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CASE REPORT

Recalcitrant pityriasis rubra pilaris in a Middle Eastern patient and arguments for early anti-IL-23 targeting

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Abstract

Pityriasis rubra pilaris (PRP) is a rare, chronic cutaneous inflammatory disorder of keratinization affecting adults, children and patients with HIV. The pathogenesis of PRP is not fully understood with clinical presentations, and severity remains highly variable. Current treatment modalities for PRP result in recalcitrant disease with potentially unfavourable therapeutic side effects and low tolerability. Due to the rarity of this condition, limited data on treatment efficacies and established management guidelines are lacking. The psychological burden of PRP is detrimental to the quality of life of patients affected with PRP and remains a persistent gap of knowledge. Here, we provide a review of the literature, summarizing new developments in the treatment of PRP and a case report of a patient treated successfully with the anti-interleukin (IL)-23p19 antibody Risankizumab with sustained clinical improvement. Risankizumab appears to be an effective and safe treatment for PRP in Asian-Arabic patients. Further studies are required to assess the efficacy, safety and tolerability of newer targeted therapies for severe PRP.

KEYWORDS
biologic, cytokine, interleukin-23, pityriasis rubra pilaris, Risankizumab, targeted therapy, therapy

INTRODUCTION

Pityriasis rubra pilaris (PRP) is a rare, generally acquired, often recalcitrant chronic skin disease. The aetiology of PRP is poorly understood. There are five different subtypes differentiated by age of onset and clinical features proposed by Griffiths in 1980.[1] A familial form, denoted by a heterozygous gain-of-function mutation in *CARD14*, has also been documented.[2] In a transgenic mouse model incorporating deletion of the E138-residue of CARD14, increased levels of IL-17A and IL-22 were found; upon treatment with the murine IL-23p19 antibody, a significant decrease in 'psoriasiform' plaques was noted.[3]

Therapy of PRP is often recalcitrant and challenging.[4] Animal studies and immunohistochemistry indicate a role of the IL-17 and IL-23 pathway in PRP; consequently, following case reports used successfully anti-IL17- or anti-IL-23-therapy.[5]

We report to our knowledge for the first time a case of severe PRP type-I in the Middle Eastern/Arab population treated successfully with Risankizumab, after unsatisfactory improvement using topicals, UV-therapy, Ixekizumab and Ustekinumab. The treatment completely and sustainably cleared his condition whilst being safe and well-tolerated.

CASE REPORT

A 48-year-old Middle Eastern male presented with a 1-month history of slowly progressive erythemato-squamous plaques of a pruritic nature starting on the trunk and then progressing over the entire body. Skin lesions were mildly pruritic (Itch score 3/10), with no joint pain. Past medical history was remarkable for gastroesophageal reflux. Apart from regular esomeprazole, the patient did not use other medications. No known history of allergies. Physical examination revealed generalized erythematous papules and plaques with orange-coloured, sharply demarcated, scaly palmoplantar hyperkeratotic plaques (Figure 1). Differential diagnoses included PRP, psoriasis, hyperkeratotic cutaneous T-cell lymphoma, hyperkeratotic lupus erythematosus and less likely pityriasis lichenoides chronica.

Results of routine blood tests, as well as latent infections and autoimmune markers, were unremarkable. Skin biopsy showed hyperkeratosis and parakeratosis with intact granular layer, mildly acanthotic epidermis with mild perivascular and perifollicular lymphocytic inflammatory infiltration. The mid dermis and deep dermis were unremarkable (Figure 2). No CARD14 gene mutation testing was done, as the test is not available, and samples cannot be sent abroad.

Based on clinical and histopathologic findings, the diagnosis of type-I PRP (classic adult) was made. The patient was started on topical mometasone and subcutaneous Ustekinumab injections (90 mg), Weeks 0 and 4, then every 12 weeks.

The patient's skin lesions improved by 70%, after which improvement halted; thus, oral isotretinoin 20 mg daily was added but stopped due to intolerable dryness. The patient also underwent phototherapy, which was soon discontinued due to intolerable pruritus and xerosis. After shifting from Ustekinumab to Ixekizumab, following the psoriasis dosage protocol for adults, the patient improved by 80%–90%. However, the patient developed recurrent fungal infections including tinea pedis, tinea corporis and intertrigo, treated with topical antifungals, but without complete control.

For better disease control, subcutaneous Risankizumab (anti-IL-23p19 antibody, 150 mg, starting every 6 weeks) was administered. One week after the first injection of Risankizumab, the erythema, scaling and hyperkeratosis improved markedly by 90% (Figure 3); over the next 3 months, the skin was 100% cleared. This effect was sustainable, and at the last visit (7 months), skin and nails were 100% cleared. Risankizumab injections were extended to every 8, later to 12 weeks, (medical interventions summarized in Figure 4).

DISCUSSION

Despite the 170 years since the first documented description of PRP, there is no consensus for a markedly efficacious, safe and well-tolerated systemic treatment.

Pubmed was used as a search tool with the following search terms and criteria, 'pityriasis rubra pilaris', 'Biologic', filters applied were Case Reports, Clinical Trials and Randomized Controlled Trials and returned 150 results, 43 articles were relevant and addressed/used biologics or small molecules as part of their management. TNF-α inhibitors were the most common biologic/small molecule inhibitor used in 17/43 studies, followed by Ustekinumab, the only IL-12/IL-23p40 inhibitor, followed by IL-17 inhibitors Secukinumab and Ixekizumab in 8/43 studies. Three articles assessed the use of Jak inhibitors (2 Upadacitinib, 1 Tofacitinib), and three the use of Il-23p-19 inhibitors. The majority of the articles reported success or at least control of the disease and symptoms; none focused on the Middle Eastern population or pattern of inherited versus sporadic cases.

Based on the recalcitrant treatment success and various side effects using retinoids, phototherapy and Ixekizumab, and limited success with Ustekinumab, and after review of the current literature, we started treatment with anti-IL-23-p19 antibody Risankizumab, first 6-weekly, later 8-weekly and 12-weekly.

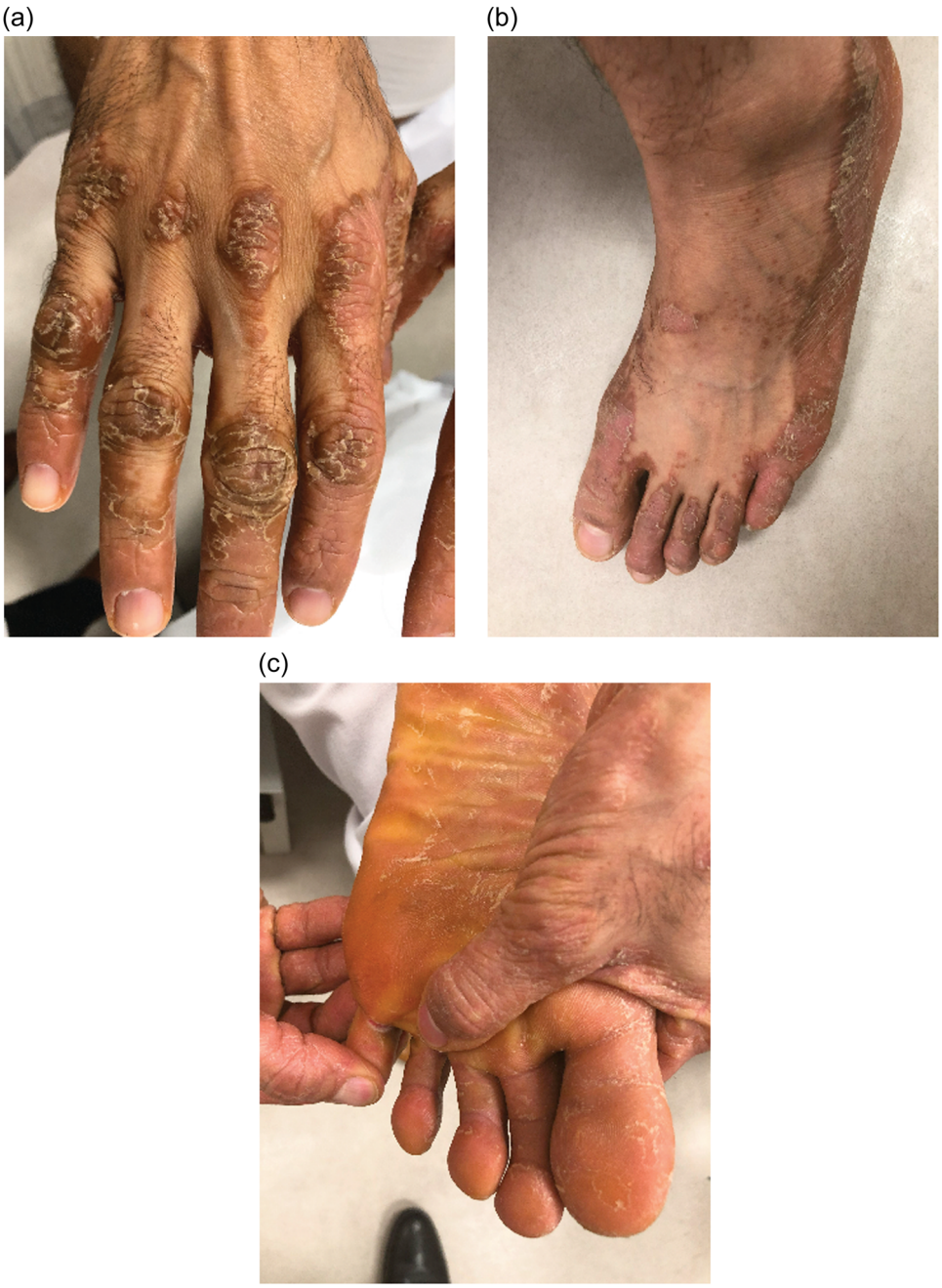

FIGURE 1 (a–c) 48-year-old male patient with severe pityriasis rubra pilaris showing erythematous papules and plaques with orange-coloured, sharply demarcated, scaly palmoplantar hyperkeratotic plaques.

As opposed to an anti-IL-17 blocker, which inhibits the release of IL-17 from Th17- and other IL17-producing cells,[6] Risankizumab binds to and inactivates the p19-subunit of IL-23, thereby inhibiting IL-23 action, and subsequently inhibiting downstream cytokines like IL-17 (partly), IL-22 and TNF.[7] Because only IL-17 produced by Th17 will be reduced and maintain the normal production of IL-17 by other cells, fungal protection remains, as in our case. Thus, in PRP patients with a history of active fungal infection, Risankizumab or other anti-IL-23p19 antibodies may be a good alternative to control this hard-to-treat disease.

To date, a few cases reported the efficacy of using anti-IL-23-p19 inhibitors in treating PRP.[5,8,9] The rapid onset of improvement and maintaining a disease-free state after 12 months noted in our case, presents Risankizumab as an excellent treatment option for this hard-to-treat and chronic disease. It further highlights the importance of IL-23 in the pathophysiology of PRP. Considering the medication cost, as well as socioeconomic costs of this chronic disease with the high impact on patients' quality of life and burden of disease, Risankizumab may be considered for the period of disease clearance, and maintenance, if possible.

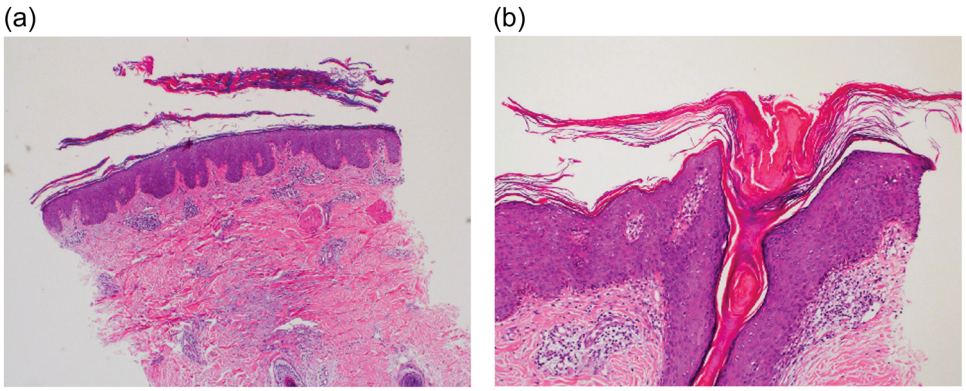

FIGURE 2 (a, b) Pityriasis rubra pilaris (PRP) histopathology. Skin biopsy reveals mild psoriasiform hyperplasia with overlying hyperparakeratosis, PRP typical alternating zones of parakeratosis and intact granular layer, follicular plugging with parafollicular parakeratosis and mild perivascular chronic inflammation in the superficial dermis (a, b, hematoxylin-eosin stain; magnifications: a, ×10, and b, ×20).

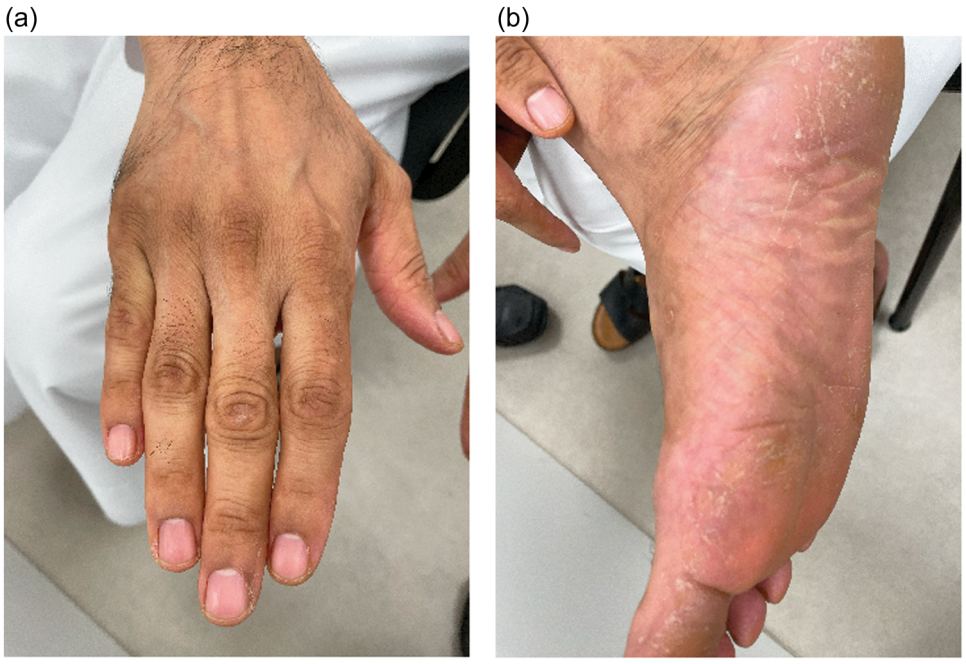

FIGURE 3 (a, b) 48-year-old male patient with severe pityriasis rubra pilaris and clinical appearance of hand and feet 1-week post first injection of Risankizumab.

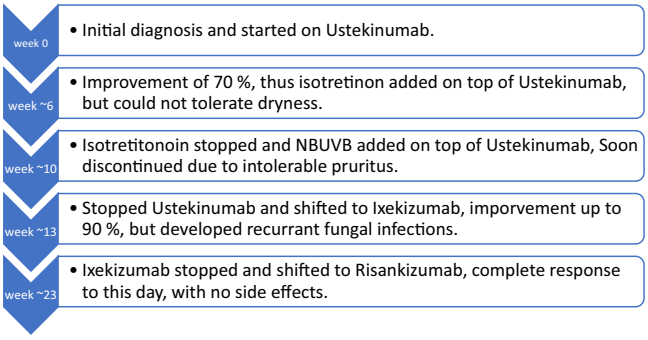

FIGURE 4 Timeline of medical intervention and clinical outcome.

To our knowledge, we report the first successful treatment of a severe case of adult PRP in the Middle Eastern/Arab population using the IL-23-p19 antibody Risankizumab with rapid, sustainable efficacy and excellent safety. IL-23-p19 antibody Risankizumab seems to be an appropriate choice of treatment in recalcitrant and difficult to treat cases with conventional treatment modalities. Placebo-controlled, randomized clinical trials or large cohort studies are needed to confirm the benefit of Risankizumab, with natural remission of classical PRP in mind, as well as other Il-23 p-19 inhibitors or targeted therapies as an excellent treatment option for adult PRP.

AUTHOR CONTRIBUTIONS

Mohammed N. Al-Abdulla and Martin Steinhoff: Conceptualization. **Mohammed N. Al-Abdulla, Wadha Al-Shafi, Joerg Buddenkotte and Martin Steinhoff**: Writing—original draft and preparation. **Mohammed N. Al-Abdulla, Wadha Al-Shafi, Hanof Ahmed, Anh Jochebeth, Febu Joy, Shahd Younis, Mahir Petkar, Joerg Buddenkotte and Martin Steinhoff**: Writing—review and editing. **Martin Steinhoff**: Overall supervision.

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CONFLICT OF INTEREST STATEMENT

Martin Steinhoff has served on advisory boards for Abbvie, Almirall, Janssen, Sanofi/Regeneron, Novartis, Pfizer, Eli Lilly, Galderma, Leo, BMS, MenloTx, and has been a consultant for Abbvie, Amgen, Galderma, Novartis, Janssen, Pfizer, Eli Lilly, Sanofi, MenloTx, Janssen, Union Tx, Galderma, Leo; and has received research funding from Galderma, Abbvie, Leo, Pfizer, Novartis, Sanofi. Joerg Buddenkotte and Febu Joy are investigators in a Novartis-sponsored clinical study. Joerg Buddenkotte holds stocks in BioNTech and Immatics NV. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their de-identified, anonymized, aggregated data and their case details (including photographs) for publication. This study has received the Medical Research Center and Institutional Review Board at Hamad Medical Corporation approval.

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