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Refractory pityriasis rubra pilaris treated with abrocitinib

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Availability of data and materials: all data underlying the findings are fully available.

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Abstract

Pityriasis rubra pilaris is a rare idiopathic papulosquamous disorder that significantly impacts quality of life and is often refractory to conventional therapies. This study presents a case of successful treatment with an abrocitinib JAK1 inhibitor after several conventional and biologic therapies failed.

Introduction

Pityriasis rubra pilaris (PRP) is a rare idiopathic papulosquamous disorder that can affect people of all ages, with a typical peak in individuals aged 50–60 years, but data on the incidence and prevalence of PRP are scarce.[1] The disease is classified into 5 subtypes, of which type I, the classic adult form, is the most common and accounts for more than half of all cases of the disease.[2] PRP type I typically has cephalocaudal spread and may progress to erythroderma with typical islands of sparing. Other characteristic signs of this disease are waxy palmoplantar keratoderma and follicular papules. The majority of patients develop nail changes such as splinter hemorrhages, subungual hyperkeratosis, nail plate thickening, and others.[2]

Pityriasis rubra pilaris has a significant impact on quality of life as it is often refractory to conventional therapies.[3] To date, numerous treatment options have also been trialed for PRP, with variable success rates. Topical corticosteroids, retinoids, and conventional systemic therapies such as azathioprine, cyclosporine, and methotrexate are typically used in the treatment of this disease. In recent years, the use of modern targeted and biologic therapies has been reported in refractory PRP cases due to similarity with other inflammatory skin diseases such as psoriasis.[4]

This case report presents a case of successful treatment with abrocitinib JAK1 inhibitor after failure of several conventional and biologic therapies.

Case Report

A 57-year-old woman without a dermatologic history suddenly developed generalized erythroderma with diffuse desquamation. Her only medication at that time was omeprazole for gastroesophageal reflux, which she had been taking for several years. She was referred to our department approximately two years after the onset of the rash. By that time, she had already undergone multiple skin biopsies with conflicting results, indicating either psoriasis or pityriasis rubra pilaris. During this period, she received intensive local treatments with topical corticosteroids and keratolytics, as well as several courses of systemic corticosteroids. Additionally, she was treated with acitretin for 4 months (25 mg daily), methotrexate for 6

months (10 mg once weekly), and azathioprine for 4 months (100 mg daily). However, all this treatment and the change in the patient's chronic medication did not lead to a significant improvement in the patient's condition.

During the first examination at our department, an erythematous scaly eruption was present, covering over 90% of the body surface (erythroderma) with some islands of sparing typical for PRP. At the same time, diffuse scaling in the scalp and yellowish hyperkeratoses were present on the soles and palms. Additional skin biopsies were performed that were compatible with a diagnosis of PRP. The patient had undergone detailed cancer screening and complex immunological and rheumatological examinations. All examinations were without significant pathology findings. Treatment with cyclosporin was started (150 mg twice daily). However, after 12 weeks, the treatment was stopped because it had no effect. The patient was given her first biological therapy with risankizumab, which had to be stopped after 16 weeks because the rash rather progressed, and the patient required further hospitalization. Similarly, adalimumab had to be stopped after 12 weeks for the same reasons.

The patient's third biological treatment was infliximab. Four days after the second infusion, the patient developed generalized lymphadenopathy with fever and a significant elevation of CRP, but without changes in the blood count. The patient was hospitalized at the Infectious Disease Department, where she underwent a comprehensive examination for infectious diseases, including anthropozoonoses. Extirpation of one of the lymph nodes was also performed, where chronic lymphadenitis with histiocytic paracortical infiltrates corresponding to dermatopathic lymphadenopathy was described. An infectious cause was ruled out. The condition was evaluated as an immunological response after infliximab administration.

The patient was afraid of further systemic therapy; therefore, chamber UVB phototherapy was started, but again, due to a significant worsening of the skin with further necessity of hospitalization, it was terminated after 11 sessions. Secukinumab was administered to the patient as the fourth biological therapy, which was also discontinued after 16 weeks, as the therapy did not show an improvement. Subsequently, the patient put herself under the care of a healer of traditional Chinese medicine, as she had already lost hope of improving her skin condition with conventional medical treatment.

After approximately half a year, the patient came to our department again, as alternative medicine did not help her; erythroderma and significant hyperkeratosis in the scalp, soles, and palms still persisted (Figure 1). Moreover, without medication, the patient suffered from severe itching of the whole body. The patient was emotionally very negatively tuned due to the very poor long-term quality of life. Therefore, the decision was made to start treatment with

abrocitinib (200 mg daily). After 16 weeks of abrocitinib therapy, significant improvement was achieved for the first time, with only isolated regressing pink macules on the trunk and limbs (Body Surface Area 11%) and no desquamation. The hyperkeratoses on the palms and soles have also regressed; only the flaking in the brush persists (Figure 2). The itching practically disappeared very quickly during the first days of abrocitinib treatment. This significant improvement persists in the patient, and no adverse effects of the therapy or laboratory changes have yet occurred.

Discussion

Correct diagnosis of PRP may be challenging, as the symptoms of the disease may initially look like psoriasis or eczematous reaction. Moreover, treatment of PRP remains challenging despite diverse treatment options that have been tested for PRP, as randomized controlled trials are lacking.[2,4] Current knowledge of the pathophysiology suggests PRP is an interleukin (IL)-17, IL-23-mediated disease with an innate immune dysregulation.[5] Consequently, the pro-inflammatory cytokines essential for psoriasis, such as tumor necrosis factor, IL-17, and more recently IL-23, have been tested in PRP therapy. However, even these very effective drugs for psoriasis are not always effective in the treatment of PRP.[6] This is likely due to the diverse nature of PRP's underlying causes. Recent studies have indicated that various pro-inflammatory cytokines, such as IL-6, IL-12, and IL-22, are elevated in the affected skin of individuals with PRP.[7]

Janus kinase (JAK) inhibitors are a new therapeutic group in dermatology currently used for the treatment of alopecia areata, atopic dermatitis, and psoriasis. Unlike biologics, JAK inhibitors target downstream intracellular signaling pathways, which are utilized by many proinflammatory molecules to mediate downstream effects and activate gene transcription. Several cytokines rely on JAK-STAT signaling to mediate downstream effects, including IL-2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-23, and others. This therapeutic strategy of targeting a wider range of cytokines would, therefore, make sense in a heterogeneous disease such as PRP. Three cases of successful therapy of treatment-resistant PRP with upadacitinib, a JAK-1 inhibitor, and one case with tofacitinib, a pan-JAK inhibitor, were recently reported.[8-11]Lately, a series of five cases highlighting the success of PRP therapy combined with abrocitinib was published.[12] This suggests that, due to their broader effect on the immune system, JAK inhibitors may be a viable treatment option for cases of PRP that are resistant to conventional therapies. Recently, safety concerns have arisen regarding the safety of JAK inhibitors based on post-marketing studies of tofacitinib in rheumatoid arthritis, which found increased risks of cancers, VTE, and major

adverse cardiovascular events.[13] However, based on current knowledge from studies in dermatological patients, JAK inhibitors had low rates of venous thromboembolism, major adverse cardiovascular events, and malignancy comparable to placebo.[14]

Conclusions

This case demonstrates a successful therapy of treatment-resistant PRP with the JAK1 inhibitor abrocitinib after several conventional and biological therapies failed.

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Figure 1. Baseline before abrocitinib treatment.

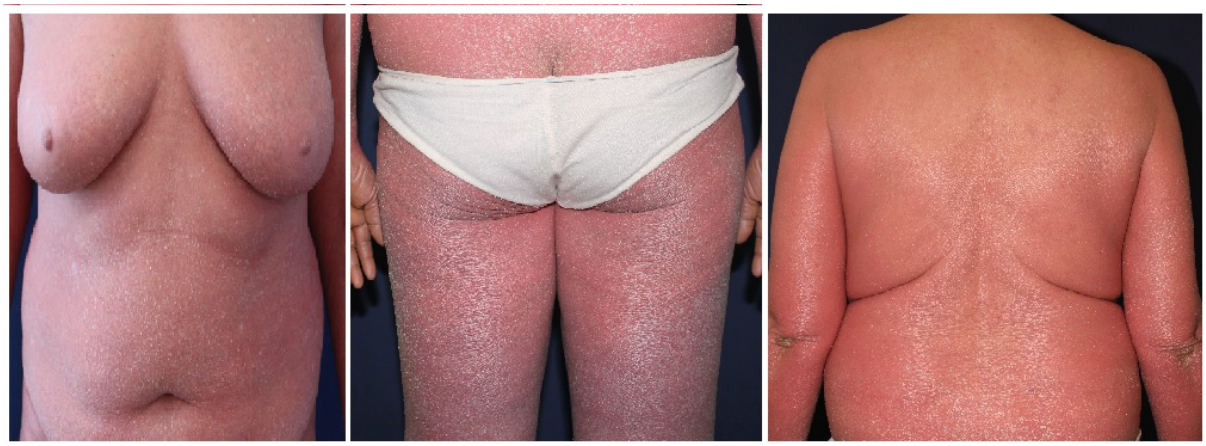

Figure 2. 16 weeks after treatment with abrocitinib.