Successful treatment of juvenile pityriasis rubra pilaris with ustekinumab in a 7-year-old girl

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INTRODUCTION

Pityriasis rubra pilaris (PRP) is an uncommon inflammatory dermatosis characterized by erythematous salmon-colored plaques with islands of sparing and palmoplantar hyperkeratosis. The etiology of PRP is not well understood.[1] Histopathologic features of PRP are variable but presents with some similarities to psoriasis.[1,2] PRP is classified into 5 subgroups, with groups III (classical juvenile), IV (circumscribed juvenile), and V (atypical juvenile) affecting the pediatric population. These subtypes occur in approximately 10%, 25%, and 5% of PRP patients, respectively.[2] The natural history is variable; some cases undergo spontaneous resolution, and others can prove extremely difficult to treat.

There are currently no formal treatment guidelines for PRP, although topical corticosteroids, retinoids, or vitamin D analogues are typically the first line of therapy. Although multiple systemic therapies have been used for refractory cases in adults, often with limited efficacy,[3] there is a reluctance to use such treatments in the pediatric population.[4] There are currently 41 reported cases of PRP in children treated with systemic therapy, 33 of which used vitamin A derivatives.[5-14] Other cases used broad-spectrum immunosuppressant drugs, such as methotrexate or cyclosporine.

There are, however, reports of successful PRP treatment in adults with biologic therapies initially approved to treat plaque psoriasis.[3] As safety data on the use of novel systemic agents in pediatric psoriasis accumulates, it is becoming clear that biologic drugs are a viable option for pediatric PRP patients as well. For instance, etanercept (a tumor necrosis factor α inhibitor) has been Food and Drug Administration (FDA)—approved for the treatment of plaque psoriasis in children. Although ustekinumab was not FDA-approved in pediatric patients at the time of initiation, a large randomized controlled trial had found ustekinumab (an interleukin 12 and 23 inhibitor) to be safe and effective for patients 12-17 years of age, and ustekinumab had been successfully used in a small child with psoriasis.[15,16]

Abbreviations used:

BSA: body surface area
FDA: Food and Drug Administration
PRP: pityriasis rubra pilaris

CASE REPORT

We report the case of a 7-year-old girl Asian girl who presented to our clinic with biopsy-proven PRP. She had initially developed symptoms at 7 months of age, with persistent erythematous plaques generalized over the trunk and extremities. Birth history, medical history, and surgical history were unremarkable, and family history was notable only for a maternal grandfather with psoriasis. Primary diagnosis at the time was psoriasis, and topical steroids were initiated. However, the lesions continued to recur, prompting a punch biopsy that

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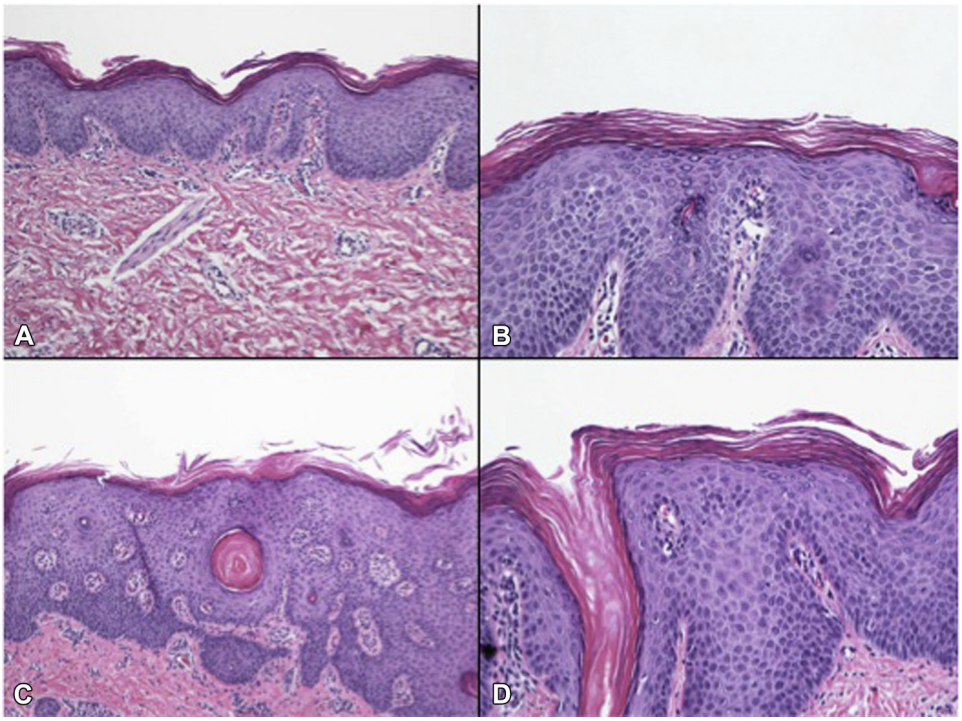

Fig 1. Histopathologic slides from punch biopsy performed at 7 months of age of patient with pityriasis rubra pilaris. Note psoriasiform hyperplasia with parakeratotic and orthokeratotic foci and follicular plugging, features consistent with a diagnosis of pityriasis rubra pilaris. (**A-D**, Hematoxylin-eosin stain; original magnifications: **A**, ×5; **B-D**, ×20.)

was consistent with a diagnosis of classical juvenile PRP (Fig 1). Systemic therapy was recommended, but the patient's family opted to continue with topical medication only. The patient was treated wutg hydrocortisone cream, topical retinoids, and topical vitamin D analogues, which provided only minor improvements. Lesions continued to recur and persist over the next 6 years, that ultimately led the patient's family to seek a secondary consult at our institution.

Upon presentation to our clinic, the patient was noted to have diffuse erythematous scaly patches covering approximately 80% of her body surface area (BSA), with areas of normal skin and hyperkeratosis of the palms and soles. Fissures were also noted on the upper and lower extremity bilaterally. Laboratory testing revealed normal serum magnesium level, normal blood count and metabolic panel, and elevated IgE. An eczematous component was considered at this time. Pretreatment screening for hepatitis B, hepatitis C, and tuberculosis were negative.

Given the severity of the lesions, the patient was started on cyclosporine 100 mg 3 times weekly. This was accompanied by biweekly phototherapy and a topical regimen of tacrolimus 0.1% ointment, triamcinolone 0.1% ointment for the body, and hydrocortisone butyrate ointment for the face. Initially, the patient responded well to these therapies with decreased erythema and scaling at 4 and 8 weeks. However, the patient experienced a flare during the fifth month of treatment. There were also several concerns with the regimen, including difficulty complying with frequent phototherapy and potential toxicity of cyclosporine.

All of these factors prompted us to consider other treatment options. The patient's parents did not wish to consider oral retinoids. Etanercept, an FDA-approved treatment for pediatric plaque psoriasis, was initially discussed, but the parents were not willing to begin a treatment that involved weekly home injections. After explaining the benefits and risks, both parents consented to the addition of a 45-mg subcutaneous injection of ustekinumab, obtained through compassionate use. The ustekinumab dosing regimen of 45 mg at weeks 0 and 4 and then every 12 weeks was used because this regimen was found to be safe and effective for plaque psoriasis in a large trial of adolescent patients.

When our patient returned for her second injection, her erythema had already diminished significantly from BSA 80% to BSA 20%. She also noted experiencing less pruritus and feeling more comfortable at school. At this time, cyclosporine was

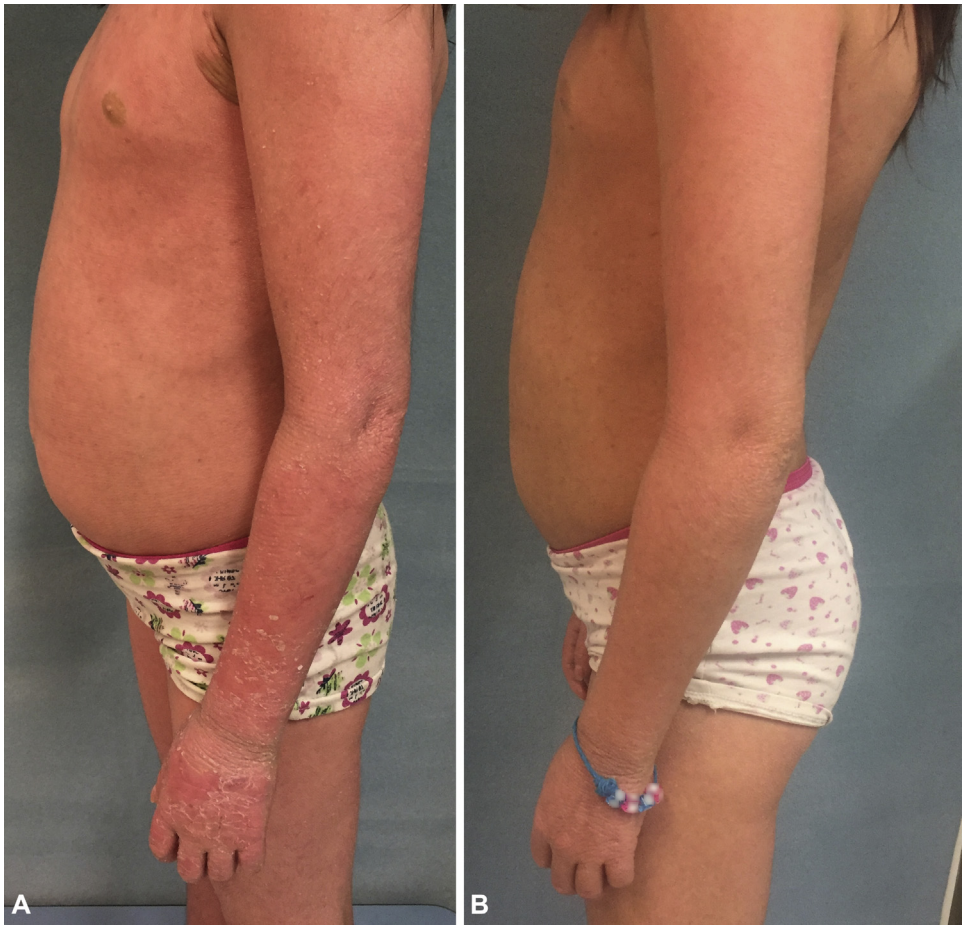

Fig 2. Left hand and forearm of 7-year-old Asian girl with pityriasis rubra pilaris at her initial appointment (**A**) and at week 8 of ustekinumab therapy (**B**). Patient's parents declined full-body photographs. By week 4 of treatment, patient was clear of generalized erythema. By week 8, hyperkeratotic plaques of the hands had resolved.

decreased to 100 mg twice weekly. The patient returned for follow-up 4 weeks after the second injection with continued clinical improvement; she was clear of generalized erythema and only continued to have some hyperkeratosis of the hands (Fig 2). Cyclosporine was decreased to once weekly at this time and subsequently discontinued at week 12. After 6 doses of ustekinumab, the patient completed 1 full year of therapy; she is currently clear of erythema and remains asymptomatic.

DISCUSSION

The etiology and pathogenesis of PRP remain poorly understood, and management relies heavily on previous case reports because of the rarity of the disease. Data involving pediatric patients is particularly scarce. Many of the therapies reported to successfully treat PRP were originally approved for the treatment of psoriasis. Ustekinumab is highly efficacious in treating psoriasis and has years of cumulative safety data supporting a favorable side effect profile in both adults and children.[15] Although not approved for PRP, ustekinumab has been previously reported as a successful alternative treatment for chronic, unremitting PRP in a single adult patient who was noted to have a remarkably rapid response.[17] This rapid resolution of generalized erythema was seen in our 7-year-old patient as well, resulting in a near-immediate improvement in quality of life.

As shown in Table I,[10-12] there are only 3 reported individual cases of pediatric PRP treated with a biologic drug. Only 1 of these was reported in a nonadolescent pediatric patient, and the drug used in that case is no longer FDA-approved in any age group. There are multiple reports of secukinumab, an interleukin 17A antagonist, outperforming ustekinumab in adults with PRP[18,19] but no data establishing its use in children or adolescents. Ustekinumab was recently approved for the

Table I. Previously reported cases of biologic therapy for PRP in pediatric and adolescent patients

Year reported	Age, y, sex	Duration of symptoms, y	Previous therapies	Treatment reported	Outcome
2007[10]	10, male	Not stated	Topical steroids, salicylic acid, topical pimecrolimus, topical Calcipotriol, NB-UVB phototherapy, PUVA, acitretin, etanercept	Efalizumab 1 mg/kg/week for 9 months	50% improvement after first dose with clinical remission maintained at 9 months
2008[11]	16, male	4	Topical steroids, topical retinoids, topical calcipotriene	Etanercept 50 mg twice weekly for 2 months	Resolution of erythroderma at 4 weeks with complete remission at 2 months (recurrence at 6 months after discontinuation with remission again after reinitiation of therapy)
2015[12]	17, male	13	Oral steroids, phototherapy, acitretin, cyclosporine, etanercept	Adalimumab 80 mg followed by 40 mg every other week	Clinical remission at 4 weeks

It should be noted that efalizumab was withdrawn from US market in 2009 because of reports of reactivation of John Cunningham virus infection.
NB-UVB, Narrow band ultraviolet B; *PUVA*, psoralen and ultraviolet A.

treatment of plaque psoriasis in patients 12-17 years of age. Although ustekinumab is not yet approved for any indication in patients under 12 years of age, there is evidence for its safe use in this population.[15,16]

The successful use of ustekinumab in our patient presents an alternative for children with recalcitrant PRP. Ustekinumab is not associated with toxicity similar to that of broad-spectrum immunosuppressants (eg, cyclosporine and methotrexate) and has a favorable safety profile even when compared with other biologics (ie, etanercept and adalimumab). Its maintenance dose schedule of 4 injections per year (compared with weekly or biweekly injections for other biologics) is also a more workable regimen for the pediatric population, who are often afraid of receiving injections.

We must acknowledge the belief that PRP is not a single uniform disease but rather a condition with similar states of diverse inflammatory processes. Thus, these robust responses to ustekinumab therapy might not be uniformly seen across all children with recalcitrant disease. We note that resolution of disease by spontaneous remission cannot be completely ruled out; however, the patient's constant symptoms from 7 months of age make this option highly unlikely. In conclusion, our observations suggest that ustekinumab should be considered as an alternate therapy in pediatric patients with chronic PRP. Further prospective studies will be helpful in establishing its efficacy in this population.

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