Ineffectiveness of tumor necrosis factor-α blockers and ustekinumab in a case of type IV pityriasis rubra pilaris

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ABSTRACT

Treatment of pityriasis rubra pilaris (PRP) may be difficult since no standardized therapeutic approach has been established. Recently, tumor necrosis factor-α (TNF-α) blockers have been demonstrated to be favorable in the management of recalcitrant PRP. The authors report a case of a patient who presented a type IV PRP or circumscribed, juvenile type. Such a condition follows an unpredictable course, presenting with diffuse, palmoplantar keratoderma and sharply-demarcated areas of follicular hyperkeratosis on the elbows and knees. Treatment with all available TNF-α inhibitors and ustekinumab did not prove to be helpful. The authors suggest that circumscribed variants of PRP could respond to therapy in ways different from classical PRP.

Key words: Pityriasis rubra pilaris, treatment, tumour necrosis factor, ustekinumab

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INTRODUCTION

Pityriasis rubra pilaris (PRP) includes a spectrum of rare chronic, idiopathic inflammatory disorders with papulosquamous eruptions of unknown cause.[1] Treatment is challenging. PRP shows consistent clinical heterogeneity; consequently, it is hard to predict the outcome of treatment. Response to therapy may vary with subtype.

CASE REPORT

A 29-year-old female presented for evaluation of a skin condition previously diagnosed as psoriasis vulgaris. There was no family history of psoriasis, palmoplantar keratoderma or other skin diseases. The lesions first appeared at age six years with no preceding trauma or infection and were characterized by palmoplantar keratoderma and demarcated, hyperkeratotic plaques on the elbows and knees. Her symptoms had a spontaneous remission between 13 and 26 years. The patient had been on many systemic treatments over the last two years without response, including cyclosporine (3 mg/kg/day for 3 months), methotrexate (15 mg/weekly for 4 months), adalimumab (two subcutaneous injection of 40 mg at day 0, a subcutaneous injection of 40 mg at day 7 and every 14 days thereafter for 16 weeks), etanercept (50 mg weekly subcutaneous injections for 12 weeks), infliximab (5 mg/kg given as an intravenous infusion at weeks 0, 2, 8).

Physical examination showed a diffuse, orange-pink palmoplantar keratoderma [Figure 1]. Well-defined keratotic follicular papules also involved the dorsal aspects of the hands and feet, elbows and knees [Figures 2 and 3]. The remainder of her medical history was not significant. A skin biopsy revealed alternating parakeratosis and orthokeratosis, pronounced irregular acanthosis, focal hypergranulosis and mild focal spongiosis. A perivascular lymphocytic infiltration was present in the papillary dermis [Figure 4]. Based on clinical and histologic findings, the patient was diagnosed having PRP, type IV (circumscribed juvenile). PUVA therapy was started 3 times for a week. After 16 weeks the treatment was stopped due to lack of efficacy. Application of keratolytic agents and even bland emollients did not give significant results. Given the childbearing age of the patient acitretin was contraindicated. After voluntary, informed consent, ustekinumab 45 mg subcutaneously at weeks 0 and 4, and quarterly thereafter (patient's weight = 55 kg) was then started, the same posology as in psoriasis. No

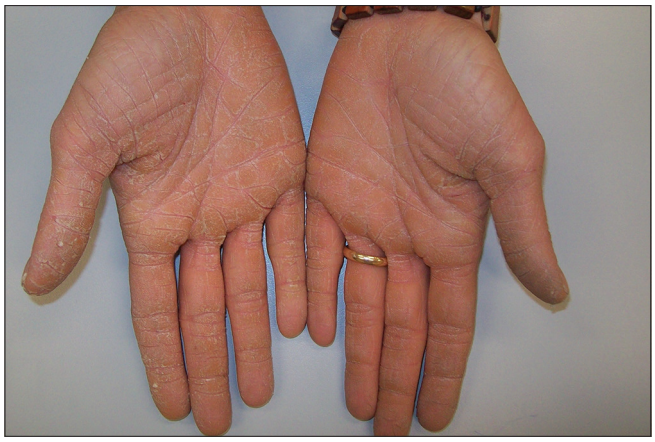

Figure 1: Keratoderma of the hands with a sharp demarcation of the borders

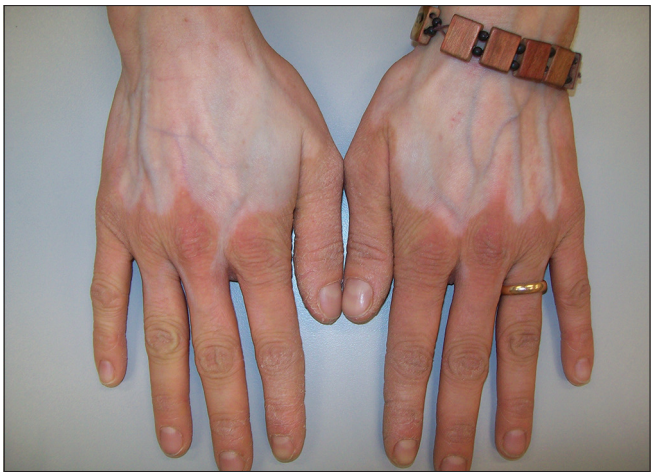

Figure 2: Diffuse transgrediens palmoplantar keratoderma on the dorsum of hands

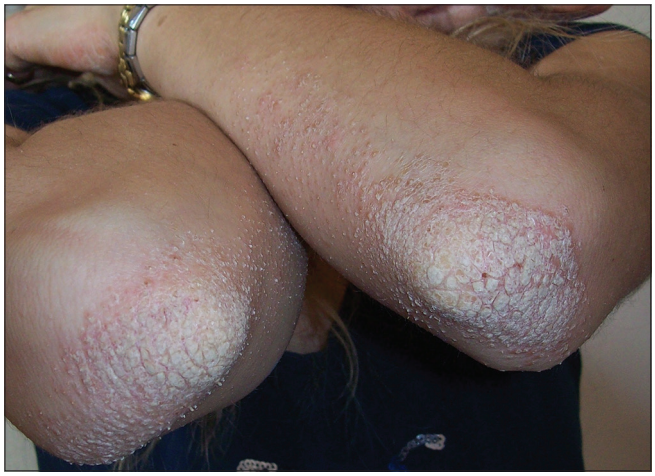

Figure 3: Follicular hyperkeratosis and erythema on the elbows

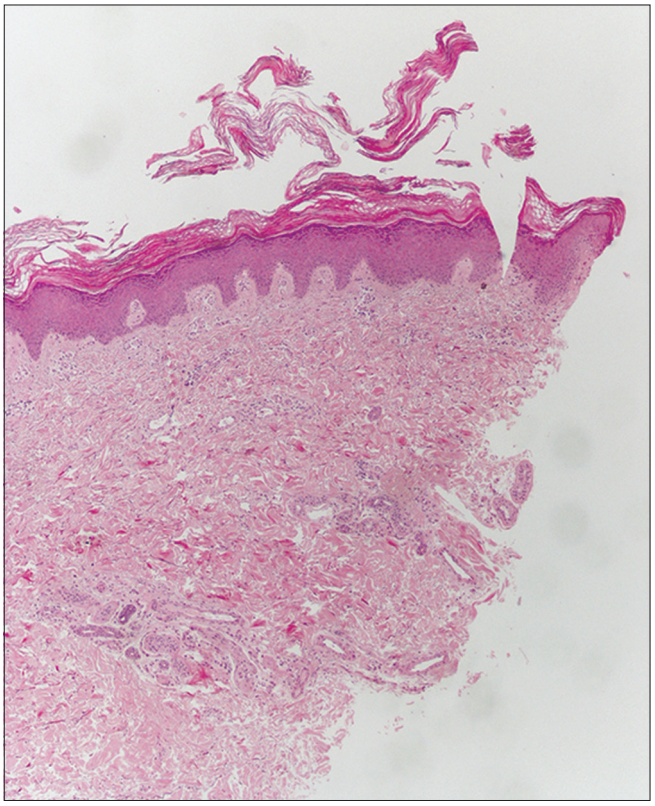

Figure 4: Alternating parakeratosis and orthokeratosis, irregular acanthosis, focal hypergranulosis and a perivascular lymphocytic infiltration in the papillary dermis (H and E ×10)

result was achieved after the third injection. The treatment was stopped, with no adverse events reported. The clinical picture is unchanged.

DISCUSSION

Pityriasis rubra pilaris occurs equally in male and female patients, with a bimodal age distribution, peaking during the first and then the sixth decade.[1] Griffiths proposed a classification for PRP in five subtypes, based upon age, duration, and type of cutaneous involvement.[2] Type I, or classic PRP, is the commonest type (50% of cases) and occurs in adults. It spreads caudally. The patient is usually erythrodermic with diffuse thickening of the palms and soles and possibly ectropion. 80% of patients experience clinical resolution within 3 years. On the basis of Griffith's classification our patient presented the circumscribed, juvenile, or type IV PRP. Clinical manifestations occurred in her prepubertal age and relapsed at age 27, after a long-lasting remission. Type IV PRP develops in prepubertal children presenting with sharply-demarcated areas of follicular hyperkeratosis and erythema on the elbows and knees. A waxy, orange-red, diffuse, palmoplantar keratoderma is also commonly observed.[3] It has an unpredictable course.[4]

Treatment of PRP can be difficult. A standard therapeutic approach does not exist as cases are few and treatment is protracted. In addition, spontaneous remissions are possible. Retinoids and methotrexate are the most frequently used medications with variable effectiveness.[1] Cyclosporine and azathioprine are considered to be alternative therapies.[1,5] An

increasing number of reports document the effectiveness of tumor necrosis factor-α (TNF-α) blockers in recalcitrant PRP.[6] Further, some case reports have documented favorable response of PRP to ustekinumab, a fully human monoclonal antibody which binds to interleukin-12 (IL-12) and IL-23 with high specificity and affinity.[7] An upregulation of TNF mRNA in lesional compared with nonlesional skin in two patients with type I PRP has been demonstrated.[8] A recent retrospective revision investigating treatment options showed a marked clinical in more than 50% of patients with type I PRP treated with TNF antagonists.[9] However, a systematic review of reports of PRP responding positively to TNF-α blockers does not recommend them due to possible reporting bias and spontaneous remissions.[10]

In the literature, the patients who achieved remission with TNF-α blockers or ustekinumab were all consistent with classical type 1 PRP. Our patient who presented a type IV PRP was unresponsive to the TNF-blockers adalimumab, etanercept and infliximab. Ustekinumab was not a helpful therapeutic approach as well. Our clinical experience suggests that in patients with type IV PRP, TNF and IL-12/IL-23 blockade may not be useful targets. Since we observed a primary lack of response to all available TNF-blockers, we suggest that yet unmapped signaling pathways may be involved in type IV PRP.

CONCLUSION

There seems to be inadequate response of circumscribed variants of PRP to standard therapies that are effective in classical PRP.

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