REVIEW

Cutaneous Adverse Reactions to TNF Alpha Blockers. Case Report and Literature Review

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Abstract

Biological therapy is used in a wide range of medical settings. Adverse reactions to biological therapy can limit their widespread use, so early detection and treatment can adjust attempts to stop these molecules. TNF Alpha blockers may cause the following skin reactions in alpha patients: injection site reactions, infections, immune-mediated reactions (psoriasis, psoriasis, drug-induced lupus, vasculitis, hidradenitis, alopecia), allergic or neoplastic reactions. We present the case of a patient with RA who developed skin lesions during biological therapy and was diagnosed with drug-induced lupus based on clinical elements, associated autoimmunity, and dermatological evaluation. The skin lesions were attributed to the interaction of three medications (biosimilar Etanercept, Leflunomide, and Isoniazid), all of which have been implicated in causing these side effects. The solutions that saved the patient were temporarily discontinuing the immunosuppressive medication and replacing it with a local corticoid, followed by the continuation of Etanercept in associated with Methotrexate, and the patient was able to continue the biological medication and obtain a favorable response to the treatment. In conclusion, skin changes caused by TNF Alpha inhibitors are common, but vary in severity, and do not warrant therapy interruption.

Keywords: biological therapy, TNF Alpha blockers, skin lesions, immunosuppressive medication.

Rezumat

Terapia biologică este folosită în multiple domenii medicale. Reacțiile adverse la terapia biologică pot limita folosirea pe scară largă a acestor molecule, de aceea recunoșterea precoce și tratamentul adecvat pot ajusta tentativele de oprire a acestor molecule. Reacțiile cutanate pe care le pot dezvoltă pacienții alfati în tratament cu blocantii TNF Alpha sunt: reacții la locul injectării, infecții, reacții mediate imun (psoriasis, psoriasis, lupus indus medicamentos, vasculita, hidradenita, alopecie), reacții alergice sau neoplazice. Prezentăm cazul unei paciente diagnosticate cu PR care la inițierea terapiei biologice a prezentat leziuni cutanate ce au fost încadrate drept drug induced lupus pe baza elementelor clinice, a autoimunitatii asociate și a evalaurii dermatologice. Leziunile cutanate au fost atribuite suprapunerii a trei medicații (Etanercept biosimilar, Leflunomide și Izoniazida), toate recunoscute a fi implicate în declanșarea acestor efecte adverse. Oprirea temporară a medicației imunosupresoare și inlocuierea cu Corticoid local, urmată de reluarea Etanerceptului în asociere cu Metotrexat au fost soluțiile salvataore și pacienta a putut continua medicația biologică și a obținut un răspuns favorabil la tratament. În concluzie modificările cutanate secundare inhibitorilor TNF Alpha sunt frecvente, dar cu severitate variabilă, iar necesitatea interuperii medicației nu este obligatorie.

Cuvinte cheie: terapia biologică, blocantii TNF Alpha, leziuni cutanate, medicație imunosupresoare.

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INTRODUCTION

Biologic therapy is an area of medicine that is rapidly expanding. Particularly in the domains of oncology, dermatology, hematology, gastroenterology, and rheumatology, biologic treatments have revolutionized medicine and today offer personalized treatment for a variety of disorders. There are, however, a few specific adverse effects associated with these cutting-edge therapies, with cutaneous side effects being the most frequently reported. Adverse cutaneous effects may restrict the use of these treatments, which not only may increase the expense of a treatment that is already expensive but may also severely restrict the therapeutic options available to some patients.[1]

While being less risky and having a better tolerability profile than conventional diseases-modifying anti-rheumatic drugs, biological agents can nonetheless result in a range of cutaneous adverse reactions, whether they are inflammatory, infectious, or neoplastic in nature.[2] These adverse events can be sorted into 5 main categories. The first is type **α** directly related to high concentrations of circulating cytokines, whereas type **β** represents a hypersensitivity response. The majority of paradoxical skin eruptions in response to biological therapy fall under type **γ** adverse effects and type **δ**, on the other hand, indicates effects that occur as a result of targeting an antigen that is also present on non-pathogenic cells. The last category is type **ε**, which refers to nonimmunologic reactions.[3,4]

The so-called paradoxical immune-mediated inflammatory reactions are a new type of adverse event that have been linked to targeted therapy using biological agents. The development of immune-mediated inflammatory tissue reactions in patients with immune-mediated inflammatory disorders receiving biological therapy is now seen as an indication of a paradoxical reaction.[5] The majority of cutaneous manifestations have a distinct mechanism involving various immune cells and inflammatory pathways (as illustrated in Figure 1). Tumor necrosis factor (TNF)-targeting biological agents can cause a variety of immune responses, including interferon **γ** (IFN**γ**)-mediated reactions like vitiligo or alopecia areata, Th1 cells being highly involved in this type of reaction. Moreover, skin disorders like psoriasis and palmoplantar pustulosis are mostly mediated by Th17 cells, while Th2 cells are accountable for disorders like eczema. Type I interferons and plasmacytoid dendritic cells appear to be involved in a number of TNF-induced cutaneous eruptions, such as paradoxical psoriasis, psoriasiform dermatitis, and lupus, though the pathogenesis is not fully understood yet.[4,6]

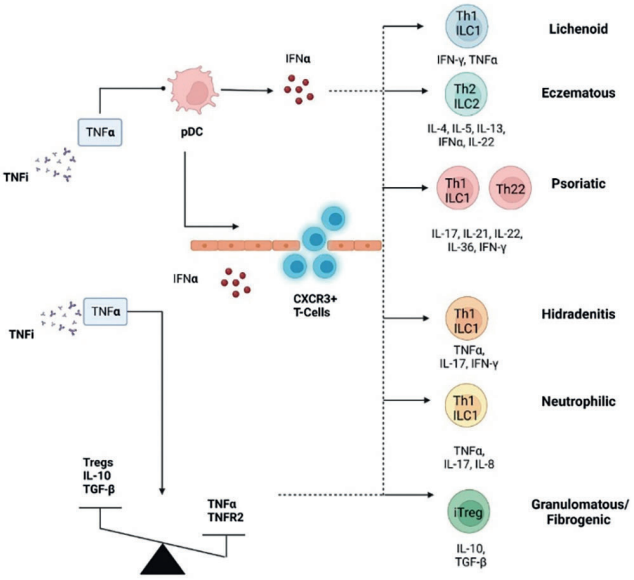

Figure 1. Skin related adverse reactions induced by tumor necrosis factor inhibitors and their inflammatory mechanisms.

When it comes to drug-induced lupus, certain medications trigger an immunological reaction that results in the development of autoantibodies. Drug-induced lupus is typically defined by the presence of ANA, which, like idiopathic lupus, tends to have a homogeneous pattern, however a speckled pattern can also be observed. Antihistone antibodies can be found in 75% of drug-induced lupus patients but they are considered nonspecific due to antihistone antibodies being present in a similar percentage of idiopathic lupus patients. Single-stranded DNA antibodies are also considered nonspecific for drug-induced lupus. On the other hand, double-stranded DNA antibodies are found in only 5% of drug-induced lupus patients, compared to approximately 50% of idiopathic lupus patients.[8]

The most commonly associated treatments with drug-induced lupus are hydralazine, isoniazid, TNF inhibitors, minocycline, procainamide, and quinidine.[9,11] The trigger drugs most frequently reported for subacute cutaneous drug-induced lupus include oral antifungals, calcium channel blockers, biological therapies (including TNF**α** inhibitors), antiepileptics, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and thrombocyte inhibitors.[7] Leflunomide has also been associated with drug-induced lupus.[10]

Clinically, drug-induced lupus has been divided into 3 categories: drug-induced subacute cutaneous lupus, drug-induced systemic lupus, and drug-induced chronic cutaneous lupus (discoid and tumidus).[7] Symptoms of drug-induced lupus usually appear after starting therapy with a new drug, but a lag period of one month to 10 years after continuous therapy is also possible. Furthermore, the risk for developing symptoms tends to increase with higher and cumulative doses, as well as longer periods of therapy with said drug.[11] The most common symptoms reported in patients with drug induced lupus are arthralgia, myalgia, fever, fatigue and serositis.[7]

Currently, there is no diagnostic test that can definitively determine whether a patient has drug-induced lupus, however, several criteria must be met in order to diagnose a patient with drug-induced lupus, including the presence of at least one systemic lupus erythematosus symptom, a positive ANA profile, and other lupus bloodwork like antihistone antibodies and complete blood count.[11,12]

The most crucial step in treating a patient with drug-induced lupus is discontinuing the trigger drug, which typically results in the remission of symptoms and aberrant blood test results. However, if the patient is taking multiple medications, it may be challenging to pinpoint the trigger drug. In terms of pharmacological treatment of drug-induced lupus, symptom relief is usually the best approach. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat arthritis, topical corticosteroids may be prescribed to treat skin rashes, and systemic medications like antimalarials, oral corticosteroids, and immune system suppressants (azathioprine or cyclophosphamide) are available to treat patients that with internal organs dameges.[7,11,12]

CASE REPORT

We present a case of a 42 year old female patient, previously diagnosed at the age of 26 with rheumatoid arthritis, who was evaluated for the first time in our clinic presenting numerous swollen and painful joints, with important morning stiffness and functional disability, in order to escalate the therapeutic approach. Initially, the patient was prescribed methotrexate 10 mg/week and increased gradually over time to 20mg/week. Four years ago, the patient received leflunomide 20 mg daily associated to metothrexate (10mg/week), but after three years the metothrexate was discontinued due to increased risk of side effects.

At the moment of the evaluation, the patient reported a high number of tender joints (N=18), as well as numerous swollen joints (N=8). The pain rating on a visual analog scale was 8/10 and she reported morning stiffness that lasted for more than two hours. The blood tests revealed positive rheumatoid factor (173,15 UI/mL, normal value <14 UI/mL) and anti-citrullinated protein antibodies (125 U/mL, normal value <7 U/mL), but also high serum markers of inflammatory reactions like elevated erythrocyte sedimentation rate (38 mm/h, normal value <20 mm/h) and C-reactive protein (23,16 mg/L normal value <5 mg/L). The ultrasonographic findings included synovial hypertrophy with moderate amounts of joint fluid and increased Doppler signal in most of the metacarpophalangeal and proximal interphalangeal joints, associated with bone erosions and tenosynovitis of the flexor digitorum, extensor digitorum and extensor carpi ulnaris tendons (as seen in Figure 2).

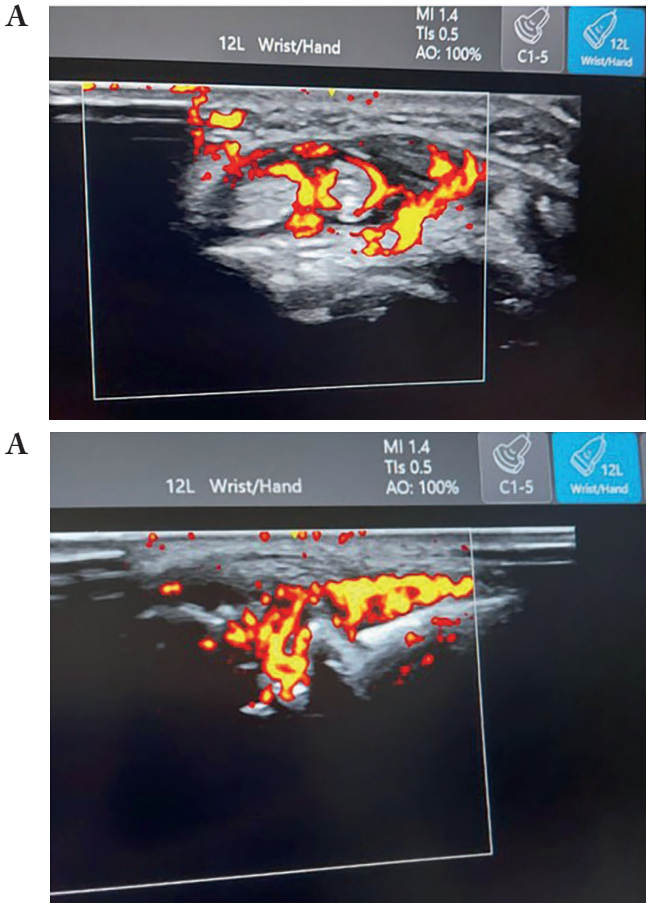

Figure 2. Ultrasound images of the hand and wrist with increased fluid reaction and high Doppler signal. **A** first compartment of extensor tendons of the wrist: Abductor Pollicis Longus and Extensor Pollicis Brevis tendons; **B** metacarpophalangeal joint

The disease activity was quantified using DAS28-CRP, which showed a high disease activity level (DAS28=6,39). According to the national guideline of rheumatic diseases, the patient was eligible for biological therapy and received the recommendations for serological testing of hepatitis B and C, which came back negative, as well as for QuantiFERON-TB Gold, which was positive.[13] In consequence, the patient was referred to the pneumologist who prescribed treatment with Isoniazid 300 mg daily for 9 months. One month later the patient started TNF-alpha inhibitors – Etanercept – biosimilar, while maintaining the leflunomide 20 mg daily.

At the two-month rheumatological check-up, her joint swelling and pain had significantly decreased, but she complained about having painful erythematous skin nodules on both of her hands, some of which had ulcers that were partially covered by hematous crusts, as well as splinter hemorrhages on the nailbeds. Taking into account drug induced lupus, the first recommendation was to stop the biological treatment and she was referred to the dermatologist. Her antinuclear antibody (ANA) panel revealed positive results for SS-A and Ro-52 antibodies, with normal results for the complement component C3 and antiphospholipid antibodies. The video capillaroscopy showed non-specific capillaroscopic changes, with evolutionary potential. The hypothesis of drug induced reactions was maintained, but the dermatologist limited the indication of skin biopsy due to localization of lesions and the increased risk that the wounds wouldn't heal properly. The patient was given the recommendation to apply topical corticosteroids with a positive outcome. The Etanercept administration was resumed after three weeks, but this time in association with metothrexate 10mg/week instead of leflunomide, being known that metothrexate is a better option for lupus skin manifestations.

At the six-month evaluation, the patient's skin lesions were entirely gone and the rheumatoid arthritis displayed a low activity score (DAS28 CRP=2,9 with delta DAS>1,2). As a result, we concluded that the last therapeutic regimen used was the most effective in managing both side effects and disease activity.

DISCUSSION

Various drugs, like leflunomide, hydralazine, procainamide, isoniazid, methyldopa, chlorpromazine, quinidine and TNF-alpha inhibitors can induce lupus.[14] Based on the clinical case presented previously, in this review we will refer mainly on drug-induced lupus erythematosus (DILE) caused by isoniazid, leflunomide and etanercept.

1. Isoniazid

Isoniazid and rifampicin are two antituberculosis drugs used frequently in antituberculosis therapeutic regimens. Isoniazid may induce a response that inhibits the subunit C4 of the complement and therefore the immune system cannot eradicate the immune complexes, finally leading to DILE.[15] Comparing to SLE, DILE typically reveal with a higher prevalence of purpura and erythema nodosum, but interrupting the isoniazid administration can reduce the symptoms.

2. Leflunomide

Leflunomide, an immunomodulatory drug used in rheumatoid arthritis, has anti-inflammatory, anti-proliferative, and immuno-suppressive properties. Even if leflunomide_brings benefits, patients have reported cutaneous adverse effects like baldness, eczema, pruritis, and dry skin. Its use has occasionally been associated with uncommon reports of skin ulceration, vasculitis, lichenoid drug rash, and DILE. [10]

3. TNF alpha inhibitors:

TNF alpha inhibitors can cause cutaneous side effects including local injection site reactions (bleeding, hematoma, erythema, pruritus, pain, swelling), infections (erysipelas, abscess, herpes zoster, herpes simplex, tinea, candidiasis), immune-mediated reactions (psoriasis, hidradenitis suppurativa, dermatomyositis, cutaneous lupus erythematosus, cutaneous vasculitis, granuloma annulare, sarcoidosis, alopecia areata, vitiligo, lichen planus, bullous dermatoses), allergic reactions (hypersensitivity, urticaria, angioedema), erythema multiforme, Stevens-Johnson syndrome and neoplasms (Squamous cell carcinoma, basal cell carcinoma, mycosis fungoides/Sézary syndrome).[1]

Infusion reactions are usually associated with infliximab and include urticaria, angioedema, flushing, pruritus and serum sickness-like reactions. Premedication with anti-histamines and acetaminophen or the administration of intravenous steroids and slowing the rate of infusion can be helpful. Itching, pain, redness, irritation, bruising or swelling are the typical findings at the injection site and occur during the first month of treatment and last 3-5 days. Preventive treatments similar to those used for infusion reactions, changing the injection site and local ice packs may be helpful. Casually, stopping the anti-TNF alpha therapy is necessary.[16]

Cutaneous infections and mainly bacterial infections. Staphylococcus was reported as the most frequent complication in a cohort study including 583 patients treated with TNF alpha inhibitors for inflammatory bowel disease. It was established that combined therapy corticosteroid-TNF alpha inhibitor led to fungal infections with Candida species, but the incidence is still unknown.[17] Frequent skin checkup and oral or topical antifungal or antibacterial therapy should be included in the management.

In patients known with psoriasis, treated with TNF alpha blockers, psoriasiform reaction is one of the most common immune-mediated reactions, also called paradoxical phenomenon. The increased expression of interferon alpha found at skin biopsy indicated that anti-TNF alpha therapy can lead to overproduction of INF-alpha.[1] UVB therapy, PUVA and topical treatment should be enough in mild cases. Interrupting the TNF-alpha inhibition or switching to a different biologic- usually on anti-IL-12 or anti-IL-23 agent is rarely needed.[18] In a study including 521 patients with inflammatory bowel disease treated with TNF alpha inhibitors, psoriasiform skin lesions were reported in 3,5% cases, involving the scalp, soles and palms.[19] In this case, the biopsy revealed histologic changes similar to those found in psoriasis, but also in allergic contact dermatitis, seborrheic dermatitis, atopic dermatitis, pityriasis rubra, and lichen simplex chronicus. Topical treatment was needed in 78% of cases, 18,6% had to interrupt the TNF alpha inhibitor and 15,2% required phototherapy or systemic therapy with methotrexate.[20]

It still remains unknown if TNF alpha blockers can be associated with the risk of developing skin cancer.[21] In four studies including 28.000 patients using anti-TNF alpha therapy, the risk of non-melanoma skin cancer was higher than in general population. Though, the use of phototherapy or other immunosuppressive drugs in the past or at the moment the study occurred can lead to inappropriate data. According to some research, people taking methotrexate, which has a photosensitizing nature, may have a higher risk in developing non-melanoma skin cancer.[22] Another research examined 9,460 patients with rheumatoid arthritis or inflammatory bowel disease and discovered that using anti-TNFs in combination with methotrexate may raise the risk of developing non-melanoma skin cancer. It is fair that all patients receiving treatment with a TNF alpha inhibitor undertake skin cancer surveillance and stop the therapy if malignant melanoma is found.[23]

Moreover, according to published statistics, 0.04% of people on TNF alpha inhibitors may develop skin sarcoidosis 24 which can manifest as erythema nodosum, pigmented scars, and nodular lesions 25. Frequently, the anti-TNF alpha drug should be stopped.

It is unclear the link between TNF alpha inhibitors and alopecia aerata, but it was emphasized that alopetic lesions can revert to normal even without interrupting or switching biologic agents. In mild cases of alopecia areata, local therapy or cyclosporin might be added to biologic treatment. Stopping the TNF alpha blockers should be considered in severe cases.[26]

A rare form of drug-induced lupus, affecting 72% of patients mostly the middle-aged women, is TAILS (TNFα inhibitor induced lupus-like syndrome) usually generated by infliximab and etanercept. The typical skin manifestations include maculo-papular rash, malar rash, photosensitivity and alopecia, but it can also generate non-cutaneous manifestations like arthritis, serositis, myositis, anemia, leukopenia, renal, and neurologic disorders. Patients might be tested for laboratory indicators of lupus if TAILS is suspected. It was established that antinuclear antibodies were positively in 91% of cases, anti-dsDNA antibodies in 64%, and antiphospholipid antibodies in 11% to 50% of cases.[27] The presence of specific SLE autoantibodies (ANA or anti-dsDNA) and at least one additional symptom, such as joint pain, fever, fatigue, serositis, or skin lesions seen in lupus and the relationship between the beginning of symptoms with the initiation of anti-TNF therapy and their resolution after stopping, are used to establish the diagnosis of anti-TNF-induced lupus. However, testing the autoantibodies without any clinical signs should be avoided.[28] Related to classic symptoms found in lupus, in TAILS we can notice less systemic involvement and more skin modification (ulcers, photosensitivity). More anti-dsDNA antibodies, higher hypocomplementemia and fewer anti-histone antibodies are detected compared to other lupus-inducing medications. TAILS often appears after three medication doses and disappear in seven weeks after interrupting the biologic.[29] Some studies in rheumatoid arthritis patients, showed that the administration of infliximab and etanercept resulted in the induction of antinuclear antibody and anti-dsDNA.[27]It should be highlighted that some patients with rheumatoid arthritis may already have underlying lupus characteristics, previously the anti-TNF alpha administration. Topical steroids, antimalarial medications, and maybe switching to a different TNF

alpha inhibitor are the mainstays of TAILS treatment. Although rare, it has been reported that Ustekinumab can induce lupus or can exacerbate lupus symptoms.[30,31]

The Department of Dermatology from University Tsu in Japan showed a case of a 28-year-old woman, diagnosed with RA who has been treated with etanercept for three months and accused generalized itching. Laboratory tests determined an increased number of eosinophils and clinical examination showed skin changes suggestive for urticaria. Because etanercept was efficient in treating the patient's RA and the urticaria was not severe, the prescription of TNF alpha inhibitor was continued. An antihistamine drug was given to the patient, which improved the symptoms of urticaria. However, the general itching persisted with erythema with scales seen on the back. Adding topical corticosteroid was effective.[32]

Also, the University of Medicine in Porto did a retrospective analysis including 290 patients with spondyloarthritis and psoriatic arthritis who received anti-TNF-α agents. Before starting the biologic medication, patients with positive ANA results were excluded. The results showed high serology conversion rates- positive ANA in 67.9% of patients with spondyloarthritis and 58.6% from those with psoriatic arthritis. Three patients with spondyloarthritis and one patient with psoriatic arthritis developed DILE caused by anti TNF alpha therapy. Two patients experienced peripheral arthritis (new onset or abrupt deterioration), one developed serositis, two suffered from constitutional symptoms, one had subnephrotic proteinuria, two lymphopenia and in one case it has been detected hypocomplementemia. The four patients received specialized care- oral corticosteroids- and they fully recovered.[33,34]

Another case, from Dermatology Institute in Rio de Janeiro, presents a 54-year-old male patient who was using hydralazine for four years, suffering from erythematous, scaly and edematous papules on the trunk, back, upper limbs and sun-exposed areas for the last two months. ANA and anti-histone tests were positive, and the histopathology exam confirmed the diagnosis of lupus erythematosus. Prednisone was prescribed in place of hydralazine and after four weeks, skin lesions quickly improved and the symptoms disappeared.[35]

A 50-year-old woman suffering from seronegative rheumatoid arthritis (RA) presented to the rheumatology department at Pt. B.D. Sharma, PGIMS, Rohtak with two months history of pruritic and erythematous rash on her arms, neck, and anterior chest and with history of alopecia. The clinical examination showed erythematous lesions on the dorsal aspect of forearms extending to the outer aspect of her arms and involving the upper part of the exposed areas of the anterior chest and neck. Her RA disease was fully controlled under leflunomide. Leflunomide was found to have a potential in inducing SLE or DILE. Serology tests showed positive results for ANA, anti-histone antibodies and for anti-SSA antibodies, but negative results for anti-dsDNA and anti-SSB antibodies, and as well normal complement levels. Skin biopsy was performed and the histopathological report showed abnormalities compatible with SLE. Leflunomide was stopped and the patient started the topical corticosteroids and methotrexate 15 mg/week and the symptoms improved. The patient may suffer from SLE caused by Leflunomide, according to the clinical profile, pharmacological history, serology, and histology together with the patient's reaction to drug withdrawal.[10]

Other data come from Departmen of Medicine, Government Medical College and Sir Takhtsinhji General Hospital, India were a 14-year-old female patient accused vomiting, fatigue and fever for 15 days. After the brain MRI was performed and revealed tuberculous meningitis, antituberculosis treatment was recommended – isoniazid. The patient was previously treated for tuberculosis, but the treatment was stopped after three months due to an adverse reaction: skin sores on the head and both limbs. After five days, the patient started to experience fever, joint discomfort, muscular weakness, convulsions, skin lesions and oral ulcers. ANA profile was positive and the patient was send to the pulmonary and dermatology departments were it has been recommended to stop isoniazid for 15 days and it was prescribed fluconazole 150 mg every 12 hours orally, clotrimazole and topical corticosteroids.[36,37,38]

In conclusion, cutaneous changes are a common adverse effect in patients using TNF-alpha inhibitors. These changes are typically minor and do not warrant therapy interruption. However, significant skin changes such as neoplasms, infections, and immune-mediated reactions are a sign that the therapy should be stopped and an alternative biologic should be used. Interdisciplinary care of cutaneous adverse events that arise during treatment with TNF-alpha inhibitors is essential.

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