

CASE REPORT

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Angioedema in a Patient with Ankylosing Spondylitis Treated with Etanercept

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ABSTRACT Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown pathogenesis. Nonsteroidal antiinflammatory and biologic drugs are used in its treatment. A 38 year old male patient diagnosed with AS was admitted to the rheumatology outpatient clinic due to swelling in both upper eyelids and around the eyes recurring for 1 month. He was at the 5th month of etanercept treatment. With the current clinic, etanercept-induced angioedema was primarily considered in the patient. Angioedema resolved spontaneously 2 days after discontinuation of the drug. In conclusion, although angioedema associated with etanercept use may develop rarely, it can lead to life-threatening results in some cases. From this point of view, it is important for clinicians to closely observe patients using etanercept and to inform the patient about side effects.

Keywords: Ankylosing spondylitis; etanercept; angioedema

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown pathogenesis. Genetic and environmental factors play a role in its etiology. AS affects 0.5% of the population. It is more common in men than women. AS causes inflammation of the sacroiliac joint and spine, as well as peripheral arthritis, enthesitis, and dactylitis. In its treatment, methotrexate and salazoprine are used in peripheral arthritis in addition to nonsteroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor (TNF) alpha inhibitors and interleukin 17A monoclonal antibodies.^{1,2} It has been found that the proinflammatory cytokine TNF is associated with inflammation, bone erosion and new bone formation, which causes structural damage to the joints in AS. Therefore, the use of anti-TNF alpha inhibitors has been approved in the treatment of AS to reduce inflammation and prevent new bone formation.³ Etanercept is a recombinant soluble fusion protein of TNF- α Type II receptor and immunoglobulin G that acts as a specific TNF- α antagonist. It binds to circulating and membrane-bound TNF- α and blocks its bi-

ological activity.⁴ Etanercept-induced angioedema cases have been reported in the literature in rheumatoid arthritis and adult-onset Still's disease.^{5,6} However, a case of etanercept-induced angioedema in AS patient was not found in our literature review.

We aimed to present a case of AS who developed periorbital angioedema following the use of etanercept.

CASE REPORT

A 38 year old male patient was admitted to the rheumatology outpatient clinic in August 2022 with recurrent swelling of both upper eyelids and around the eyes for 1 month. When he was first diagnosed in November 2021, the patient had inflammatory back and neck pain for 10 years, and limitation in joint movements. In laboratory tests, C-reactive protein (CRP) 35 mg/dL sedimentation 20 mm/hour and human leukocyte antigen B27 positive. In direct sacroiliac joint radiograph showed ankylosis on the left and joint narrowing and sclerosis on the right (Figure 1). The Bath Ankylos-

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FIGURE 1: Bilateral sacroiliac joint narrowing, sclerosis and ankylosis.

ing Spondylitis Disease Activity Index (BASDAI) score was 8.1. His father and sister also had AS in his family history. He had no history of psoriasis or inflammatory disease. After the patient was diagnosed with AS, indomethacin 4×25 mg tablet/day and acemethacin 1×90 mg tablet/day were started at one month intervals. However, there was no clinical or laboratory response to the treatment. Both NSAIDs were discontinued and etanercept was started at 50 mg/week subcutaneously. At the follow-up 3 months later, his BASDAI score decreased to 3.4. No additional complications were observed. Response to etanercept treatment was obtained and the patient's treatment was continued. In the 5th month of the treatment, swelling and pain occurred around the eyes, which started 6-8 hours after etanercept subcutaneous administration and resolved spontaneously 2 days later. The patient photographed the newly developed swelling in his eyes and applied to the ophthalmology unit with the present complaints (Figure 2). No

pathology was detected in the ophthalmological examination. Later, the patient who applied to our outpatient clinic stated that from the 5th month of the treatment, every week after the medication, there was sometimes unilateral, sometimes bilateral swelling in the eyes and spontaneously resolved. He did not have any complaints in the first 5 months of his treatment with etanercept. There was no history of taking any medication (NSAID, angioconverting enzyme inhibitor, etc.) and a different food on the days when the eyelids were swollen. He had no family history of allergies and/or angioedema.

In the physical examination; his blood pressure was 120/70 mmHg, heart rate was 92/min, respiratory rate was 17/min, and fever was 36.3 °C. Peripheral pulses were being taken. There was swelling in both eyes, more prominently on the upper lid around the right eye. The patient stated that there was no itching in his eyes, but there was pain. There was no swelling of the tongue and lips, difficulty in swallowing and shortness of breath. He did not describe vision loss. Cardiovascular system and gastrointestinal system examination were normal.

In laboratory analysis, white blood cell 6350/mm³ N(4000-10000), neutrophil 4010/mm³ N(2000-7000), eosinophil 270/mm³ N(20-500), hemoglobin 15.7 g/dL N(11-16), platelet 252000/mm³, urea 32 mg/dL N(17-43), creatinine 0.85 mg/dL (0.67-1.17), alanine transaminase 16 U/L N(0-50), aspartate transaminase 18 U/L N(0-50), total protein 7.23 g/L N(6.6-8.3), albumin 4.34 g/L N(3.5-5.2), CRP 4 mg/dL N(0-5), erythrocyte sedimentation rate 4 mm/h (N: 0-20), C-1 esterase inhibitor 0.25 g/L N (0.23-0.41), C3 1.204 g/L N(0.8-1.9), C4 0.269 g/L N(0.2-0.6) antinuclear antibody negative,



FIGURE 2: Edema of the right and left eyelids.

rheumatoid factor negative, p antineutrophilic cytoplasmic antibody negative, c antineutrophilic cytoplasmic antibody negative, thyroid-stimulating hormone 1.09 IU/mL N(0.35-5.5), free T4 1.07 ng/dL N(0.89-1.76), free T3 3.97 pg/mL N(2.3-4.2). With the current findings, the patient's newly developed allergy picture was thought to be due to the etanercept he was using, and the drug was interrupted. After discontinuing the drug, his complaints spontaneously regressed within 2 days and did not recur. Patient consent was obtained.

DISCUSSION

Angioedema is a self-resolving clinical condition that causes swelling and edema in the lower layers of the skin and mucosa for several days. It is characterized by a vascular reaction in the mucosal, deep dermal and subcutaneous tissues, with localized increased vascular permeability resulting in tissue swelling in the affected area.⁷ Angioedema is mediated by histamine, bradykinin and mast cell mediators. Angioedema and urticaria due to histamine and mast cells cause a clinical picture together.⁸ Bradykinin-mediated angioedema occurs due to hereditary or acquired causes such as C1 inhibitor deficiency.⁹ Angioedema; drug and food intake, insect bites, environmental allergens, infection, physical stimulation and autoimmune causes. Although the face area is mostly affected, life-threatening symptoms related to edema in the gastrointestinal tract and larynx mucosa can be seen in the clinic.⁸ Our patient also had bilateral recurrent and spontaneously resolved angioedema around the eyes due to etanercept.

Anti-TNF alpha inhibitors such as etanercept have been used in the treatment of AS with the recommendation of 2003 Assessments in Ankylosing Spondylitis Group.¹⁰ It is associated with anti-TNF-related redness, pain, swelling, infusion reactions at

the injection site, cytopenia, hepatotoxicity, infection, demyelizing diseases such as multiple sclerosis, lymphoma, skin reactions, heart failure, and autoimmunity.^{11,12} Although the cause of angioedema due to anti TNF- α inhibitors is not known exactly, it is thought to be related to the change in cellular immunity due to TNF- α blockade. Etanercept is an immunogenic drug. Mild reactions related to etanercept occur in the first months, but their frequency decreases in later applications.¹³ Drug-induced angioedema usually occurs one week after taking the drug.¹⁴ In the literature, angioedema developed in a rheumatoid arthritis patient who used etanercept 4 months later.⁶ Angioedema developed in our patient at the 5th month of treatment.

In conclusion, although angioedema associated with etanercept use may develop rarely, it can lead to life-threatening results in some cases. In this regard, it is important for clinicians to closely monitor patients using etanercept and to inform the patient about side effects. We think that it is necessary to increase the awareness of clinicians and to be more careful in terms of drug-related side effects in encountering such cases.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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