Etanercept induced erectile dysfunction

Ozge Sonmez[1]*, Serdal Ugurlu[2]

European Journal of Medical Case Reports
Volume 8(8):158–160
DOI: 10.24911/ejmcr.173-1702315757

ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial spine. Etanercept is a Tumor necrosis factor-alpha inhibitor (anti-TNF) that is widely used in the treatment of AS. The most common side effects of etanercept are infection, rash, and injection site reaction. Here, we reported an adverse event probably associated with etanercept.

Case Presentation: A 30-year-old male patient with AS initiated etanercept due to uncontrolled back pain despite adequate doses of non-steroidal anti-inflammatory drugs. He developed erectile dysfunction (ED) within 1 month of etanercept treatment. ED disappeared after switching to secukinumab.

Conclusion: There is limited data on the potential effects of anti-TNF on sexual function. ED might be a rare side effect of etanercept that resolves upon discontinuation of the drug. Secukinumab might be considered as an option in case of etanercept-induced ED. Even though ED is not a life-threatening side effect, switching medications could significantly improve patients' quality of life.

Keywords: Etanercept, tumor necrosis factor-alpha inhibitor, erectile dysfunction, ankylosing spondylitis, case report.

Received: 11 December 2023 **Accepted:** 12 May 2024 **Type of Article:** CASE REPORT **Specialty:** Internal Medicine

Correspondence to: Ozge Sonmez
*Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey.
Full list of author information is available at the end of the article.

Background

Axial spondylarthritis (SpA) is a chronic inflammatory disease that predominantly effect spine. The terms Axial SpA encompasses both a non-radiographic form and a radiographic form which is also termed ankylosing spondylitis (AS). Patients generally presented with chronic back pain and morning stiffness. Peripheral arthritis, enthesitis, and dactylitis could also occur in the course of the disease. AS is more prevalent among men and it typically begins the third decade of life [1].

The main aims of treatment are relieving symptoms, and maintaining spinal flexibility and joint mobility. Non-steroidal anti-inflammatory drugs (NSAID) are the first-line drugs of AS treatment. Tumor necrosis factor (TNF)-alpha inhibitors (Anti-TNF) including etanercept are other options for patients with high disease activity index, despite conventional treatment. Secukinumab (anti-interleukin-17A monoclonal antibody) is also an efficient and safe treatment option [2].

Sexual health is important for quality of life. Thereby, rheumatologists should be aware of possible sexual dysfunction due to rheumatological disease. Previously, it has been shown that sexual functioning might be impaired in patients with AS [3]. The most frequent side effects of etanercept are injection side reactions, rash, abnormal hepatic function, and infection [4]. However, there might be some post-marketing side effects that clinicians could experience difficulties in recognizing and managing.

Here, we reported a patient with AS who suffered from ED under etanercept treatment.

Case Report

A 30-year-old male patient with an unremarkable medical history presented with increasing back pain persistent for 5 months. He was complaining of insidious onset pain with morning stiffness lasting about 10 minutes. The pain was worse at night and early in the morning and it improved with exercise. He did not have peripheral arthralgia, psoriasis, diarrhea, or uveitis. He had right-sided-enthesitis. There was no preceding history of trauma to the back or infection. He did not have a family history of rheumatological disease. He was sexually active and he had a regular partner. Laboratory values were as follows: white blood count 9,600/µl, serum c-reactive protein 9,1 mg/dl (reference range was < 5 mg/dl), and erythrocyte sedimentation rate of 4 mm in the first hour. Rheumatoid factor, anti-cyclic citrullinated peptide antibody, and antinuclear antibodies were negative. The human leukocyte

antigen (HLA) B51 was positive but HLA B27 was negative. Sacroiliac joint X-ray film demonstrated sclerosis in the right sacroiliac joint. Sacroiliac magnetic resonance imaging revealed grade 3 sacroiliitis. NSAID provided adequate pain relief. A diagnosis of AS was made. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 3. Exercise was recommended. Despite a continuous regimen of two different NSAIDs for 10 months, the patient still had back pain. Etanercept was administered in combination with NSAID. One month later, under etanercept treatment, he presented with erectile dysfunction (ED) despite decreased back pain. He referred to urology. Physical examination, urinalysis, spermiogram, and urinary ultrasound did not reveal any pathology. His testosterone level was 600 ng/dl (reference range 280–800). Luteinizing hormone (LH) and Follicle-stimulating hormone levels were 6.03 ng/dl and 2.23 ng/dl respectively. He did not receive any specific medication including sildenafil for ED. He did not have any psychological stressor that might possibly cause ED. Etanercept was switched to secukinumab. ED was resolved within 1 week upon switching to secukinumab. He is still on the secukinumab treatment and he has not experienced ED during the 8-months follow-up.

Discussion

We reported a young adult male patient with AS who suffered from ED. Sexual dysfunction related to AS might be overlooked. Higher levels of ED among AS than the normal population were reported in the literature. Higher disease activity, longer disease duration, limited joint mobility, depression, and anxiety might be associated with sexual dysfunction in patients with AS. [5,6]. Disease activity might contribute in some extent to the ED in our patient but he did not have any depressive symptoms or anxiety which might be an indicator of another underlying cause besides disease activity. There is a scarce number of studies regarding the potential effect of anti-TNF therapy on ED [7]. In animal models, Carneiro et al. [8] displayed that TNF-α infusion in mice resulted in an increased contractile response, decreased non-adrenergic non-cholinergic nerve-mediated relaxation related to decreased endothelial nitric oxide synthase (eNOS), and neuronal nitric oxide synthase (nNOS) expression which could trigger ED [8]. Demirtaş Sahin et al. [9] conducted a study on rats and their findings demonstrated inhibition of TNF with etanercept increases the eNOS and nNOS expression of cavernosal tissue and elevated testosterone levels. Thus, they concluded that TNF-antagonism might be used in the treatment of ED [9]. However, rat and human discrepancy should be taken into consideration in real-life practice. In a study from Korea, erectile function was assessed by a self-reported questionnaire, before and after anti-TNF treatment in AS patients. Erectile function significantly improved after treatment with anti-TNF in addition to diminishing disease activity [10]. Inflammation is related to ED [11]. Therefore, sexual dysfunction in these patients might improve due to the reduced inflammation and disease activity after treatment. On the contrary, Abhishek et al. [12] reported. One of their rheumatoid arthritis patients who experienced ED on etanercept treatment [12]. His symptoms improved after cessation of the drug. Moreover, Hidalgo-Rios et al. [13] reported a patient with Crohn's disease suffered from ED under both adalimumab and sertolizumab. ED resolved after switching to Ustekinumab (anti-interleukin 12 and 23 biologic drug) [13]. ED was resolved after etanercept discontinuation in our patients as well. The mean half-life of etanercept is 102 ± 30 hours [14]. Therefore, we would expect the effect of etanercept to diminish after a week of cessation, as observed in our patient.

There is a dilemma on the potential sexual effects of anti-TNF. Although in animal models, TNF antagonism has promising results as a therapeutic agent for ED; in real life, ED has been reported as a rare side effect of the anti-TNF especially in the early days of the treatment. On the other hand, sexual function might improve after several months of anti-TNF treatment probably due to the reduced disease activity.

Conclusion

We present a case of ED associated with etanercept in a patient with AS, resolved by switching to secukinumab. Therefore, we would like to highlight that ED might be a rare side effect of etanercept. Switching to an alternative agent might improve quality of life of patients.

What is new?

The authors reported a young male patient with AS who presented with ED under etanercept treatment. Even a prominent portion of AS patients experience ED, there is not enough data for potential effects of TNF-α inhibitors on ED. Additionally, to the authors' knowledge, this is the first case reporting etanercept induced ED in an AS patient.

List of Abbreviations

Anti-TNF	Tumor necrosis factor (TNF)-alpha inhibitor
AS	Ankylosing spondylitis
BASDAI	The Bath Ankylosing Spondylitis Disease Activity Index
ED	erectile dysfunction
FSH	Follicle-stimulating hormone
HLA	human leukocyte antigens
LH	Luteinizing hormone
eNOS	endothelial nitric oxide synthase
nNOS	neuronal nitric oxide synthase
NSAID	Non-steroidal anti-inflammatory drug
SpA	Spondylarthritis

Declarations

Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

Funding
None.

Consent for publication
Due permission was obtained from the patient to publish the case and the accompanying images.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Author details
Ozge Sonmez[1], Serdal Ugurlu[2]
1. Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey
2. Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey

References
1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017 Jul;390(10089):73–84. https://doi.org/10.1016/S0140-6736(16)31591-4
2. Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019 Aug;7(1):22. https://doi.org/10.1038/s41413-019-0057-8
3. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: a systematic review. Semin Arthritis Rheum. 2020 Jun;50(3):557–73. https://doi.org/10.1016/j.semarthrit.2020.02.002
4. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. Mod Rheumatol. 2011 Aug;21(4):343–51. https://doi.org/10.1007/s10165-010-0406-3
5. Dincer U, Cakar E, Kiralp MZ, Dursun H. Assessment of sexual dysfunction in male patients with Ankylosing spondylitis. Rheumatol Int. 2007 Apr;27(6):561–6. https://doi.org/10.1007/s00296-006-0248-7
6. Dhakad U, Singh BP, Das SK, Wakhlu A, Kumar P, Srivastava D, et al. Sexual dysfunctions and lower urinary tract symptoms in ankylosing spondylitis. Int J Rheum Dis. 2015 Nov;18(8):866–72. https://doi.org/10.1111/1756-185X.12683
7. Cooley LF, Wren J, Keeter MK, Lam I, Bennett N, Brannigan RE. Anti-TNF agents and potential effects on male fertility: are men being counseled? BMC Urol. 2020 Jul;20(1):111. https://doi.org/10.1186/s12894-020-00658-7
8. Carneiro FS, Zemse S, Giachini FR, Carneiro ZN, Lima VV, Webb RC, et al. TNF-alpha infusion impairs corpora cavernosa reactivity. J Sex Med. 2009 Mar;6 Suppl 3(Suppl 3):311–9. https://doi.org/10.1111/j.1743-6109.2008.01189.x
9. Demirtaş Şahin T, Yazir Y, Utkan T, Gacar G, Furat Rençber S, Gocmez SS. TNF-α antagonism with etanercept enhances penile NOS expression, cavernosal reactivity, and testosterone levels in aged rats. Can J Physiol Pharmacol. 2018 Feb;96(2):200–7. https://doi.org/10.1139/cjpp-2017-0113
10. Oh JS, Heo HM, Kim YG, Lee SG, Lee CK, Yoo B. The effect of anti-tumor necrosis factor agents on sexual dysfunction in male patients with ankylosing spondylitis: a pilot study. Int J Impot Res. 2009;21(6):372–5. https://doi.org/10.1038/ijir.2009.44
11. Kaya-Sezginer E, Gur S. The inflammation network in the pathogenesis of erectile dysfunction: attractive potential therapeutic targets. Curr Pharm Des. 2020;26(32):3955–72. https://doi.org/10.2174/1381612826666200424161018
12. Abhishek A, Badcock L. Erectile dysfunction in rheumatoid arthritis patient on etanercept. Rheumatology. 2008;47:133.
13. Hidalgo-Rios S, Alonso-Moreno M, Iserte JT, Herrera-Justiniano JM. A rare case of drug-induced erectile dysfunction with adalimumab and certolizumab solved after switch to ustekinumab in a Crohn's disease patient. Curr Drug Saf. 2023;18(3):374–8. https://doi.org/10.2174/1574886317666220429111341
14. Medical Economics Company Inc. Prescribing information: Enbrel®. In Physicians' Desk Reference®. Montvale, NJ: 2002. 3504–7 pp.

Summary of case

1	Patient (gender, age)	20 years, male
2	Final diagnosis	Etanercept associated erectile dysfunction
3	Symptoms	Erectile dysfunction after etanercept administration
4	Medications and clinical procedure	Switched to the secukinumab
5	Result	Erectile dysfunction was resolved
6	Specialty	Internal medicine