

## CASE REPORT

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# Paradoxical Side Effect Related With Anti-Tumor Necrosis Factor Alpha Treatment

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### ABSTRACT

**Introduction:** Anti-tumor necrosis factor (anti-TNF) treatments are effective in controlling disease activity in many immune-mediated diseases such as psoriasis and ankylosing spondylitis (AS). Although side effects such as infection and skin reactions are predictable in anti-TNF treatment; susceptibility to psoriasis is considered as a paradoxical side effect. **Case report:** We report a case of forty-year-old male patient with 7 years of AS was taking anti-TNF therapy. He admitted our clinic with widespread guttate sized round, crusty rashes at feet, legs and elbows. In pathological examination of lesions; focal parakeratosis, mild acanthosis, capillary proliferation in the papillary dermis and focal extravasated erythrocytes were observed. He was diagnosed as anti-TNF induced guttate psoriasis. Although there is no definite treatment option, topical treatments, interrupting drug treatment or adding a disease-modifying agent for psoriasis are recommended. In this case report, we aimed to share our clinical approach to the paradoxical psoriasis manifestation which developed after two different anti-TNF treatments in a patient with AS.

**Keywords:** Anti-tumor necrosis factor, paradoxical, psoriasis, side effect.

## 1. INTRODUCTION

Tumor necrosis factor (TNF) alpha is a proinflammatory cytokine which plays a key role in inflammatory response (1). It has been shown that anti-TNF alpha treatments are effective in various immune-mediated diseases such as ankylosing spondylitis (AS), rheumatoid arthritis (RA), psoriasis and inflammatory bowel diseases (IBD) and in controlling disease activity (2). Although these treatments are evaluated as relatively safer, increased risk for infection and malignancy due to these treatments have been reported. Skin lesions that develop along with drug use are numerous. Drug eruptions, vasculitis, skin infections, maculopapular rash, lupus erythematosus, non-melanoma skin cancers and even psoriasis are some of these (3-6). Side effects of these treatments such as skin reactions and increased risk for infection are predictable, however, predisposing of these treatments to psoriasis for which they are used in treatment is considered to be a paradoxical phenomenon (2, 7).

In the literature, there are many cases of psoriasis which develops due to anti-TNF treatment, however there is no consensus on the pathophysiological mechanism and

treatment approach. Stopping using a biological agent, changing of the drug and topical steroid use can be included among treatment options (2, 4). In this case report, we aimed to share our clinical approach to the paradoxical psoriasis manifestation which developed after two different anti-TNF treatments in a patient with AS.

## 2. CASE REPORT

Forty year-old male patient diagnosed with AS with axial involvement admitted to our rheumatology diseases follow-up outpatient clinic with round, crusted, about 1-cm diameter lesions on feet, legs and elbows (Figure 1). Lesions had manifested a week ago. He did not mention about peripheral arthritis, aphthous ulcer, abdominal pain, recent infection, fever or weight loss. He had no nail finding. Morning stiffness was lasting for approximately 10 minutes. Disease activity index (BASDAI) was calculated as 2.5. In his medical history, there was nothing specific other than 15 packs/year smoking. He had no history for any drug use for any systemic disease. The patient was under treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and Golimumab

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50 mg/month. Laboratory results were within normal limits. In radiological evaluation, sacroiliitis and degenerative changes on lumbar vertebral discs were found. Patient was consulted to Department of Dermatology. Biopsy was performed from skin lesions. In pathological examination, mild capillary proliferation and focal extravasated erythrocytes were observed beneath the epidermis exhibiting focal parakeratosis and mild acanthosis. These histopathological findings were supportive for both phthiriasis rosea and psoriasis, however, its definite differentiation from guttate psoriasis were performed with clinical findings. The patient hadn't used any other suspicious drugs, didn't have a family history of psoriasis or manifestations of infection before the lesions appeared. Also, his clinical and radiological findings were not compatible with psoriatic arthritis with axial involvement. Clinical status of the patient was ensured to be guttate psoriasis which developed due to anti-TNF use. Topical steroid treatment was started and anti-TNF treatment was stopped. During his follow-up, rashes of the patient were gradually lost within 2 weeks. However, after 2 months, the patient was re-admitted to our outpatient clinic with complaints of back-hip pain and morning stiffness. He had difficulties in fulfilling his daily routines due to exhaustion and pains. There was no sign of infection but it seemed to be active on laboratory tests. BASDAI calculated as 5. Anti-TNF treatment was changed and decided to be restarted and his treatment was organized as Etanercept 50 mg/week. After 10 days from the initial dose of treatment with Etanercept, complaint of rash similar to previous lesions on his ankles recurred. Topical steroid was applied but lesions persisted. Because of the fact that lesions began to extend, treatment with Etanercept was stopped after 4<sup>th</sup> dose. All lesions were regressed within a week. The patient re-admitted to our outpatient clinic after 1 month with active disease presentation. At this time, treatment with Adalimumab 40 mg/2 weeks and oral methotrexate 10 mg/week was planned. The patient's informed consent was obtained. Clinical follow-up of the patient has been ongoing with lower disease activity and without rashes for last 5 months.

### 3. DISCUSSION

Psoriatic rashes may be encountered in all patients using anti-TNF and against almost all anti-TNFs. Iborra et al. (2) reported the prevalence of this side effect as between 1.5% and 5% in patients who were using anti-TNF due to IBD. Incidence obtained from of English and Spanish rheumatology databases was reported to be 1-3/1000 patients among patients with rheumatoid arthritis who were using anti-TNF (6).

Factors thought to cause development and getting worse of psoriasis are trauma, physical and emotional stress, arid and cold climate, alcohol abuse and drug use. It has been suggested that some drugs such as anti-malarial drugs, NSAIDs and beta-blockers are also effective in triggering of the disease (7). Histologically, in psoriatic lesions; increased proliferation of keratinocytes, speed up in cell cycle and keratin overexpression which is not



Figure 1. Rashes of the patient on anterior surface of tibia and on ankle

observed under physiological conditions are observed (5). Various mechanisms have been suggested in order to explain pathophysiology of lesions which develop due to anti-TNF. The most commonly described hypothesis is the one including IFN-alpha. TNF-alpha inhibits synthesis of plasmacytoid dendritic cells which secrete IFN-alpha. It has been thought that TNF-alpha blockade causes psoriatic lesions by causing IFN-alpha overexpression (8). Increased IFN-alpha expression has been detected in psoriatic lesions of the patients under treatment with TNF-alpha (5).

In most cases, rashes develop within first month of treatment but this duration may range from shortly after from initial administration of the drug and following 7 years. In families of majority of the patients, no history of psoriasis exists. Approximately half of the reported cases were treated with infliximab (1, 2). There are also some patients reported which experienced the same side effect against different anti-TNFs, as it is in our patient. In these patients, type of psoriasis developed against the 2<sup>nd</sup> anti-TNF agent was as same as the initial psoriatic rash. However, in patients who have new psoriatic rashes while being under treatment for psoriasis, rashes are in different localizations than previous lesions and have different morphologies. These findings support that psoriasis which develop during treatment with anti-TNF is not an aggravation of pre-existing psoriasis and is a de-novo psoriasis (8).

Some authors has reported that these lesions may not be psoriasis, but a drug-induced hypersensitivity reaction (4). Psoriasis-like skin lesions in paradoxical cases from which biopsies are taken are histologically differ-

ent from pustular skin lesions due to drug eruptions. It exhibits typical psoriasis findings such as epidermal hyperplasia, parakeratosis, epidermal lymphocytic infiltrates, dilated capillaries and intraepidermal pustulosis. In immunochemical analysis of the lesions, T and B cells, macrophages, Interferon mRNA, TNF mRNA and vascular endothelial growth factor levels were indistinguishable from idiopathic psoriasis (9).

The most commonly used treatment is steroids (8). It is recommended that treatment with anti-TNF should be continued for mild cases which respond treatment well and have mild skin lesions. However, in case of severe (involving more than 5% of body surface) lesions, taking a break in using drugs is possible if lesions are intolerable and patient agrees. Although literature data lays drug change as a condition, changing for another biological agent depending on the case may come up (2). In more severe or acute systemic reactions, addition of cyclosporine or methotrexate may be beneficial (10). In compilation of Cullen et al. (6) published in 2011 which included patients with inflammatory bowel disease who developed psoriasis during anti-TNF use, approximately 41% of 148 cases responded to topical treatment, managed to continue the drug they used and recurrence was observed in 52% of them, which were followed-up under an alternative anti-TNF. Steroid preparations were the most commonly used topical therapy. In literature compilation of Jayou et al. (8) published in 2012 which included 241 patients which were using anti-TNF due to different rheumatological indications, they reported that more than half of the patients responded to symptomatic treatment and treatment was required to be stopped in about half of the patients.

Paradoxical psoriasis is a phenomenon which is likely to develop during anti-TNF use and has an unascertained pathophysiology. In differential diagnosis, detailed anamnesis, exclusion of infections and histopathological evaluation of lesions are recommended. Topical treatments, depending on the case, taking a break in using the drug, changing to another biological agent or addition of an additional disease modifying agent for psoriasis can be considered.

- **Ethics Committee Approval:** None (case report)
- **Informed Consent:** Written informed consent was obtained from the patient.

- **Author contributions:** Concept – A.A., E.G., A.T.; Design–A.A., E.G., A.T.; Supervision–A.A., E.G., A.T.; Resource–A.A., E.G., A.T.; Materials–A.A., E.G., Ü.D.; Data Collection and/or Processing–A.A., E.G., Ü.D.; Analysis and /or Interpretation–A.A., E.G., Ü.D.; Literature Search–A.A., E.G., A.T.; Writing–A.A., E.G., A.T.; Critical Reviews–A.A., E.G., A.T., Ü.D.
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