OLGU SUNUMU CASE REPORT

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A Case of Acute Urticaria and Angioedema Due to Inhaled Tiotropium Bromide

İnhaler Tiotropium Bromüre Bağlı Gelişen Akut Ürtiker ve Anjioödem Olgusu

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ABSTRACT Although there are many reasons for the etiology of urticaria-angioedema, drugs play a very common role. Tiotropium is an anticholinergic agent and commonly used in chronic obstructive pulmonary disease (COPD). There has been no report of urticaria-angioedema in the literature due to tiotropium. We aimed to present a case of urticaria-angioedema due to tiotropium. A 55-year-old male patient was prescribed inhaled tiotropium with the diagnosis of acute exacerbation of COPD. Two days after he started using the drug, he applied to our outpatient clinic again due to widespread rash, swelling of the eyelids. No additional risk factor was found to explain his current clinic. It was consulted with the dermatology clinic. The patient was diagnosed with urticaria-angioedema, and was hospitalized. Tiotropium was stopped. The patient's complaints disappeared within a few days. With the present findings, it was thought that the picture of urticaria and angioedema was due to inhaler tiotropium.

Keywords: Tiotropium bromide; urticaria; angioedema

ÖZET Ürtiker ve anjioödem etiyolojisinde birçok sebep olmakla birlikte ilaçlar çok sık rol oynar. Tiotropium bromür kronik obstrüktif akciğer hastalığında (KOAH) sıkça kullanılan uzun etkili inhaler antikolinerjik bir ajandır. Literatürde inhale tiotropium bromüre bağlı gelişen ürtiker ve anjioödem bildirimine rastlanmamıştır. Burada tiotropium bromüre bağlı gelişen, ürtiker anjioödem olgusunu sunmayı amaçladık. Elli beş yaşında erkek hastaya KOAH atak nedeniyle inhale tiotropium bromür reçete edildi. İlacı kullanmaya başladıktan 2 gün sonra vücutta yaygın döküntü, göz kapaklarında şişlik nedeniyle tekrar polikliniğimize başvurdu. Mevcut kliniğini izah edecek ek bir risk faktörü tespit edilemedi. Dermatoloji kliniği ile konsülte edildi. Hastaya ürtiker anjioödem tanısı kondu ve hasta yatırıldı. Tiotropium bromür stoplandı. Hastanın şikâyetleri birkaç gün içinde azalarak kayboldu. Mevcut bulgular ile ürtiker ve anjioödem tablosunun inhaler tiotropium bromide bağlı olduğu düşünüldü.

Anahtar Kelimeler: Tiotropium bromür; ürtiker; anjioödem

The airways have a very rich cholinergic innervation. Cholinergic nerves act on the muscarinic receptor via acetylcholine. These muscarinic receptors are located centrally in the airways. M3 is found in the smooth muscle cell and submucosal glands. While M1 and M3 are responsible for bronchoconstriction and stimulation of the submucosal glands, M2 (autoreceptor) acts on neural conduction through a negative "feedback" mechanism. In a healthy person, basal cholinergic innervation provides basal motor tonus and is reversible. Therefore, it is the only reversible component of airway narrowing. The role of the cholinergic system in the bronchoconstriction and mucus hypersecretion in chronic obstructive pulmonary disease (COPD) is quite high. Anticholinergic agents cause vagal blockade through muscarinic receptors. It is a competitive agonist of acetylcholine. Anticholinergics with a high affinity for M1 and M3, or low affinity for M2, are ideal drugs in the treatment of COPD. Tiotropium bromide is a potent, long-acting, selective muscarinic receptor antagonist. Its receptor affinity is 10 times greater than ipratropium

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bromide. Although tiotropium bromide and ipratropium bromide bind to M1 and M3 receptors at the same rate, tiotropium dissociates 100 times slower than the receptors, so it has a long-lasting effect. On the other hand, it dissociates from M2 receptors very quickly, so M2 inhibition is not seen with this drug.[1] Tiotropium has a wide therapeutic margin due to its poor gastrointestinal absorption so it has a very low systemic bioavailability. No adverse interactions have been reported between tiotropium and other drugs to date. The most common side effects are dry mouth, dyspepsia, and reflux.[2] However, in the "Possible side effects" section of the Tiotropium package insert, itching, redness, swelling of the lips, tongue, or throat are stated in the "allergic reactions and symptoms" section. However, these reactions were not mentioned in the safety data review.[3] In this article, we aimed to present a case of urticaria and angioedema due to inhaled tiotropium bromide. An informed consent note was obtained from the patient.

CASE REPORT

A 55-year-old male patient was admitted to our outpatient clinic due to an increase in shortness of breath for the last 4 months. He did not describe cough or increased sputum. There was a smoking history of 28 packs/year in his background. With the diagnosis of COPD, he had been using inhaled formoterol+budesonide (12/400 mcg) and short-acting bronchodilators in case of need for 4 years. There was no known additional disease. On physical examination, expirium was long and difficult, no crackles or ronchus was heard. Chest radiography was emphysematous. Laboratory parameters (complete blood count, C-reactive protein, biochemical parameters) were normal. An obstructive disorder was found in the pulmonary function test (FEV1 42%, FVC 57%, FEV1/FVC: 63%). Tiotropium bromide was added to the patient's treatment. Two days after he started using the drug, he applied to our outpatient clinic again due to widespread rash and swelling of the eyelids (Figure 1). The photos were used with the permission of the patient. Eosinophils and immunoglobulin E (IgE) levels (87 IU/mL (0-100) were normal. When the patient was questioned, no additional risk factor was found to explain his current clinic. It was consulted with the dermatology clinic. On examination, there were urticarial papules and plaques on the trunk and edema on the eyelids (Figure 2). The patient was diagnosed with urticaria-angioedema and treatment for angioedema was given. Tiotropium bromide inhaler was stopped. Inhaled formoterol+budesonide (12/400 mcg) was continued. The patient's complaints disappeared within a few days. The skin prick test and drug provocation test could not be performed because the patient did not approve. Based on the present findings, it was thought that urticaria and angioedema were due to inhaler tiotropium bromide.

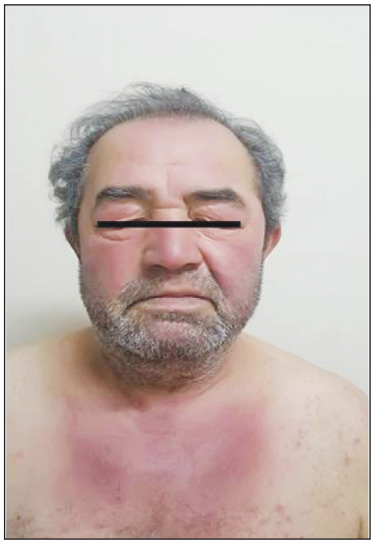

FIGURE 1: Edema, hyperemia, and swollen eyelids on the patient's face.

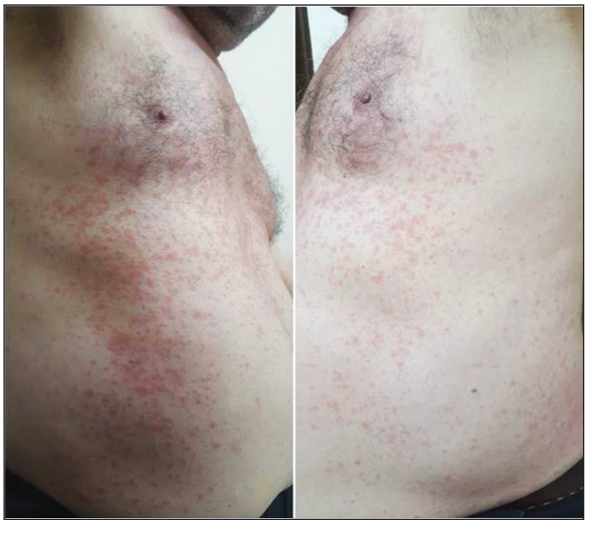

FIGURE 2: Urticarial papules and plaques on the trunk.

DISCUSSION

Tiotropium bromide is a long-acting, selective anticholinergic. It provides bronchodilation in COPD patients, significantly improves hyperinflation, dyspnea, health status, exacerbations, and mortality, but does not reduce the rate of FEV1 decline in COPD.[2] Tiotropium is an important option in the treatment of COPD with its once-daily administration, good patient compliance, safety, and response to treatment.[1,4]

Drug side effects is an important health problem, causing increased mortality and morbidity. Since tiotropium is absorbed through the mucosa at a minimal rate, systemic side effects are not seen much, and they are generally safely administered. Low rates of dry mouth, metallic taste, and mild cough can be seen. Prostatism, bladder neck obstruction, constipation, and an increase in glaucoma have been reported. Failure to apply the correct inhalation technique can lead to an increase in acute glaucoma symptoms.[5]

Urticaria is a vascular reaction that develops against various stimuli. It is characterized by itching, erythematous, edematous papules, and plaques. Clinical urticaria picture occurs as a result of mediator release from mast cells or basophils after contact with the triggering stimulus. Vasodilation and transudation from small vessels caused by these mediators provide the development of erythematous, edematous, and itchy papules and plaques that are characteristic for the picture. A pathogenic mechanism that provides mediator release can be induced immunologically or non-immunologically. Among the immunological mechanisms that cause urticaria, the most common type I hypersensitivity reaction due to IgE is seen (early hypersensitivity). Non-immunologically mechanisms are direct (drugs such as opium alkaloids, polymyxin, tubocurarine, radiocontrast agents or direct effect of physical factors such as heat, cold, UV, exercise, high fever) or indirect (aspirin, tartrazine, nonsteroidal anti-inflammatory, benzoate) effects from basophils or mast cells. They may cause mediator release.[6,7]

Perhaps the most common causes of urticaria and angioedema are drugs, most frequently penicillin and penicillin derivative antibiotics. Apart from penicillins, aspirin, sulfamides, and diuretics, especially the thiazide class, are relatively common causes of urticaria. In drug-related cases, clinical symptoms usually occur 1-2 hours after drug intake. However, this period may be shortened to 15 minutes or extended up to 15 days. For this reason, it is important to question the drug intake up to 15 days when questioning the anemnesis.[6]

Although a limited number of cases with itching, lichenoid reaction, and oral ulcer due to tiotropium bromide has been reported in the literature, urticaria angioedema due to inhaled tiotropium bromide has not been reported.[8-10] Our patient had no known allergy history. There were no individuals with allergies or asthma in his family history. There was no use of a new drug or consumption of new food. There was no evidence of a new bacterial or viral infection. Laboratory findings (including antinuclear antibodies) were normal. Therefore, it was thought that the development of urticaria and angioedema was due to inhaler tiotropium bromide.

Inhaled tiotropium may play a role, albeit very rarely, in the etiology of urticaria and angioedema.

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

This study is entirely author's own work and no other author contribution.

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