is evidence of increased expression of the interleukin IL-12/IL-23 and IL-17 axes in the affected skin. 2 There are various reported associations with PRP, including infections, autoimmunity, drugs, and malignancies. Still, more research is needed to understand these connections thoroughly.[2] In familial cases, a specific gene mutation called CARD14 has been identified. [2] The incidence and prevalence of PRP are still unknown, but it is estimated to affect about 1 case per 400,000 of the population. [3] It tends to occur most commonly in the first and fifth decades of life affecting both men and women of all races equally. [4] The histopathologic characteristics of PRP are variable, however, it sometimes resembles psoriasis in its presentation. [5]PRP is classified into six subgroups based on the age of onset, disease severity, prognosis, and other associated characteristics.[6] The subgroups: III (classical juvenile), IV (circumscribed juvenile), and V (atypical juvenile) most commonly affect children. [6] About 10%, 25%, and 5% of PRP patients, respectively, are classified in these subtypes. [7]

The course of the disease is variable; while some cases resolve spontaneously, others may be very challenging to treat.[1] There are no official recommendations, therefore management is largely based on previous case reports. Topical corticosteroids, retinoids, and vitamin D analogs are often used as first-line therapy. [3,8] There is insufficient data regarding pediatric patients. [9] Furthermore, there is resistance to systemic therapy in children, however, it has been tried for refractory cases in adults. [10] While oral retinoids are considered the

first choice as a systemic treatment, using high-dose acitretin for a long time in children carries an increased risk of side effects. [11] Currently, other systemic therapies including immunosuppressants and biologics are used for the treatment of juvenile PRP. [9] Here we present an infantile case of type III PRP successfully treated with cyclosporine A (CsA). Additionally, the use of CsA in juvenile-onset PRP is reviewed.

Case presentation

An 18-month-old girl presented to our clinic with a one-month history of non-pruritic red-orange papules that started on the scalp and spread to the face, trunk, and extremities. She was a healthy full-term newborn with a normal birth weight. She had no systemic manifestation, no history of allergies, and she had received all vaccinations. Her family history and review of systems were unremarkable. The physical examination showed multiple discrete hyperkeratotic papules on the forehead, and bilateral cheeks with fine and powdery scales, extending to the scalp. There were also multiple reddish to orange scaly papules affecting the chest and arms resembling nutmeg grater appearance. Subsequently, the same papules were prominent with the tendency to coalesce into orange-red plaques on both knees (Figure 1). Developmental and neurological evaluations of the patient were both normal.

Methods

Laboratory tests such as complete blood count, biochemistry, and urine analysis were within normal ranges. A punch biopsy of the knee lesion was obtained with a differential diagnosis of psoriasis and PRP. The histopathological study revealed a psoriasiform epidermal hyperplasia with alternating hyperorthokeratosis and parakeratosis in horizontal and vertical directions. Additionally, there was hypergranulosis, mild spongiosis, and moderate superficial perivascular infiltration, which were more indicative of pytriasis rubra pilaris (PRP) (Figure 2). Based on clinicopathologic correlation, the patient was diagnosed with type III juvenile PRP. Treatment with topical corticosteroid and tacrolimus 0.1% ointment was initiated. Unfortunately, the disease was progressive and there was no response to topical treatment. After discussing systemic therapy options with the parents, cyclosporine A (CsA) 25 mg daily (2.5 mg per kg) was initiated, with regular monitoring of blood pressure and electrolytes.

Conclusion and results

Four weeks after treatment initiation, the lesions began to regress, and after two months, complete clearance was achieved, leaving behind residual postinflammatory hypopigmentation. The dose of CsA was tapered to 25 mg every other day for an additional month before discontinuation. The patient did not experience any adverse effects and had no recurrence during the three-month follow-up after stopping CsA.

Discussion

PRP is an uncommon inflammatory skin condition that shares characteristics with psoriasis and shows heterogeneity in its phenotype.[1] The pathophysiology includes triggers such as bacterial or viral infections, autoimmune disorders, neoplasia, and CARD 14 mutations that activate the Th17 pathway. [3] Since this disorder is quite rare and tends to improve spontaneously, it is still challenging to determine the effectiveness of treatment options in clinical trials. [8] As a result, case reports and case series are the primary sources for evaluating treatments, and it may be necessary to try multiple medications to manage the condition effectively. [3,8]

Currently, topical treatments are primarily used in children, although they are only effective in mild forms of the disease.[9] CsA is one of the medications previously used in PRP. [12, 13] CsA is a medication that suppresses the immune system and targets calcineurin.[14] Nephrotoxicity, an increased risk of hypertension, hypertrichosis, and gingival hyperplasia are among the side effects that have been seen during treatment. In clinical practice, CsA is administered at a dose of 2.5 to 5.0 mg/kg per day, and most patients show improvement after 8 weeks of treatment. [14] The exact mechanism of action of CsA for PRP and its efficacy is still unclear. The histological changes observed in PRP align with a proliferative pattern of keratinocytes. Moreover, Marsili *et al.*[15] found that CsA may suppress keratinocyte growth in vitro. It has been demonstrated that

CsA is a very successful medication for treating severe inflammatory dermatoses in children.[16] However, using CsA for treating PRP is still limited, and there are conflicting findings in various case reports regarding its effectiveness. To the best of our knowledge, 11 case reports involving 13 patients, have evaluated the efficacy of CsA in treating juvenile PRP (Table 1). Among these cases, three patients, including our patient, showed complete clearance of symptoms after a short course of CsA (mean duration: 16.67 ± 4.16 weeks), without any reported adverse effects or relapses. All these three patients were diagnosed with PRP type III, and the mean age of onset was 2.33 ± 1.44 years. [17,18] Five cases reported a partial response to CsA, [19, 20, 21]while CsA was ineffective in two cases. [22,23] In one case a good response to CsA was reported initially, but unfortunately, it was discontinued due to disease recurrence and concerns about side effects. [24]Overall, a total of 23% of cases demonstrated a complete response to CsA, which is consistent with a previous case series of 28 patients with adult-onset PRP. [25] None of the reported cases mentioned any adverse effects during treatment with CsA.

In the present case, there was a complete clearance after 2 months of low-dose CsA therapy. There was no increase in blood pressure or any negative impact on renal function during the treatment. Furthermore, there was no recurrence of PRP over more than 3 months of follow-up after the cessation of CsA. Since potential side effects of CsA therapy typically appear after prolonged use, short-term therapy appears to be safe.

It is challenging to determine the effectiveness of treatment options for pityriasis rubra pilaris (PRP) due to its rarity and tendency to improve spontaneously. In this study, we reviewed using CsA as an alternative treatment option for juvenile-onset PRP. The results of this study were consistent with previous findings for adult-onset PRP. We recommend considering the use of CsA as an alternative option for a short period to treat juvenile-onset PRP.

Author contributions

Afsaneh Sadeghzadeh Bazargan: Conceptualization, Methodology, Supervision. Elnaz Pourgholi: Data curation, Investigation, Writing – original draft. Khatere Zahedi: Conceptualization, Methodology, Supervision. Toktam Safari Giv and Alireza Jafaezadeh: Data curation, Writing – review & editing.

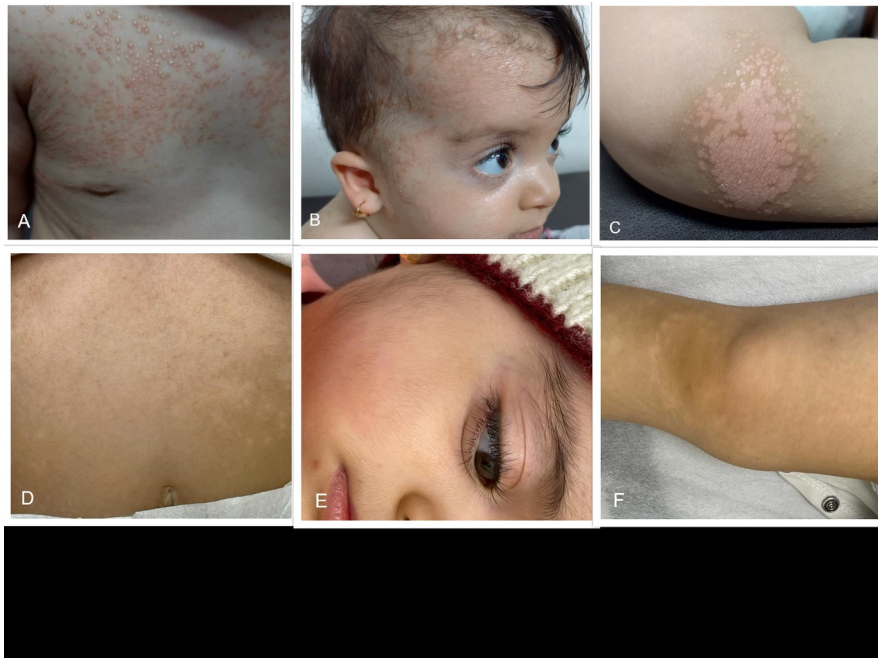

Figure 1: Clinical manifestation of the patient at the first appointment: multiple hyperkeratotic papules

on the chest and arms**(A),** forehead and lateral face **(B),** and red-orange plaque on the knee **(C).** Complete clearance of the symptoms 8 weeks after treatment: trunk **(D),** lateral face **(E),**right knee **(F)**

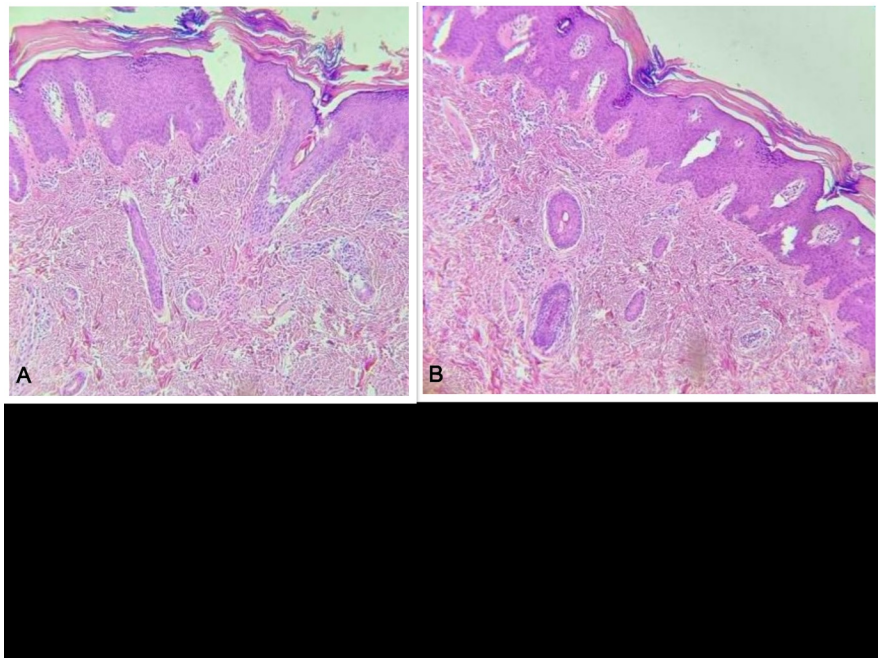

Figure 2 : Histopathologic slides from a punch biopsy of the patient. Note psoriasiform hyperplasia with parakeratosis and orthokeratosis, features consistent with a diagnosis of pityriasis rubra pilaris. (**A,B** ; Hematoxylin-eosin stain; original magnifications: A,B ×20)

Table 1 : Clinical data of juvenile PRP patients treated with cyclosporine A

	Reference	Age (year)/sex	PRP type	Previous treatment	CsA dosage and duration	Clinical outcome
1	Current report	1.5/ F	III	Topical corticosteroid and tacrolimus 0.1% ointment	2.5 mg/kg 3 month	Complete clearance
2	Wetzig T. *et al.* 2003 [17]	4/ M	III	topical, low-potency corticosteroids and urea 10% ointment	3 mg/kg 18 weeks	Complete clearance
3	Chen *et al.* 2022 [18]	1.5/ M	III	low-potency corticosteroids and moisturizing cream	3 mg/kg 20 weeks	Complete clearance
4	Craigrow *et al.* 2018[19]	1:3months/NR 2: 1month/ NR	CARD14-associated	MTX, etanercept, PUVA	NR	1: Partial 2: Partial

	Reference	Age (year)/sex	PRP type	Previous treatment	CsA dosage and duration	Clinical outcome
5	Signa *et al.* 2019[20]	1: 7/ M 2: 7/ M	CARD14-associated	topical and systemic steroids, etanercept	1: 5mg/kg 3 month 2: 5mg/kg 3 month	1: Partial 2: Partial
6	Liang *et al.* 2020 [22]	7 / M	V	Corticosteroids, calcineurin inhibitors, MTX, acitretin, isotretinoin	75 mg 2 month	Ineffective
7	Maloney *et al.* 2017[26]	4 / M	V	Acitretin, MTX	50 -125 mg 3 weeks	unknown
8	Lora *et al.* 2018[23]	13 / M	III	Acitretin, MTX	3 mg/kg 4 weeks	Ineffective
9	Bonomo *et al.* 2018 [24]	7 / F	III	tacrolimus 0.1% ointment, triamcinolone 0.1% ointment	300 mg 5 month	Initially, it showed a good response, then CsA had to be discontinued due to a flare-up of symptoms and concerns about adverse effects
10	Kim *et al.* 2015 [27]	17 / M	III	oral steroids, phototherapy, acitretin	NR	Ineffective
11	Chiramel *et al.* 2020[21]	7 / M	CARD14-associated	acitretin	3-4.5mg/kg 4 month	Partial

Abbreviations: F: female; M: male; MTX: methotrexate; PUVA: psoralen plus ultraviolet-A radiation; NR: Not reported.

References:

1. Klein A, Landthaler M, Karrer S. Pityriasis Rubra Pilaris. American Journal of Clinical Dermatology. 2010;11(3):157-70.

2. Wang D, Chong VC, Chong WS, Oon HH. A Review on Pityriasis Rubra Pilaris. American journal of clinical dermatology. 2018;19(3):377-90.

3. Brown F, Badri T. Pityriasis Rubra Pilaris. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Talel Badri declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

4. Klein A, Landthaler M, Karrer S. Pityriasis rubra pilaris: a review of diagnosis and treatment. American journal of clinical dermatology. 2010;11(3):157-70.

5. Cohen PR, Prystowsky JH. Pityriasis rubra pilaris: A review of diagnosis and treatment. Journal of the American Academy of Dermatology. 1989;20(5, Part 1):801-7.

6. GRIFFITHS WAD. Pityriasis rubra pilaris*. Clinical and Experimental Dermatology. 1980;5(1):105-12.

7. Cohen PR, Prystowsky JHJJotAAod. Pityriasis rubra pilaris: a review of diagnosis and treatment. 1989;20(5):801-7.

8. Roenneberg S, Biedermann T. Pityriasis rubra pilaris: algorithms for diagnosis and treatment. Journal of the European Academy of Dermatology and Venereology: JEADV. 2018;32(6):889-98.

9. Guenther J, Novack D, Kamath S, Worswick S. Treatment Options for Juvenile Pityriasis Rubra Pilaris. Paediatric drugs. 2023;25(2):151-64.

10. Eastham AB, Femia AN, Qureshi A, Vleugels RA. Treatment Options for Pityriasis Rubra Pilaris Including Biologic Agents: A Retrospective Analysis From an Academic Medical Center. JAMA Dermatology. 2014;150(1):92-4.

11. Sadowska M, Narbutt J, Skibińska M, Lesiak A. Pros and cons of using systemic acitretin in the pediatric population. Postepy dermatologii i alergologii. 2022;39(1):34-8.

12. Rosenbach A, Lowe NJ. Pityriasis rubra pilaris and cyclosporine. Archives of dermatology. 1993;129(10):1346-8.

13. Usuki K, Sekiyama M, Shimada T, Shimada S, Kanzaki T. Three cases of pityriasis rubra pilaris successfully treated with cyclosporin A. Dermatology (Basel, Switzerland). 2000;200(4):324-7.

14. Amber T, Tabassum S. Cyclosporin in dermatology: A practical compendium. 2020;33(6):e13934.

15. Marsili F, Travaglini M, Stinco G, Manzoni R, Tiberio R, Prignano F, et al. Effectiveness of cyclosporine A in patients with moderate to severe plaque psoriasis in a real-life clinical setting in Italy: the TRANSITION study. The Journal of dermatological treatment. 2022;33(1):401-7.

16. Frantz T, Wright EG, Balogh EA, Cline A, Adler-Neal AL, Feldman SR. Topical and Oral Therapies for Childhood Atopic Dermatitis and Plaque Psoriasis. Children (Basel, Switzerland). 2019;6(11).

17. Wetzig T, Sticherling M. Juvenile pityriasis rubra pilaris: successful treatment with ciclosporin. British Journal of Dermatology. 2003;149(1):202-3.

18. Chen P-J, Liang J-Y, Li C-X, Zhang X-B. Successful Treatment of Severe Pityriasis Rubra Pilaris with Cyclosporine A in An Infant. 2022;05(02):110-2.

19. Craiglow BG, Boyden LM, Hu R, Virtanen M, Su J, Rodriguez G, et al. CARD14-associated papulosquamous eruption: A spectrum including features of psoriasis and pityriasis rubra pilaris. Journal of the American Academy of Dermatology. 2018;79(3):487-94.

20. Signa S, Campione E, Rusmini M, Chiesa S, Grossi A, Omenetti A, et al. Whole exome sequencing approach to childhood onset familial erythrodermic psoriasis unravels a novel mutation of CARD14 requiring unusual high doses of ustekinumab. Pediatric rheumatology online journal. 2019;17(1):38.

21. Chiramel MJ, Sathishkumar D, Edison ES, George R. Two cases of CARD14-associated papulosquamous eruption from India. Pediatric dermatology. 2020;37(4):692-4.

22. 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. Dermatologic therapy. 2020;33(6):e14097.

23. Lora V, De Felice C, Cota C, Graceffa D, Morrone A, Bonifati C. A case of juvenile pityriasis rubra pilaris type III successfully treated with etanercept. Dermatologic therapy. 2018;31(1).

24. 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 reports. 2018;4(2):206-10.

25. Kromer C, Lippert U, Schön MP, Mössner R. Treatment of pityriasis rubra pilaris: a case series of 28 patients. European journal of dermatology : EJD. 2020;30(5):569-79.

26. Maloney NJ, Hisaw LD, Worswick S. Refractory pityriasis rubra pilaris treated with etanercept, adalimumab, or ustekinumab: A retrospective investigation. Dermatologic therapy. 2017;30(6).

27. Kim BR, Chae JB, Park JT, Byun SY, Youn SW. Clinical remission of pityriasis rubra pilaris with adalimumab in an adolescent patient. The Journal of dermatology. 2015;42(11):1122-3.