Paradoxical Reactions under Adalimumab, Report of two Cases

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Abstract

We report two observations illustrating two cases receiving Adalimumab for ankylosing spondylitis that had developed respectively psoriasis and pyoderma gangrenosum. We discuss these dermatoses as a paradoxical effect of TNFα antagonist.

Keywords: Paradoxical reactions, TNFα antagonist, dermatosis.

INTRODUCTION

Anti-TNFα is widely used in rheumatology to treat chronic inflammatory rheumatism, especially spondylitis. We describe two cases of patients followed for ankylosing spondylitis who presented skin reactions to Adalimumab. It is psoriasis in the first case and pyoderma gangrenosum in the second case.

CASE REPORTS

Case 1

A 38-year-old man follow-up for ankylosing spondylitis since 2012, with inflammatory low back pain and bilateral buttock pain.

Plain radiography and MRI showed bilateral grade IV sacroiliitis, and staged syndesmophytes in the first four lumbar vertebrae. Furthermore, the patient had no personal or familial history of psoriasis.

The patient was initially treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Adalimumab was started in 2016, after failure of NSAIDs at a subcutaneous dosage of 40 mg given every two weeks.

In February 2017, the patient developed pustular palmoplantar psoriasis and plaque psoriasis of the elbows and knees (Figures 1a and 1b), without psoriasis of nails, scalp or inverse psoriasis.

We decided to stop Adalimumab and switch to Etanercept (50 mg / week). After two months, all psoriatic lesions had disappeared. On the articular level, the patient remained in remission under the new biological. In 2021, the patient is still on Etanercept and has never had psoriasis.

Case 2

A 41-year-old man, followed since 2012 for axial, peripheral and enthesic ankylosing spondylitis. The patient initially received NSAIDs then methotrexate. Following the failure of conventional treatment, Adalimumab was started in 2015 at a subcutaneous dosage of 40 mg every two weeks.

The patient is seen every three months with BASDAI remission. In March 2020, the patient presented with skin ulcers involving the right wrist and left hand (Figure 2).

On the right wrist, the lesion is ulcerative, necrotic and surrounded by an erythematous halo. Its edges are purplish, hypertrophic and well defined.

A bullous, tense with serohematic content, lesion was located in the metacarpophalangeal joint of the index finger of the left hand.

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The surrounding skin tissue is erythematous and infiltrated. Faced with these ulcers, a paradoxical
Effect was suspected and Adalimumab was discontinued.

A skin biopsy was taken from the right wrist and left hand. Histological study revealed a dermal infiltrate of inflammatory cells predominantly of neutrophils without signs of vasculitis. The diagnosis of pyoderma gangrenosum was retained.

Laboratory workup found a biological inflammatory syndrome (CRP at 162 mg / L, procalcitonin at 0.42 ng / ml, ESR at 128 mm, hyperleukocytosis at 14,890).

The aetiological workup did not show any evidence in favor of malignant hematologic disease or chronic inflammatory bowel disease or tumor syndrome.

The immunological assessment (anti-nuclear antibodies, anti-citrullinated protein antibodies, Latex, Waaler-Rose, and ANCA) was negative.

Non-specific antibiotic treatment with the protected amoxcillin was initiated. A local treatment comprising a topical corticosteroid, silver sulfadiazine and fucidic acid was started.

The lesions continued to progress despite this initial treatment. Faced with this severe dermatosis, corticosteroid therapy based on prednisone has been proposed at a dosage of 1 mg / kg / day.

A switch was made to Golimumab at a dosage of 50 mg / month by the subcutaneous route. At two months of follow-up, healing was achieved without sequelae. On the articular level, ASA remained controlled under Golimumab.

**DISCUSSION**

Anti-TNFα is biological drugs which have been shown to be effective in controlling the inflammatory reaction, by reducing serum TNFα levels.

They have revolutionized the management of chronic inflammatory rheumatism and in particular spondyloarthritis.

Anti-TNFα is generally well tolerated but they are not without side effects. Their usual side effects are opportunistic infections, solid tumors and lymphomas [1].

Some dermatological complications have been described with anti-TNFα, for example: injection site reactions, eczema-like dermatitis, lupus-like skin lesions, vasculitis, drug eruptions, lichen planus and viral, bacterial and fungal skin infections [2].
The paradoxical effects of anti-TNF α are rare events. Regarding paradoxical skin effects, psoriasis is the most widely described lesion [2].

It occurs anytime while taking anti-TNFα and without a predisposing factor [2]. The current pathophysiological mechanism explaining induced psoriasis is based on deregulation of plasmacytid dendritic cells and an increase in alpha interferon [3].

In addition, Ma et al. had found an immunoregulatory role of TNF (tumor necrosis factor) on Th17 and Treg cells, leading to exacerbation of skin inflammation in some patients receiving anti-TNF [4].

In true psoriasis, the inflammatory processes involved, lead to hyperplasia and disturbances in keratinocyte differentiation, vascular hyperplasia and a leukocyte infiltrate rich in dendritic cells, T lymphocytes and polymorphonuclear neutrophils which characterize the psoriatic skin [5].

Our first patient had no history of psoriasis. This dermatosis occurred when the disease was well controlled. Since stopping Adalimumab, the patient has not made any new lesions. Thus, the causal link of Adalimumab was retained.

The skin reaction described in the second patient was a pyoderma gangrenosum (PG). It is a rare, female-dominated autoinflammatory dermatosis [7]. It is idiopathic in 25 to 50% of cases [7].

Classically, it presents as a painful ulcerative lesion mistaken for an ischemic or infectious lesion [6]. PG can be associated with a variety of systemic diseases including chronic inflammatory bowel disease, rheumatoid arthritis, and hematologic malignancies [8].

PG can also be part of autoinflammatory syndromes such as PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum and Acne) and PASH syndrome (Pyoderma gangrenosum, Acne, Hidradenitis Suppurativa) [9].

Its physiopathological mechanism remains unknown [7]. An immunologic abnormality may exist due to its frequent association with autoimmune diseases [7]. Polynuclear neutrophil dysfunction has been suggested [11, 12]. Lack of chemotaxis, abnormalities in migration and phagocytosis, and limited bactericidal capacity has also been implicated [12].

Marzano et al. demonstrated a significant overexpression of interleukin-1 and its receptor, TNFα, interleukin-8, interleukin-17, the chemokines CXCL1 / 2/3, CXCL16 and metalloproteinase 2 and 9 compared to normal skin [12, 13].

These cytokines enhance the inflammatory response and the recruitment of neutrophils [13]. This suggests that PG should be classified as an autoinflammatory disease [12]. The first-line treatment is systemic corticosteroid, at 1 mg / kg / day [12]. In case of failure or contraindication, Ciclosporin at 3 mg / kg / day may be indicated [10].

The maintenance therapy, and in the case of corticosteroid dependence, involves Dapsone, at 100-200 mg / day or Azathioprine 100 mg / day [10].

Biotherapies seem to be promising in PG. The molecule with the most evidence of efficacy is Infliximab, in a placebo-controlled trial [10]. Adalimumab also has a very good response rate in a small number of patients [10].

In our patient, we offered Golimumab. This is the second case described in the literature, where this anti-TNFα has shown efficacy in paradoxical reactions, this was a 68-year-old patient treated with Infliximab and Adalimumab for ulcerative colitis (UC).

Golimumab was introduced in combination with corticosteroid therapy to treat severe lesions of PG. This biologic was effective on dermatosis and UC [14].

**Conclusion**

The occurrence of a skin lesion in a patient under treatment with an anti-TNFα, should raise a possible responsibility for this treatment.

Thus, the dermatologist and the rheumatologist must think of the side effects but also of the paradoxical reactions of the biological drugs and consider its immediate cessation and multidisciplinary management.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


