

Paradoxical pityriasis rubra pilaris during adalimumab therapy in juvenile idiopathic arthritis

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ABSTRACT

Pityriasis rubra pilaris (PRP) is a rare papulosquamous dermatosis in childhood, and its occurrence during anti-tumor necrosis factor therapy is exceptionally uncommon. We report a 9-year-old girl with juvenile idiopathic arthritis who developed biopsy-confirmed PRP after the third dose of adalimumab. Dermatological examination revealed widespread pruritic salmon-colored to erythematous finely scaly plaques, follicular accentuation, follicular hyperkeratotic papules, and focal islands of spared skin involving the trunk and upper extremities. Skin biopsy showed focal parakeratosis, irregular acanthosis, and prominent neutrophilic exocytosis at the follicular ostia, supporting the diagnosis of PRP. Alternative diagnoses, including paradoxical psoriasis and other papulosquamous or drug-related eruptions were considered; however, clinicopathological correlation favored PRP. The eruption resolved within three weeks after adalimumab discontinuation and recurred after re-exposure, supporting a probable adalimumab-associated paradoxical mechanism. The patient was subsequently switched to tocilizumab and achieved sustained clinical and laboratory remission without recurrence of cutaneous manifestations. This case emphasizes that PRP should be considered among rare papulosquamous eruptions occurring during anti-TNF therapy in children.

Keywords: Adalimumab, adverse drug reaction, juvenile idiopathic arthritis, pediatrics, pityriasis rubra pilaris

Introduction

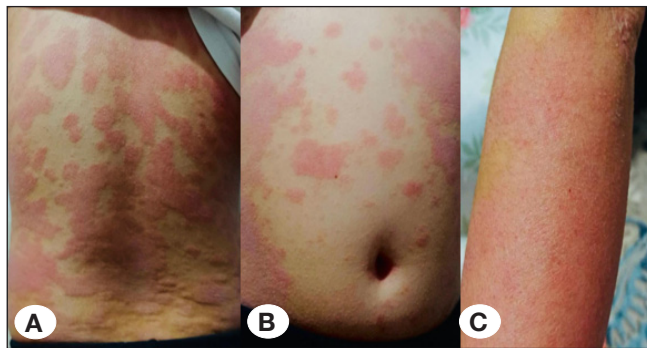
Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. In patients with persistent active disease or inadequate response to conventional disease-modifying antirheumatic drugs (DMARDs), biologic agents, particularly tumor necrosis factor-alpha (TNF-alpha) inhibitors, are widely used and effective treatment options (1). Although generally well tolerated, anti-TNF therapies may cause paradoxical inflammatory reactions, most commonly psoriasiform eruptions (2). Reliable overall pediatric incidence estimates are unavailable; however, paradoxical psoriasis has been reported in approximately 4.6% of treated children (3).

Pityriasis rubra pilaris (PRP) is a rare pediatric inflammatory dermatosis characterized by papulosquamous lesions, follicular hyperkeratosis, and variable clinical course. Its association with anti-TNF therapy remains poorly defined. We present a pediatric patient with JIA who developed early-onset biopsy-confirmed PRP during adalimumab therapy, with resolution after drug withdrawal and recurrence after re-exposure.

Case Report

A 9-year-old girl presented with a two-month history of right hip pain and morning stiffness associated with limping, accompanied by pain and swelling of the left knee during the preceding week. Her medical history revealed a right ankle sprain approximately five months prior to presentation, followed by persistent swelling lasting nearly four months. Magnetic resonance imaging (MRI) performed after the trauma demonstrated effusion of the tibiotalar joint with accompanying bone marrow edema. These findings were initially interpreted as post-traumatic, and no treatment was initiated.

At admission, laboratory investigations revealed no cytopenia; antinuclear antibodies, anti-double-stranded DNA antibodies, and the extractable nuclear antigen panel were negative; rheumatoid factor, HLA-B27, and viral serologies were also negative. The erythrocyte sedimentation rate was elevated at 62 mm/hour, and the C-reactive protein level was increased to 9.8 mg/L. Physical examination showed normal range of motion of the hip joint, while the left knee exhibited warmth, pain, and swelling consistent with arthritis. Examination of other joints was unremarkable, and no signs of enthesitis were detected. MRI of the left knee demonstrated



diffuse synovial contrast enhancement, consistent with arthritis and synovitis. The patient's personal and family medical histories were unremarkable.

Although the ankle findings were initially attributed to trauma, subsequent involvement of an additional joint supported the diagnosis of inflammatory arthritis. Based on the clinical, laboratory, and imaging findings, including involvement of the right ankle and left knee during the first six months of disease, the patient was classified as having oligoarticular JIA. Systemic corticosteroid therapy was initiated at a dose of 1 mg/kg/day. During gradual tapering of corticosteroids, worsening swelling of the left knee prompted initiation of subcutaneous methotrexate at a weekly dose of 15 mg/m². Because the left knee remained clinically active and acute-phase reactants remained elevated during the early phase of methotrexate therapy, an intra-articular corticosteroid injection was administered for prompt local disease control while methotrexate was continued.

Following intra-articular therapy, the arthritis initially improved; however, after approximately two months of methotrexate treatment, recurrent arthritis of the left knee and persistently elevated erythrocyte sedimentation rates were observed. Due to inadequate response to DMARD therapy and persistent active arthritis, biologic treatment with adalimumab was initiated.

After the third dose of adalimumab, the patient developed a widespread pruritic papulosquamous eruption characterized by salmon-colored to erythematous finely scaly plaques, follicular accentuation, and follicular hyperkeratotic papules (Figure 1). The lesions predominantly involved the trunk and upper extremities and showed focal islands of spared skin. There was no mucosal involvement, nail change, or systemic manifestation. Histopathological examination demonstrated focal parakeratosis, irregular epidermal acanthosis, accumulation of serum and polymorphonuclear leukocyte debris between keratin lamellae, and prominent neutrophilic exocytosis at the follicular ostia. Together with the characteristic clinical morphology, these findings supported the diagnosis of PRP.

The differential diagnosis included paradoxical psoriasiform eruption, plaque psoriasis, pityriasis rosea, dermatophytosis, eczematous dermatitis, viral exanthem, and maculopapular drug eruption. However, the presence of follicular accentuation, salmon-colored scaly plaques, focal islands of spared skin, and clinicopathological correlation favored PRP. Discontinuation of adalimumab resulted in complete resolution of the cutaneous lesions within three weeks. Reintroduction of adalimumab led to recurrence of morphologically identical skin lesions, supporting

a causal association between adalimumab exposure and PRP development. The patient experienced complete recovery from the rash following permanent cessation of adalimumab.

During follow-up, a subsequent rise in acute-phase reactants and development of arthritis in both knees prompted initiation of tocilizumab therapy. Under tocilizumab treatment, the patient achieved sustained clinical and laboratory remission without recurrence of cutaneous manifestations.

Discussion

PRP is a rare chronic inflammatory dermatosis with an incompletely understood etiology and a broad clinical spectrum. Various triggering factors have been described, including viral infections, vaccinations, and systemic medications (4). Among reported drug-associated cases, tyrosine kinase inhibitors were the most common triggers, followed by toll-like receptor 7 agonists and phosphoinositide 3-kinase inhibitors (5). In contrast, PRP associated with anti-TNF therapy appears to be exceedingly rare. In a systematic review by Mufti et al. (5) evaluating drug-associated PRP, only a single adult case related to infliximab was identified, with no pediatric cases reported.

Paradoxical psoriasis is a recognized class effect of TNF inhibitors in children, with adalimumab among the most frequently implicated agents (2). This diagnosis was specifically considered because PRP and psoriasis may overlap clinically and histopathologically. However, the salmon-colored finely scaly plaques, follicular hyperkeratotic papules and accentuation, focal islands of sparing, and biopsy findings interpreted in the clinical context favored PRP (4).

The present case differs from previously reported drug-associated PRP cases in several clinically relevant aspects. First, the patient was a child receiving adalimumab for JIA. Second, the diagnosis was supported by dermatological assessment and histopathological confirmation. Third, the dechallenge-rechallenge pattern strengthened the suspected relationship between adalimumab exposure and PRP development. These features support the novelty and clinical relevance of the case.

Interestingly, adalimumab has been reported as an effective therapeutic option for refractory PRP in adult patients, underscoring the paradoxical nature of the reaction observed in our case (4,6–8). Although latency data specific to anti-TNF-associated PRP are unavailable, pediatric TNF inhibitor-induced psoriasiform eruptions have shown median latencies of 14.5 months (IQR, 9–24 months) in a multicenter series and 16.9 months (IQR, 8.8–38.5 months) in a single-center cohort, making the onset after the third adalimumab dose in our patient notably early (2,9). However, the temporal proximity to adalimumab exposure, resolution after discontinuation, and recurrence after re-exposure support a probable drug-associated paradoxical mechanism in this patient. Therefore, this case may represent an early-onset paradoxical PRP occurring during adalimumab therapy.

Although PRP is generally considered a chronic inflammatory dermatosis, the relatively rapid resolution observed in this patient may reflect removal of a drug-related trigger rather than the natural course of idiopathic PRP. Therefore, prompt

improvement after adalimumab discontinuation does not exclude the diagnosis of PRP but supports the interpretation of drug-associated paradoxical PRP in this case.

The underlying mechanism remains unclear. Paradoxical inflammatory reactions during anti-TNF therapy have been hypothesized to involve cytokine imbalance, particularly relative activation of type I interferon pathways following TNF- α blockade (10). Interferon signature analysis was not performed, as it was not part of the routine clinical evaluation. In clinical practice, careful dermatological evaluation and clinicopathological correlation are essential when atypical papulosquamous eruptions occur during biologic therapy. Switching to an alternative biologic agent with a different mechanism of action may be considered when the suspected drug is clinically implicated and the underlying rheumatologic disease remains active.

Conclusion

To the best of our knowledge, this is the first reported pediatric case of biopsy-confirmed PRP developing during adalimumab therapy. Although causality cannot be definitively established from a single case, the temporal relationship, histopathological confirmation, improvement after drug discontinuation, and recurrence after re-exposure support a probable adalimumab-associated paradoxical PRP. Clinicians should consider PRP in the differential diagnosis of papulosquamous eruptions occurring during anti-TNF therapy in children.

Contribution of the authors

Study conception and design: HIT, AO, BKD; clinical data collection: HIT, AO; dermatological evaluation and interpretation: AO; analysis and interpretation of clinical findings: HIT, AO, BKD; draft manuscript preparation: HIT; critical revision of the manuscript for important intellectual content: AO, BKD. All authors reviewed the manuscript and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

Patient confidentiality: Written informed consent was obtained from the patient's parent/legal guardian for participation in the study and publication of the patient's clinical information.

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