Electronic Journal of General Medicine
2024, 21(6), em610
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Case Report **OPEN ACCESS**

The immunological implications of paradoxical reactions in rheumatoid arthritis and psoriasis treatment: A case report

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Citation: Budair FM, AlHemli HA, Zeidan AA, Alshehri A, Alratroot J, Hasan M. The immunological implications of paradoxical reactions in rheumatoid arthritis and psoriasis treatment: A case report. Electron J Gen Med. 2024;21(6):em610. https://doi.org/10.29333/ejgm/15521

ARTICLE INFO

Received: 04 Jul. 2024

Accepted: 15 Oct. 2024

ABSTRACT

Psoriasis and rheumatoid arthritis (RA) are common chronic diseases with distinctive histological and molecular features. However, there are similarities in their immunological pathogenesis, leading to the use of some similar systemic biological treatment. In 5% of patients using biological therapy such as the anti-tumor necrosis factor alpha (anti-TNF-α), a paradoxical reaction (i.e., the exacerbation or development of one disease while treating the other) may develop. We report a case of a 27-year-old female diagnosed with seropositive RA who developed paradoxical psoriasis (PP) after the use of Adalimumab, an anti-TNF-α, and paradoxical eczema due to the use of Ixekizumab, an anti-interleukin-17A, for the treatment of PP. This case demonstrates the occurrence of two different types of paradoxical skin reactions in a single patient. This case also highlights the importance of the selection and cessation of biological treatment in similar cases, as well as the factors that might predict the development of paradoxical reactions to promote the safe usage of biological therapy.

Keywords: psoriasis, rheumatoid arthritis, eczema, paradoxical, treatment, immunology

INTRODUCTION

Psoriasis is a common chronic inflammatory dermatological disorder recently recognized as a systemic rather than local disease [1]. Rheumatoid arthritis (RA), on the other hand, is a chronic debilitating, systemic autoimmune disease that leads to joint destruction and synovial inflammation [2]. The etiopathogenesis for each disease is complex and has its distinctive histological and molecular characteristics [3, 4]. However, some similarities exist in their immunological pathogenesis leading to the similarity in some of the systemic biological treatment options utilized for these diseases [5].

Different studies have shown that tumor necrosis factor alpha (TNF-α) plays a critical role in the onset and progression of both diseases [5, 6]. In psoriasis, it stimulates the T cell's migration to the skin and the production of TH17-cytokines such as IL-17A and IL-17 which ultimately leads to excessive keratinocyte proliferation [7]. In RA, the TNF-α leads to the co-stimulation of dendritic cells, T cells, and B-cells which cause T-cell activation and functional differentiation [8]. Accordingly, the anti-tumor necrosis factor alpha (anti-TNF-α) therapies are very effective for plaque psoriasis as well as RA [9, 10]. However, due to some of the shared immunological pathway components between both diseases, the exacerbation or development of one disease while treating the other by anti-TNF-α, i.e., paradoxical reaction, can develop. This occurs in 5% of patients which requires, in some severe cases, the cessation of therapy and a switch to another class of medication resulting in partial or total resolution of the reaction [11, 12]. However, in rare instances, the development of a different, subsequent paradoxical reaction while on the switched drug can occur. This necessitates alerting physicians using these drugs about this rare incidence which presents an emerging challenge to the treating physicians [13].

Accordingly, we report a case of two different consecutive paradoxical skin reactions; psoriasis and eczema, in a patient diagnosed with RA receiving anti-TNF-α followed by anti-IL17-A. The occurrence of both types of paradoxical reactions in a single patient is the first to be reported.

CASE PRESENTATION

A 27-year-old Saudi female with a positive family history of psoriasis was diagnosed as a case of seropositive RA 13 years ago. It was managed by Adalimumab (a TNF- α inhibitor) 40 mg every 2 weeks, maintaining her RA in a state of remission. Ten years later, she presented to the dermatology clinic with the complaint of multiple, non-itchy, annular erythematous scaly plaques over the dorsum and sole of the feet bilaterally for 4 months duration (part A in **Figure 1**). The lesions were associated with nail changes (onycholysis) in the right big toe

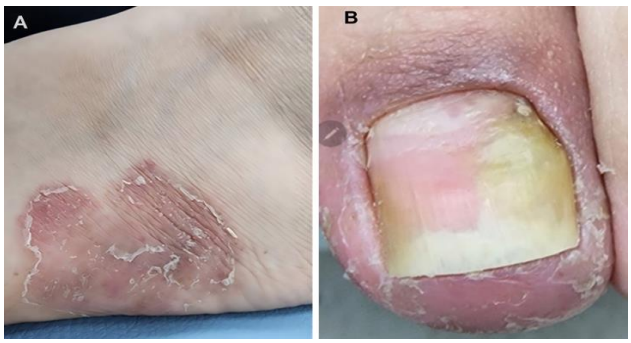

Figure 1. Paradoxical psoriasis developed while the patient was on anti-TNF-α therapy: (A) erythematous scaly plaques over the lateral dorsum of the foot & (B) onycholysis of the big toe (reprinted with permission of the patient)

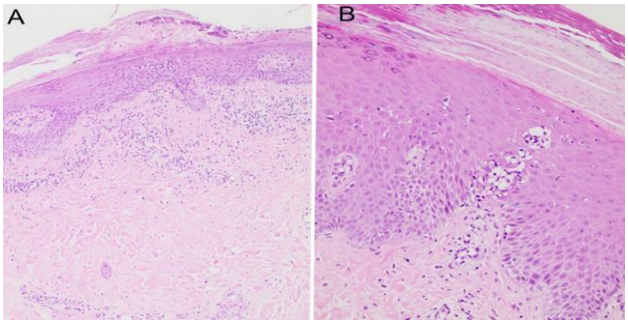

Figure 2. Histology of the paradoxical psoriasis: (A) hematoxylin-eosin slide shows parakeratosis, elongated rete ridges, neutrophils collections in the stratum corneum and regular acanthosis (hematoxylin-eosin, original magnification × 100) & (B) magnified image from the same slide showing hyperkeratotic epidermis, confluent parakeratosis, focal hypogranulosis, mild spongiosis with elongated rete ridges (original magnification × 200) (reprinted with permission of the patient)

(part B in **Figure 1**). There was no history of joint pain, swelling, or deformities.

Biopsies were performed from 3 different skin lesions and revealed psoriasiform dermatitis (part A and part B in **Figure 2**). Hence, the patient was diagnosed with Adalimumab-induced psoriasis or paradoxical psoriasis (PP).

The patient was given a trial of calcipotriol/betamethasone ointment (daivobet) for 2 months. Yet, the lesion was still present. Accordingly, adalimumab was discontinued, and the patient was started on Ixekizumab (anti-IL-17A) to control the RA at a loading dose of 160 mg subcutaneously, followed by a maintenance dose of 80 mg.

Two weeks after the first dose of Ixekizumab, the patient returned to the dermatology clinic with marked improvement in the psoriatic lesions but presented with newly developed extensive, multiple, rounded erythematous scaly plaques over the back, hands, and legs. The lesions were oozing clear fluid (part A and part B in **Figure 3**).

A biopsy was taken from the lesion in the back and showed significant spongiosis with regular acanthosis. The upper dermis exhibited a moderate perivascular lymphohistiocytic infiltrate with perifollicular inflammation on deeper levels (part A and part B in **Figure 4**). Consequently, a diagnosis of Ixekizumab-induced eczema was given. Accordingly, Ixekizumab was discontinued, and the patient was given

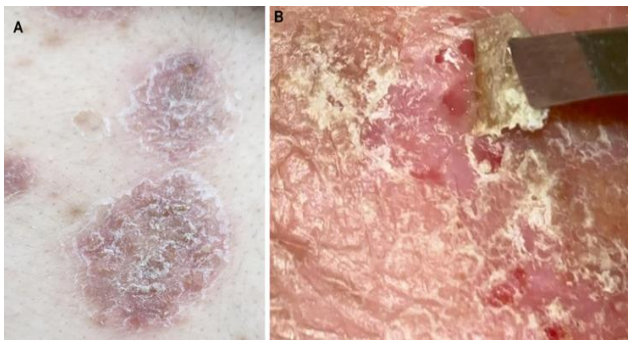

Figure 3. Paradoxical eczema developed while patient was on anti-IL-17A: (A) multiple erythematous crusted plaques in the back & (B) the lesions were oozing clear fluid when the crust is removed (reprinted with permission of the patient)

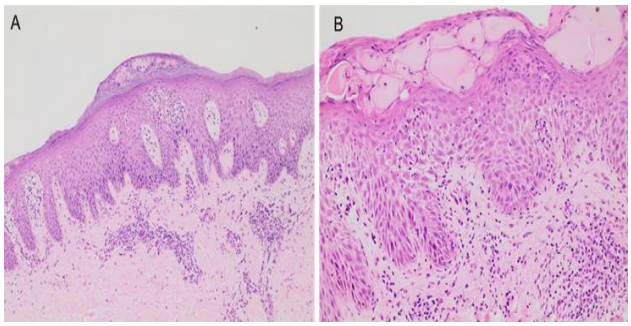

Figure 4. Histology of paradoxical eczema lesion: (A) the hematoxylin-eosin slide shows spongiotic psoriasiform dermatitis and dermal marked perivascular T-cell and histiocyte infiltrate (original magnification × 100) & (B) magnified image from same slide showing the crust formation, exocytosis, and significant spongiosis (original magnification × 200) (reprinted with permission of the patient)

topical steroids for 1 week followed by tacrolimus for 2 weeks. As a result, the eczematous lesions disappeared completely leaving post-inflammatory hyperpigmentation.

The patient was referred back to the rheumatology clinic for RA assessment. It is planned to start the patient on a Janus kinase inhibitor (upadacitinib) to control her RA symptoms.

DISCUSSION

This case represents a typical picture of what is called a true paradoxical reaction; a term that applies to the development of immune-mediated diseases in which the effect of biological therapy is clearly established [14]. The first developed paradoxical reaction in our patient is a well-known reaction of the anti-TNF-α therapy [15]. It has been shown that the occurrence of this reaction is increased in patients with a family history of psoriasis and in those who carry genetic single nucleotide polymorphisms (SNPs) in the HLA-C genomic region [16, 17]. In our patient, despite the absence of gene analysis results, a positive family history of psoriasis was clearly established raising the possibility of genetic susceptibility for the PP.

The time interval between initiation of treatment and onset of skin disease in our case, 10 years, is considered significantly long, especially considering that the mean time to reaction in literature ranged from 2 to 36 months [18, 19]. This

late-onset development of the paradoxical reaction raises several unanswered questions. These questions pertain to the nature of the late trigger that stimulated the occurrence of the reaction as well as the reason for the delayed response of the skin immunological cells contributing to the PP, the use of anti-TNF-α therapy, and the efficacy of the anti-TNF-α therapy in controlling immune-mediated diseases after a long period of consumption.

Regarding the etiologies that could be playing a role in causing this skin reaction, studies have shown that in addition to the patient's genetic susceptibility caused by SNPs in IL23R, FBXL19, and ATPs, the imbalance between TNF-alpha and interferon (IFN)-α, caused by the inhibition of the former, will stimulate the uncontrolled production of the latter from plasmacytoid dendritic cells [17]. This seems to be related to the paradoxical reaction as this was illustrated by Fania et al., who found, by immunohistochemistry, that IFN-β and IFN-α2a (two type I IFNs) were highly expressed in PP. Moreover, the infiltration of TH17 and its related cytokines (i.e., IL17) in the PP lesions may play a significant role in PP development. This was observed in various studies revealing the polarization skewing of immune cell subtypes in PP [20-22]. However, the exact mechanisms by which the abovementioned immunological cells and their cytokines promote the PP are not yet known due to the limited samples and research to date.

The resolution of the patient's psoriatic lesions while she was on anti-IL17A can be explained in different ways: the withdrawal of the anti-TNF-α drug caused the return of (IFN)-α to its normal levels, or the use of anti-IL17A affected the immunological microenvironment of the PP lesions. Here, we believe that both factors contributed to the reaction's resolution.

Interestingly, switching the patient to a different biologic group resulted in the development of a different type of paradoxical skin reaction with itchy eczematous lesion clinically and an acute dermatitis picture histologically. Whether this is a true paradoxical reaction or a side effect of the anti-IL17A therapy is a debatable subject. However, since the reaction type has an immune-mediated nature, and subsided after the discontinuation of anti-IL17a, it could be considered paradoxical eczema [23].

The rapid development of this paradoxical reaction just 2 weeks after starting the therapy, compared to the 10 years after the anti-TNF-α therapy, may be due to the readiness of the skin's cellular microenvironment from the previous exposure to anti-TNF-α therapy as this exposure resulted in cellular and cytokine changes [20, 22]. This is especially unique considering that the reported average time to develop a paradoxical eczematous reaction to anti-IL17 was 16.9 ± 17.0 weeks after treatment [24]. This shows how the occurrence of a paradoxical reaction depends on a combination of multiple factors related to the type and number of biological agents used in addition to patient-specific factors [16, 25].

The development of paradoxical eczema may be due to the immunological imbalance induced by blocking the IL-17A in the blood and skin, resulting in the inhibition of the Th1 pathway and favoring an increased activity of the opposing Th2 pathway [26]. Additionally, the IL-17A inhibition could induce a negative feedback loop in the IL-23/IL-17 axis, resulting in IL23 elevation, which in turn stimulates TH-17 cells to produce IL-22. The latter can play a key role in atopic dermatitis-like inflammation by stimulating epidermal thickness and skin barrier dysfunction [27].

CONCLUSION

In conclusion, this is the first reported case of a patient who developed PP and then paradoxical eczema when using two consecutive different biological therapies. Consequently, clinicians should be aware that changing the biological treatment to treat the PP does not always solve the problem, and another type of paradoxical reaction could be triggered. Clinical research and studies on related mechanisms, as well as on the factors that could predict the development of the reaction, should be conducted to provide a basis for safe biological treatment usage among patients.

Author contributions: FB, HAH, AAZ, & JR: writing–original draft preparation; **JR, FB, & MH:** investigation; **HAH, AAZ, & FB:** conceptualization; **FB & AS:** methodology; **HAH, AAZ, AS, FB, & JR:** resources; data curation, formal analysis; **FB, MH, & JR:** visualization & project administration; **FB, JR, MH, & AS:** writing–review & editing. All authors agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: The authors stated that ethical approval was obtained from Institutional Review Baord at Imam Abdulrahman Bin Faisal Universitry on 3 June 2024 with approval number: IRB-2024-01-433. Additionally, a written informed consnet was obtained from the patient.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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