DOI: http://dx.doi.org/10.3315/jdcr.2013.1127

Journal of Dermatological Case Reports

Long-term ustekinumab treatment for refractory type I pityriasis rubra pilaris

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Key words:

acitretin, cyclosporine, interleukin-12, interleukin-23, methotrexate, pityriasis rubra pilaris, psoriasis, treatment, ustekinumab

Abstract

Background: Pityriasis rubra pilaris is a rare, chronic erythematous squamous disorder of unknown etiology. The disease is characterized initially by small follicular papules that coalesce into yellowish pink scaly plaques, palmoplantar keratoderma, diffuse furfuraceous scale of the scalp, and frequent progression to exfoliative erythroderma. Generally it is difficult to discern pityriasis rubra pilaris from other skin conditions but key-clinical features help in the diagnosis such as "islands" of spared skin within generalized erythroderma, follicular keratotic plugs, and an orange hue of the involved skin. Treatment options include topical vitamin D analogues, keratolytics, systemic acitretin, methotrexate, cyclosporine, azathioprine, fumaric acid esters, phototherapy, and anti-TNFα agents. Cases, of pityriasis rubra pilaris, successfully treated with a short-course ustekinumab therapy, have been reported.

Main observations: We report a 31-year-old man with pityriasis rubra pilaris, refractory to conventional treatments, successfully treated with ustekinumab monotherapy for over 64 weeks.
After failing conventional systemic agents (cyclosporine, aciretin and methotrexate), ustekinumab 45 mg has been prescribed, with the same dosing regimen as in psoriasis. The patient improved dramatically within 4 weeks of the first injection, with markedly less erythema and pruritus. Long-term control of the disease of the disease was achieved (64 weeks of treatment).

Conclusion: We report this case in order to show the striking and rapid efficacy of ustekinumab in reducing the signs and symptoms of the disease. Complete remission was achieved after the third injection, but also a long-term control of the disease. The therapy was well-tolerated in our patient and no adverse events occurred.
(*J Dermatol Case Rep*. 2013; 7(1): 5-9)

Introduction

Pityriasis rubra pilaris (PRP) is an uncommon papulosquamous keratotic dermatosis of unknown origin and considerable clinical heterogeneity. The incidence is estimated between 1: 5.000 and 1: 50.000 and equally affecting men and women.[1] It has a bimodal distribution of age onset concentrating in the first and fifth to sixth decades.

The pathogenesis has not been yet clarified but it is thought to be the result of an abnormal immune response to some antigenic stimuli including streptococcal infection.[5]

Griffiths[2,3] divided PRP into 5 categories based on clinical features, age of onset, and prognosis: classic adult type, atypical adult type, classic juvenile type, circumscribed juvenile type, and atypical juvenile type. To these, an HIV-associated variant has been added to this classification system.[4] Table 1.

Classically PRP is characterized by small follicular papules, scaly yellow-pink (salmon-colored) patches, and palmoplantar hyperkeratosis. Lesions are usually symmetrical and diffuse, with areas of normal skin (islands of sparing). Progression to erythroderma is common as well as nail involvement

characterized by distal yellow-brown discoloration, subungual hyperkeratosis, longitudinal ridging, nail plate thickening and splinter hemorrhages.

Pruritus may occur in the early stages of the disease. Patients may complain of pain and irritation in the mouth; mucous membrane changes include a diffuse whitish appearance of the oral mucosa, lacy whitish plaques, grayish-white papules and plaques, erythema, or possible erosions. Patients with extensive disease may develop ectropion, and they have also reported blurred vision and dryness. Topical therapeutic options include corticosteroids, vitamin D analogues, and keratolytics, that are prescribed for mild and localized forms, while for severe forms of PRP, systemic retinoids (eg, acitretin) are used as first-line therapy, although the results are variable.[6]

Other systemic agents such as methotrexate, cyclosporine, azathioprine, fumaric acid esters, phototherapy,[7-9] and, most recently, biological agents, have been reported as effective in the treatment of PRP.

In literature, Tumor necrosis factor (TNF) blockers including etanercept, adalimumab, and infliximab showed to be effective and they are currently available as a therapeutic modality for PRP.[10,11]

Whereas, in the literature there are only two reported cases about the usage of ustekinumab in type I PRP.[12,13]

Case Report

We report a 31-year-old man with severe PRP, refractory to conventional topical and systemic therapies, since the age of 18. Since 2010, the patient showed a progressive erythroderma and cyclosporine has been prescribed at the dosage of 5 mg/kg/day. After eight weeks the lesions progressed and the patient received acitretin (50 mg/day) for 3 months, without any improvement.

In January 2011 patient was referred to our Department with a progressive hitching rash with erythema and scales involving more than 80% of the body surface area (BSA) with "islands" of spared skin. Palms and soles were hyperkeratotic. Nails showed thickening of the nail plate, subungual hyperkeratosis and longitudinal ridging (Fig. 1A,B,C). Also the patient reported symptoms of pruritus.

The diagnosis of type I PRP was confirmed by histological examination displaying irregular epidermal hyperplasia, with alternating foci of parakeratosis and orthokeratosis in both vertical and horizontal levels (the so-called "checkerboard pattern") without neutrophils' microabscesses, parakeratotic follicular lipping and a sparse infiltrate of lymphocytes around dilated venules of the superficial plexus.

Clinical investigations and laboratory tests were performed in order to rule out the presence of systemic infections,

Table 1. Types of pityriasis rubra pilaris.

Clinical Type	Lesions' distribution	Physical findings	Natural course	Percentage
Classical Adult	Generalized	Onset is acute, and the features are classic, including erythroderma with islands of sparing, palmoplantar keratoderma, and follicular hyperkeratosis	Remission in 3-4 y	55
Atypical Adult	Generalized	Characterized by ichthyosiform lesions, areas of eczematous change, alopecia	Chronic intractable	5
Classic Juvenile	Generalized	Very similar to type I; its onset is within the first 2 years of life	Remission in 1-2 y	10
Circumscribed Juvenile	Localized	It occurs in prepuberal children and is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema of the knees and the elbows	Unpredictable	25
Atypical Juvenile	Generalized	It has an early onset and runs a chronic course. It is characterized by prominent follicular hyperkeratosis, sclerodermalike changes on the palms and the soles, and infrequent erythema	Chronic intractable	5
HIV-Associated Type	Face and upper trunk	Similar to type I, in HIV-positive patients	Refractory	Increasing

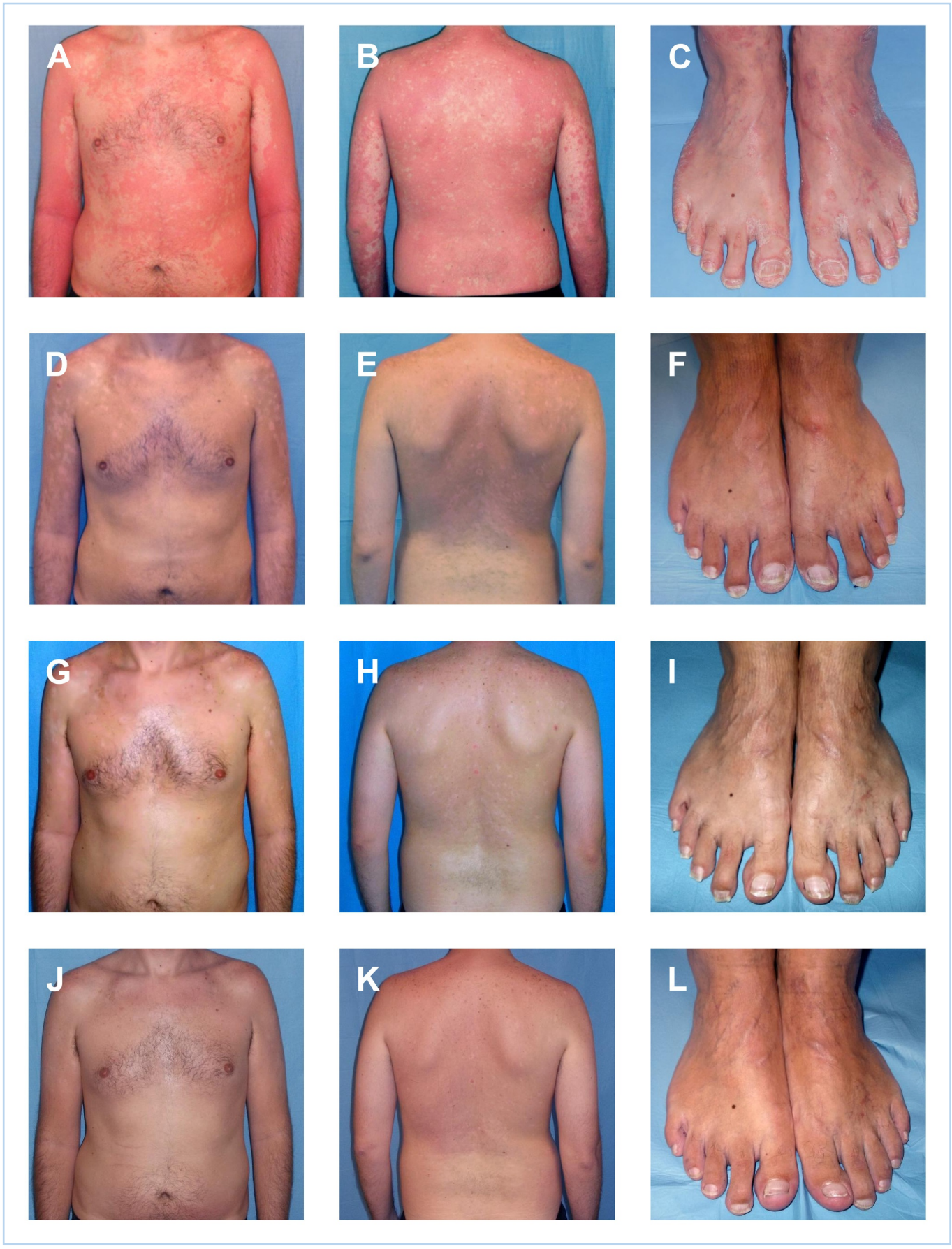

Figure 1

A,B,C: Rash with erythema and scales before treatment; D,E,F: Clinical improvement after first injection; G, H, I: Complete remission after third injection; J, K, L: week 64 of ustekinumab treatment.

autoimmune diseases, comorbidity, and malignancies.

Based on the clinical and laboratory data, we prescribed methotrexate 7,5 mg/week for 2 weeks, followed by methotrexate 10 mg/week and folic acid for another 4 weeks. Because of the ineffectiveness of methotrexate, we decided to perform the mandatory panel of screening tests for biological drugs, including chest X ray, ECG, and Quantiferon TB-Gold.

After obtaining the patient's written consent and the approval of our local ethical committee, ustekinumab 45 mg (patient's weight = 80 kg) was administered subcutaneously at week 0 and 4, and then quarterly, according to psoriasis dose regimen.

Within the first 4 weeks of therapy, the patient markedly showed an improvement of erythema, pruritus, and nail lesions. Overall, he showed a good improvement after the first injection of ustekinumab (Fig. 1D,E,F).

Complete remission was achieved after the third injection (Fig. 1G,H,I) and it was maintained for 64 weeks (Fig. 1J,K,L), with no adverse events reported. Currently, the patient continues ustekinumab treatment at the dosage of 45 mg every 12 weeks, with a significant improvement in quality of life.

Discussion

The unclear pathogenesis of PRP is chiefly responsible for the multiple and different treatments that have been used for its management (including steroids, azathioprine, fumaric esters, methotrexate, retinoids-currently deemed as the first line treatment, cyclosporine, etc.).

Its low incidence hinders us from carrying out controlled clinical trials, and so all the data available regarding therapy is based on case reports and small case series.[11] Therapeutic approaches to the erythro-desquamative skin disorders have significantly changed with the introduction of TNF-alpha blockers and other biological therapies. As mentioned, the use of infliximab, etanercept, and adalimumab, for the treatment of PRP, in a monotherapy regimen, or combined with methotrexate or acitretin is well documented, with different degrees of success.

Ustekinumab is a fully human IgG1 K-kappa monoclonal antibody, which suppresses both Th1 and Th17 pathways, inhibiting the p40 subunit shared by interleukin (IL)-12 and IL-23, that are crucial for T helper differentiation.

Ustekinumab is approved for the treatment of moderate-to-severe psoriasis whereas, for PRP, its use is off-label.[14]

The information about the effect of ustekinumab on PRP does not meet the requirements of evidence-based medicine.

In the case reported here, ustekinumab has been considered as the best therapeutic choice since it shows rapid efficacy, easy way of administration, with no hospitalization and a prolonged time-gap between subsequent administrations. Indeed, because of its 4-time subcutaneous administration per year, ustekinumab has low impact on patient's working and social life quality of life with a very high compliance to treatment. Moreover, Ustekinumab demonstrated a striking and rapid efficacy in reducing the signs and symptoms of disease within 4 weeks of treatment and in inducing complete remission after 28 weeks, and a long-term control of the disease (64 weeks of treatment). The therapy was well-tolerated in our patient and no adverse events occurred.

In our experience, Ustekinumab is a tailor-made therapy, especially comfortable for young people having (or running) an active social and professional life (i.e. our patient is freelance journalist).

Conclusion

PRP is an uncommon chronic or chronic relapsing inflammatory skin disease of juvenile or adult onset. The etiology is unknown, and treatment is challenging as standard therapies are lacking.

In our patient it is highly likely that ustekinumab was responsible for the clinical response. Failure of the cyclosporine, acitretin and methotrexate therapies to control the disease, and the rapid improvement related to the ustekinumab administration, suggest an active role of the drug. The patient experienced a significant improvement after the first injection at week 4. In view of the response in the case described here and the previous successful reports[12,13] ustekinumab could be included as an alternative agent for treating adult-onset PRP. However, further studies are necessary to more precisely evaluate its safety and efficacy.

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Note: Alessandro Di Stefani and Marco Galluzzo have equally contributed to this paper.