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Dermatology

Paradoxical Plaque Psoriasis on Infliximab in a Patient with Behçet's Disease

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Abstract **Case Report**

TNF inhibitors are used in a number of diseases, including Behçet's disease and particularly its ophthalmological manifestations in cases of resistance or progression under conventional systemic treatments, notably corticosteroids. These TNF inhibitors are not without side effects, some of which are paradoxical in that they manifest themselves in diseases classically treated by these agents, such as psoriasis. Our case report is about a 25-year-old Behçet patient who received infliximab for corticoresistant uveitis. His uveitis has subsided but he developed a diffuse psoriasiform eruption 21 months after its introduction. Infliximab was discontinued and the patient was treated with emollients, dermocorticoids and phototherapy with a favorable outcome. Paradoxical psoriasis occurs from a few days to several years after the introduction of TNF inhibitors, it may resemble psoriasis vulgaris or differ from it in terms of flexural fold involvement, more frequent pustular involvement of the palms and soles, and scalp involvement complicated by severe non-scarring alopecia. The histology of paradoxical psoriasis typically combines psoriatic, eczematiform and lichenoid patterns. When paradoxical psoriasis is moderate or severe, and the underlying pathology is controlled, we can treat the psoriatic flare and switch to another TNF inhibitor, something the Internal Medicine Department has not been very receptive to.

Keywords: Behçet Disease, TNF Inhibitors, Paradoxical Psoriasis, Management.

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INTRODUCTION

TNF is a powerful pro-inflammatory cytokine known to coordinate immune responses and play an important role in limiting the spread of infectious pathogens.

Several TNF-targeted biologic agents have been developed, each with a different structure for specific indications.

These include infliximab, adalimumab, etanercept, golimumab and certolizumab.

The frequent use of these biologic agents has been accompanied by the emergence of adverse effects, some of which are said to be paradoxical because they manifest as pathologies classically cured or improved by TNF inhibitors.

The prototype of these paradoxical manifestations is the psoriasiform eruption, but there are also cutaneous vasculitis, alopecia, lupus, lichen planus and hidradenitis suppurativa, neutrophilic dermatoses such as pyoderma gangrenosum or Sweet's syndrome, granulomatous dermatoses such as granuloma annulare, granulomatous interstitial dermatitis, lipoid necrosis and sarcoidosis, and uveitis.

Pathologies treated with anti-TNF include ankylosing spondylitis, IBD, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, rheumatoid arthritis and Behçet's disease, particularly in its posterior ocular form.(Wendling *et al.*, 2014). We report a case of paradoxical psoriasiform eruption on infliximab in a patient with Behçet's disease.

CASE REPORT

This is a 25-year-old patient, a 10-pack-year smoker, followed for Behçet's disease since november

2021, due to the association of anterior and posterior uveitis and oral and genital bipolar aphthosis. The patient initially benefited from a bolus of methylprednisolone at a dose of 1g per day for 03 days, followed by oral prednisone at 60mg/day, azathioprine 50mg x 3/day, and colchicine 1mg/day.

This treatment was continued for 02 months, and following the worsening of his ocular picture, the patient was put, on january 2022 on infliximab 300mg every 08 weeks preceded by an induction at weeks 0, 2 and 6. The evolution was favorable, with complete regression of the uveitis.

The patient also developed a psoriatic rash in November 2023. By this stage, the patient had received 11 courses of infliximab. The eruption occurred in a context of preserved general condition. Dermatological examination revealed erythematosquamous plaques on the trunk (figure 1) and upper limbs (figure 2), in small and medium-sized patches with slight infiltration. The wax candle and bloody dew signs were positive.

The lower limbs were covered with large, erythematous plaques infiltrated with psoriasiform scales (figure 3). The patient had no keratoderma.

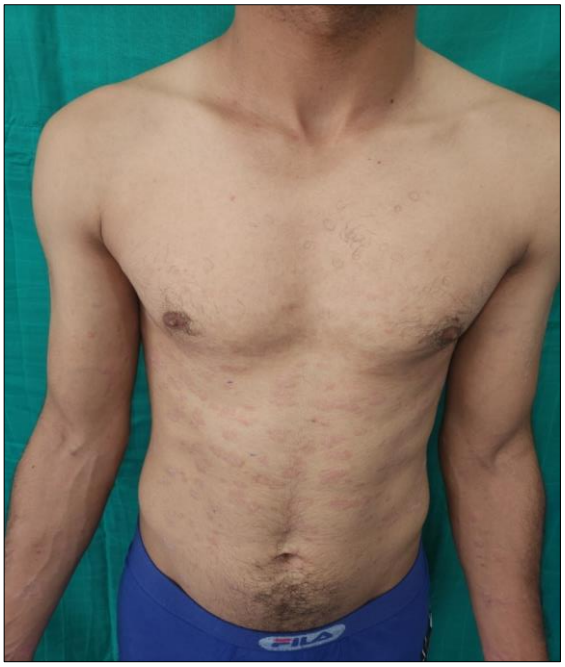

Figure 1: Psoriasiform erythematosquamous lesions on the trunk in a patient with paradoxical psoriasis

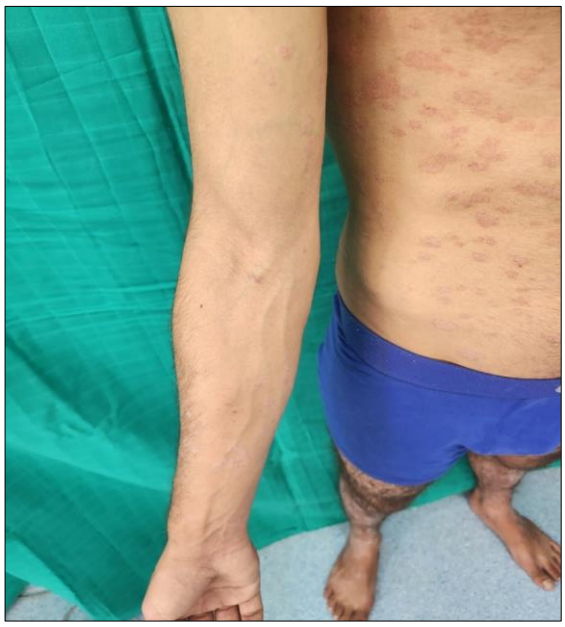

Figure 2: Psoriasiform erythematosquamous lesions on the trunk and arm in a patient with paradoxical psoriasis

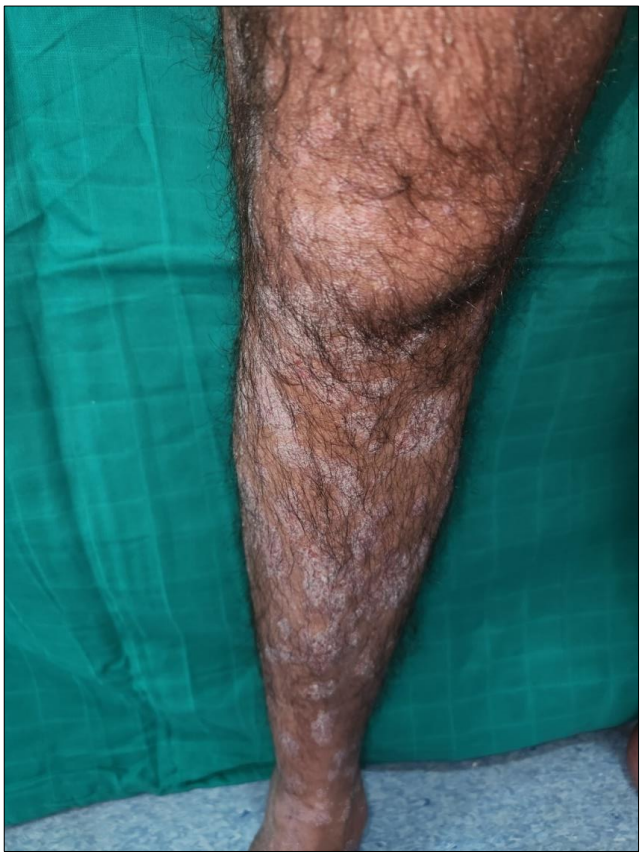

Figure 3: Psoriasiform erythematosquamous lesions on the right thigh and leg in a patient with paradoxical psoriasis

Dermoscopy revealed a dotted vascular pattern with a few white scales in polarized light (figure 4).

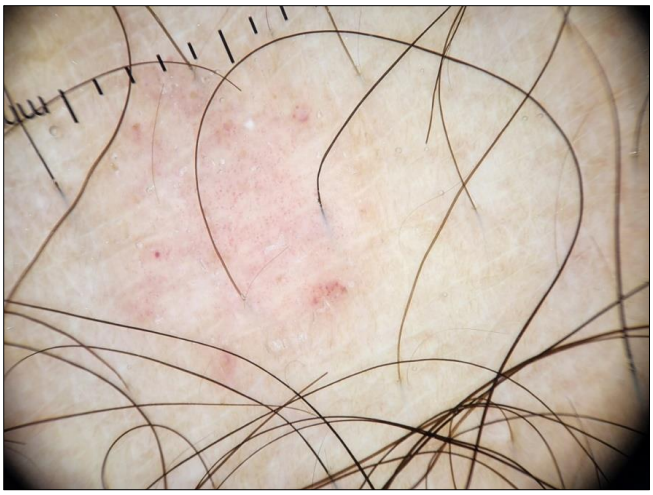

Figure 4: Dermoscopic image showing dotted vessels and fine scale in a patient with paradoxical psoriasis (Dermlite DL4, polarized light, original magnification 10x)

There was no mucosal or phanerial involvement, in particular no scalp involvement, no onycholysis, no subungual hyperkeratosis, no nail depression, and no salmon patches.

There was no joint involvement.

The affected skin surface was 30%, PASI was estimated at 11.5, DLQI was initially at 12.

A skin biopsy was performed and showed a regular orthokeratotic epidermis with a slight non-specific inflammatory infiltrate, essentially perivascular with no spongiosis and no histological sign of malignancy (figure 5).

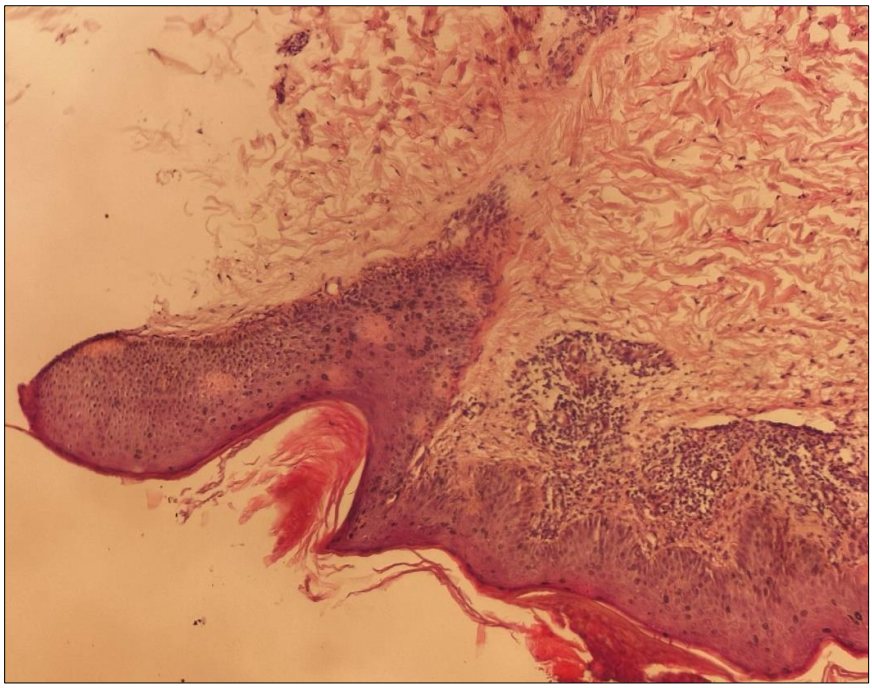

Figure 5: Histopathology showing regular orthokeratotic epidermis and a slight non-specific inflammatory infiltrate, essentially perivascular in the dermis (Hematoxylin & eosin stain, x10 magnification)

In view of this paradoxical psoriatic eruption, infliximab was discontinued.

Therapeutically, the patient received topical treatment with corticosteroids and emollients, with partial improvement, followed by 10 sessions of phototherapy, with a good evolution rated PASI80.

The course of the disease was marked by a relapse of ocular involvement.

DISCUSSION

Paradoxical psoriasis can manifest as plaque, guttate or pustular psoriasis, or eczematous lesions. It appears independently of the underlying disease or the type of the TNF inhibitor used.

It can occur anywhere from a few days to several years after initiation of treatment, with classical onset after 05 months.

Typically, lesions regress on discontinuation of the TNF inhibitor, demonstrating that paradoxical psoriasis is a side-effect of the TNF inhibitor and not de novo psoriasis.

In 50-80% of cases, recurrence occurs if the same or another anti-TNF drug is reintroduced.

There are certain clinical and histological features that differentiate paradoxical psoriasis from psoriasis vulgaris:

- Paradoxical psoriasis frequently affects flexural folds, whereas psoriasis vulgaris tends to affect extension zones.
- Palmo-plantar involvement, often associated with the presence of pustules, is found in up to 50-80% of cases, as opposed to 2-19% in the vulgaris form
- Scalp involvement can be complicated by severe secondary, non-scarring alopecia. This complication is extremely rare in psoriasis.
- Histologically, there are three possible patterns:

o Psoriatic pattern: acanthosis, papillomatosis, hyperkeratosis, parakeratosis
o Eczematiform pattern in the form of spongiosis
o Lichenoid pattern, with interface dermatitis
Typically, these three patterns are found simultaneously in a skin biopsy of paradoxical psoriasis.

Pathogenically, psoriasis vulgaris is characterized by the presence of activated plasmacytoid dendritic cells (pDCs) which produce interferon-alpha, enabling the activation of conventional dendritic cells (cDCs), which in turn produce TNF. TNF induces the maturation of dendritic cells, which lose their ability to produce interferon-alpha. In this way, TNF controls IFN alpha production via a negative feedback loop.

In paradoxical psoriasis, in the absence of TNF, there is no maturation of classical dendritic cells, nor negative feedback on plasmacytoid dendritic cells, leading to overproduction of IFN alpha. On the other hand, due to the lack of mature classical dendritic cells, IFN alpha overexpression fails to induce T-cell autoimmunity, resulting in ongoing innate inflammation. Since there is no genesis of autoreactive T cells,

inflammation continues until the TNF inhibitor is stopped. This is what some authors have described as Yin and Yang: TNF and interferon-alpha represent two opposing vectors in a dynamic system in which TNF controls the production of IFNalpha.(Mylonas *et al.*, 2018)

It used to be accepted that paradoxical psoriasis is a TNF inhibitors related paradoxical manifestation occurring in 2-5% of patients treated with these agents. It is currently accepted that paradoxical psoriasis is not specific to anti-TNFs and can also occur with ustekinumab, secukinumab, rituximab, abatacept, tocilizumab or anakinra, but the pathogenesis of paradoxical psoriasis with these biotherapies remains unclear.

Regarding the management of TNF inhibitors induced paradoxical psoriasis:

- If the rash is mild and the underlying disease controlled: it is advisable to continue the TNF inhibitors and to treat psoriatic symptoms with topical corticosteroids or UVB phototherapy, or methotrexate or ciclosporin or acitretin, or dapsone in the case of pustular psoriasis; bearing in mind that complete resolution occurs in only 29% of patients.
- If the rash is mild but the underlying disease is uncontrolled: change the current TNF inhibitor to another and treat psoriatic symptoms; bearing in mind that complete resolution occurs in only 3% of patients.
- If the rash is moderate to severe and the underlying disease is controlled: change the TNF inhibitor and treat psoriatic symptoms.
- If the rash is moderate to severe and the underlying disease is uncontrolled: switch to a different class of biotherapy and treat psoriatic symptoms (Li *et al*., 2019)

Although randomized controlled trials are lacking, several biotherapies are used in the treatment of Behçet's disease, including TNF alpha, IL1, IL6, IL12 and IL17 inhibitors. By consensus, TNF inhibitors and interferon are the most effective in treating the major organic manifestations of Behçet's disease, namely ocular and vascular manifestations. (Alibaz-Oner *et al.*, 2021).

Following the above algorithm, we found that since our patient presented with moderate to severe psoriasis on infliximab, and responded well to UVB phototherapy and dermocorticoids, we suggested to the ophthalmologists and internists that we switch to adalimumab, which they were reluctant to do.

CONCLUSION

Our patient is the second case reported in the literature of paradoxical psoriasis occurring on anti-TNF therapy during the course of Behçet's disease. Although he responded well to the usual psoriasis treatments, he must also benefit from background treatment with another TNF inhibitor to slow the progression of his Behçet's disease, which remains a major cause of blindness.

Acknowledgments: None

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