Case Report / Olgu Sunumu

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Case Report: Acute Unilateral Uveitis Induced by Infusion of Zoledronic Acid

Olgu Raporu: Zoledronik Asit İnfüzyonuyla İndüklenen Akut Unilateral Üveit

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Abstract

Bisphosphonates are a group of drugs that inhibit osteoclast-mediated bone resorption, used for treating osteoporosis, Paget's disease, metastatic bone disease, and hypercalcemia caused by malignancy. Zoledronic acid treatment, which is the most potent member of the group and is administered annually, is frequently preferred due to high patient compliance. The most common side effect in the first 3 days after administration is transient flu-like syndrome, which has also been reported to cause serious ocular adverse events. Although the most common ocular side effect is nonspecific conjunctivitis, it can also cause serious symptoms such as uveitis and scleritis. A limited number of cases diagnosed as uveitis triggered by zoledronic acid have been reported in the literature. In this article, we presented the occurrence of unilateral anterior uveitis 24 h after the application in a 62-year-old female patient who was under oral letrozole therapy for breast cancer diagnosed previously and was treated with zoledronic acid for osteoporosis. A detailed ophthalmologic medical history should be taken for patients who will be prescribed zoledronic acid. Additionally, recent bisphosphonate use should be questioned in patients presenting with symptoms of uveitis. Clinicians should warn patients about symptoms that may develop related to uveitis, which is a very rare but serious side effect of bisphosphonates and should promptly evaluate patients by an ophthalmologist when any symptoms develop.
Keywords: Bisphosphonates, zoledronic acid, uveitis, side effect, osteoporosis

Öz

Bifosfonatlar; osteoporoz, Paget hastalığı, metastatik kemik hastalıkları ve ayrıca malignite kaynaklı hiperkalsemi tedavisinde kullanılan osteoklast aracılı kemik rezorpsiyonunu inhibe eden bir ilaç grubudur. Grubun en potent üyesi olan ve yıllık intravenöz olarak uygulanan zoledronik asit tedavisi hasta uyumunun yüksekliği nedeniyle sıkça tercih edilmektedir. Uygulamadan sonra ilk 3 günde en sık görülen yan etkisi geçici grip benzeri sendrom olup bunun dışında ciddi oküler advers olaylara da yol açtığı bildirilmiştir. En sık görülen oküler yan etkisi non-spesifik konjunktivit olsa da üveit ve sklerit gibi ciddi semptomlara yol açabilen durumlara da sebep olabilir. Literatürde kısıtlı sayıda zoledronik asit tarafından tetiklenen üveit tanısı alan olgular raporlanmıştır. Bu yazıda daha önce tanısı koyulmuş meme kanseri nedeniyle oral letrozol tedavisi altında olan ve gelişen osteoporoz nedeniyle zoledronik asit tedavisi uygulanan 62 yaşında bir kadın hastada, uygulamadan 24 saat sonra unilateral ön üveitin ortaya çıkışını sunmayı amaçladık. Zoledronik asit reçete edilecek hastalarda detaylı oftalmolojik medikal öykü alınmalıdır. Ayrıca üveit semptomları ile başvuranlarda yakın zamanlı bifosfonat kullanımı sorgulanmalıdır. Klinisyenler bifosfonatların çok nadir ama ciddi bir yan etkisi olan üveit ile ilgili gelişebilecek semptomlar açısından hastaları uyarmalı, herhangi bir semptom geliştiğinde hastaların oftalmolog tarafından ivedilikle değerlendirilmesini sağlamalıdır.
Anahtar kelimeler: Bifosfonatlar, zoledronik asit, üveit, yan etki, osteoporoz

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Introduction

Bisphosphonates (BP) are frequently used in the treatment of osteoporosis, Paget's disease, metastatic bone diseases and malignancy induced hypercalcemia (1). Zoledronic acid (ZA) is the most preferred BP, especially for patient compliance, because it is used intravenously once a year owing to its potency. The most common adverse event is an acute-phase reaction, which occurs in nearly half of the patients following ZA infusion, despite that the symptoms generally last briefly with less intensity (2). Hypocalcemia, changes in other serum electrolyte and creatinine levels, bone pain, emesis, constipation, and osteonecrosis of the jaw are mostly known side effects (3). Although ocular side effects have been reported, their frequency is very low. Conjunctivitis, scleritis, episcleritis and uveitis have been identified among the ocular side effects of ZA (4). Few cases of ZA infusion-associated uveitis (ZAIU) have been reported in the literature since 2005 (5-22). According to our database research, the only case published from Turkey is a case of uveitis after ZA infusion for the treatment of bone metastasis of breast cancer by Kilickap et al. (22). We describe a case accompanied by unilateral uveitis occurring during the management of drug-induced osteoporosis with ZA infusion. This case report aims to increase clinicians' awareness of ZAIU and to review the treatment for osteoporosis in patients describing ocular adverse events.

Case Report

A 62-year-old female who still using letrozole 2.5 mg orally because of breast cancer history (diagnosed in 2016) was prescribed 5 mg ZA iv for drug-induced osteoporosis. She had no previous history of oral BP therapy. Approximately 6 hours after the infusion, severe muscle pain consistent with myalgia started, and after 24 hours unilateral pain, blurry vision, and redness in her right eye developed**.** She was admitted to ophthalmology outpatient clinic with these complaints. She had no medical history of ocular diseases. On ocular examination, the ophthalmologist found reduced visual acuity (Snellen charts of right eye: 3/10, left eye: 10/10), normal intraocular pressure for both eyes, ciliary and conjunctival injection and a medium number of cells and flare in the anterior chamber. Additionally, the existence of a 2 mm blood-clothed hypopyon was noted. She was also evaluated for any other situations that may induce acute anterior uveitis such as rheumatological diseases, viral infections, and lung diseases. These laboratory and radiological investigations did not represent any aberrancy. When all these findings were reviewed and there was no additional concomitant drug use, the patient was diagnosed with ZAIU. Topical hydrocortisone and dexamethasone were started for three weeks. After the topical steroid therapy was completed, her ocular symptoms resolved completely. Because of this situation, denosumab treatment was planned for drug-induced osteoporosis in the second application of the patient to our clinic. The patient was informed that her data would be used in a scientific publication and her consent was obtained.

Discussion

BP increase bone mineral density and reduce the risk of fracture in benign skeletal system diseases such as osteoporosis, Paget's disease and malignant conditions affecting the skeletal system such as malignancy and multiple myeloma. ZA is the most potent member of the BP that inhibits osteoblast-mediated bone resorption. ZA is administered as a once-a-year intravenous (IV) therapy IV infusion in patients with postmenopausal or drug-induced osteoporosis in cases where there is a lack of tolerance or benefit of oral BP. In addition, ZA was featured as the member with the highest drug adherence among BP (23). One of the most known side effects is the appearance of temporary flu-like symptoms characterized by nausea, arthralgia, and low-grade fever, especially within the first three days (2). It has been reported that ZA infusion may also cause ocular inflammation of varying location and severity in the same periodic process. Most of the typical ocular involvement is typically mild and limited to nonspecific conjunctivitis (24). However, although rare, more serious ocular pathologies such as uveitis and scleritis can be observed. According to a multicenter prospective randomized trial, patients treated with ZA had a significant increase in inflammatory ocular adverse events, most commonly conjunctivitis, compared to the control group two weeks after infusion (25). Several cases diagnosed with ZAIU have been reported in the past. In a previous incidence study, the frequency of ZAIU was reported as 0.8%-1.1%. In the same study, risk factors for ZAIU could not be demonstrated due to its low incidence (26,27).

Although the pathophysiology of ZAIU has not been clarified yet, it is thought that ocular inflammation is triggered by the release of IL-1 and IL-6 cytokines originating from T cells due to the similar structure of BP to pyrophosphate molecules (28,29).

In similar cases reported in the literature, although topical steroid administration was initially given, more than half of the patients required oral or iv steroid management. In a study, re-administration of ZA with prophylactic steroid therapy has been tried in patients with a history of ZAIU and it has been reported that it can provide tolerance (6). In one review, no ocular adverse events were reported in subsequent infusions with or without steroid prophylaxis in patients who developed ocular toxicity after initial exposure. For this reason, re-administration of BP in patients diagnosed with ZAIU was not considered an absolute contraindication (5). However, considering the seriousness of possible ocular side effects and the reducing effect of high-dose steroids on bone mineral density, the benefit-risk relationship should be evaluated separately for each patient. When necessary, drugs that increase bone mineral density other than BP should be preferred.

In this article, we presented a case of unilateral anterior uveitis after the infusion of ZA at a patient who was diagnosed with drug-induced osteoporosis. Clinicians should be aware of this rare side effect. The fact that ZA, which is used in many indications by clinicians today, can cause ocular inflammatory

pathologies should be considered. A detailed medical history of ocular pathologies should be included in the clinicians' questioning of patients before BP therapy. Likewise, detailed drug history should be questioned in patients presenting with uveitis symptoms. Therefore, patients should be warned about possible ocular side effects. If necessary, the clinicians should see the patient again after ZA administration and appropriate patients should be evaluated quickly by the ophthalmologist.

Ethics

Informed Consent: The patient was informed that her data would be used in a scientific publication and her consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.S., D.B., Concept: Ö.E., Design: K.S., Ö.E., Data Collection or Processing: K.S., D.B., Analysis or Interpretation: K.S., Ö.E., Literature Search: K.S., D.B., Ö.E., Writing: K.S., D.B.

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