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Case Report

Is there a paradoxical side effect? Is it a case of inefficiency? Peripheral ulcerative keratitis in a patient with rheumatoid arthritis in remission treated with tocilizumab

Yasemin Tombak, Methiye Kubra Sezer, Ajda Bal, Emel Eksioglu, Deniz Dulgeroglu

Department of Physical Therapy and Rehabilitation, University of Health Sciences, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Tocilizumab is a monoclonal antibody to interleukin-6 that has recently been used in rheumatoid arthritis (RA) treatment. Treatment with tocilizumab may be associated with paradoxical manifestations that are poorly understood. Patients that developed peripheral ulcerative keratitis while on tocilizumab treatment were studied in a case series. It was discovered that this could be a paradoxical side effect or ineffectiveness. Herein, we present a patient with seropositive RA who was followed for 22 years, using tocilizumab for seven years, and who developed peripheral ulcerative keratitis while in remission. Consequently, even in remission, extra-articular involvement can occur in RA patients, and medication-related paradoxical side effects can arise.

Keywords: Peripheral ulcerative keratitis, rheumatoid arthritis, tocilizumab.

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis characterized by symmetrical involvement of small joints, and extra-articular findings may also be present. Keratoconjunctivitis sicca is the most common extra-articular ocular finding in RA.[1] Episcleritis, scleritis, retinal vasculitis, peripheral ulcerative keratitis (PUK), and interstitial keratitis are some of the other conditions that might appear.[2] Among systemic diseases, RA is one of the most common noninfectious causes of PUK.[3]

Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin $G1_k$ subclass directed against soluble and membrane-bound interleukin (IL)-6 receptors that has recently been employed in the treatment of RA.[4] Patients who acquired PUK while using tocilizumab were studied in a case series, and it was found that this could be a paradoxical side effect or ineffectiveness.[5] Due to the incomplete understanding of the paradoxical effects of other biologics, including tocilizumab, we present a patient with seropositive RA who was followed for 22 years, using tocilizumab for seven years, and who developed PUK while in remission.

CASE REPORT

A 64-year-old female patient with known diabetes mellitus, who was followed for 22 years with the diagnosis of seropositive RA, presented with complaints of redness, stinging, and pain in her eye to her follow-up. The patient had previously used methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept, but they were discontinued due to inefficacy or adverse effects. The patient initially began 560 mg/month intravenous tocilizumab infusion seven years ago and later continued with 162 mg/week subcutaneous tocilizumab treatment. There was no sore and swollen joint during the musculoskeletal system evaluation, and morning stiffness was not mentioned. Patient global assessment

Corresponding author: Yasemin Tombak, MD. SBÜ, Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, 06110 Altındağ, Ankara, Türkiye.
E-mail: yasemintombak@hotmail.com

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(0-10 mm) was 10. In laboratory examination, the erythrocyte sedimentation rate was 5 mm/sec, and C-reactive protein was 0.48 mg/L. Hemogram and biochemical testing came out normal. Disease activity index-28 was calculated as 1.27, and the patient was considered in remission. The patient was consulted with the ophthalmology clinic and diagnosed with PUK, and systemic 32 mg/g corticosteroid treatment was given. Tocilizumab treatment was continued. The patient's ocular problems were gone at the one-month follow-up, and her RA remission status remained unchanged. The six-month follow-up revealed no new eye issues, and there was no PUK relapse.

DISCUSSION

Cohen et al.[5] introduced and reported the only case series in the literature to develop PUK as a paradoxical side effect of tocilizumab. In our case, the patient also developed PUK while on tocilizumab treatment, and she was in remission at the time. It is not exactly known whether PUK occurs in patients as a paradoxical side effect or due to the ineffectiveness of the drug.

Peripheral ulcerative keratitis is a disease characterized by ulceration or thinning of the peripheral part of the cornea. The peripheral cornea is the region of the cornea closest to the conjunctiva, which contains immune-stimulating mediators. Peripheral ulcerative keratitis can be seen together with diseases based on immune etiopathogenesis such as RA, granulomatosis with polyangiitis, systemic lupus erythematosus, polyarteritis nodosa, and ulcerative colitis.[6] Among systemic disorders, RA and Sjögren's syndrome are the most common causes of noninfectious PUK.[3]

In one study, PUK was linked to RA in 34% of patients diagnosed with PUK.[7] The most common disease associated with PUK was found to be RA.[7] It is more common in individuals with long-term RA and in those who have both anti-CCP (anti-cyclic citrullinated peptide antibody) and RF (rheumatoid factor) positive serology.[3] The condition had been present for 22 years in our patient, and both RF and anti-CCP tests came out positive, which was consistent with the literature.

In RA, an imbalance of proinflammatory and anti-inflammatory cytokines creates a microenvironment that promotes collagen breakdown, resulting in keratitis, which extends from the perilimbal cornea to the central cornea and leads to melting and perforations in the cornea.[8,9] According to this information, immunosuppressive medicines such as anti-TNF (tumor necrosis factor) and IL-6 blockers may help to prevent the development of keratitis. Many articles include biological medicines as useful treatments for the treatment of PUK.

Paradoxical reactions during treatment with a biological agent can be characterized as the emergence or exacerbation of a pathological condition that usually responds to this class of drugs while treating a patient for another condition that is generally under control. Paradoxical reactions have been documented in patients treated with anti-TNF-α agents and have been described as isolated case reports or case series. In addition to the efficacy and side effects of biological drugs used in RA, some paradoxical side effects such as palmoplantar pustular reactions, psoriasis, hydradenitis, inflammatory bowel disease, uveitis, pyoderma gangrenosum, granulomatous reactions, and vasculitis may also occur.[10]

Tocilizumab, a monoclonal antibody that inhibits IL-6, plays a crucial role in the regulation of immune cell proliferation and differentiation.[11] Urticaria, abdominal pain, mouth ulceration, gastritis, gastrointestinal system perforations, neutropenia, and, the most prevalent, infection (subcutaneous infections are the most reported) are all recognized side effects of tocilizumab.[12] Tocilizumab, like numerous biological agents, can have paradoxical side effects. Paradoxical ophthalmic symptoms associated with tocilizumab have been rarely reported. These include cases of anterior uveitis, scleritis, and PUK. Interleukin-6 has a crucial function in wound healing, tissue repair, and corneal epithelial renewal. It is suspected that blocking these actions causes paradoxical ophthalmic adverse effects.[13] Peripheral ulcerative keratitis occurred during a diagnosis of the disease in a patient with RA described by Huang et al.,[14] and both RA and PUK went into remission after starting tocilizumab treatment.

Cohen et al.[5] presented a case series of four PUK cases in 2021, and all of the patients had RA and were using tocilizumab. PUC developed in two of these four patients after disease remission was achieved with tocilizumab; in the other two cases, PUK developed while the disease was active under tocilizumab treatment. In another case who developed PUK and whose tocilizumab infusions were interrupted, tocilizumab treatment was

terminated due to PUK relapse twice.[15] Paradoxical eye inflammation may occur under IL-6 blockade in inflammatory arthritis.[15]

In our case, PUK emerged while the patient was in remission using tocilizumab, prompting us to consider the likelihood of a paradoxical side effect. However, the improvement of ocular complaints and findings with corticosteroid treatment without discontinuation of tocilizumab brought to mind the possibility of ocular involvement due to RA.

In conclusion, it should be kept in mind that extra-articular involvement may occur in patients with RA even when the disease is in remission, and paradoxical side effects may develop due to the drugs they use. More case reports are needed to confirm that PUK may develop as a paradoxical side effect due to tocilizumab.

Patient Consent for Publication: A written informed consent was obtained from patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: Incidence trends and risk factors over 46 years. Ann Rheum Dis 2003;62:722-7.
2. Zlatanović G, Veselinović D, Cekić S, Zivković M, Dorđević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci 2010;10:323-7.
3. Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol 2014;10:108-16.
4. Assessment Report for RoActemra. European Medicines Agency; 2009; London, United Kingdom. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000955/WC500054888.pdf
5. Cohen F, Gabison EE, Stéphan S, Belkhir R, Nocturne G, Best AL, et al. Peripheral ulcerative keratitis in rheumatoid arthritis patients taking tocilizumab: Paradoxical manifestation or insufficient efficacy? Rheumatology (Oxford) 2021;60:5413-8.
6. Pelit A, Aydın Akova Y, Dursun D. Periferik ülseratif keratitler. T Oft Gaz 2004;33:84-91.
7. Tauber J, Sainz de la Maza M, Hoang-Xuan T, Foster CS. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea 1990;9:66-73.
8. Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: A case series. Rheumatology (Oxford) 1999;38:1245-8.
9. Prada J, Noelle B, Baatz H, Hartmann C, Pleyer U. Tumour necrosis factor alpha and interleukin 6 gene expression in keratocytes from patients with rheumatoid corneal ulcerations. Br J Ophthalmol 2003;87:548-50.
10. Puig L. Paradoxical reactions: Anti-tumor necrosis factor alpha agents, ustekinumab, secukinumab, ixekizumab, and others. Curr Probl Dermatol 2018;53:49-63.
11. Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: Designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 2018;17:395-412.
12. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (Actemra). Hum Vaccin Immunother 2017;13:1972-88.
13. Brahe CH, Dehlendorff C, Østergaard M, Johansen JS, Ørnbjerg LM, Hørslev-Petersen K, et al. Circulating serum interleukin-6, serum chitinase-3-like protein-1, and plasma vascular endothelial growth factor are not predictive for remission and radiographic progression in patients with early rheumatoid arthritis: Post-hoc explorative and validation studies based on the CIMESTRA and OPERA trials. Scand J Rheumatol 2018;47:259-69.
14. Huang J, Chen Z, Zhao L, Cheng Y, Gao M, Huang C, et al. Tocilizumab in rheumatoid arthritis-associated peripheral ulcerative keratitis: A 1-year follow-up case report. Rheumatol & Autoimmun 2022;2:45-50.
15. Wendling D, Dernis E, Prati C, Frisch E, Delbosc B. Onset of inflammatory eye disease under tocilizumab treatment for rheumatologic conditions: A paradoxical effect? J Rheumatol 2011;38:2284.