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Bisphosphonates: Ally or Enemy in the Fight Against Rheumatological Diseases? Two Case Report

Bifosfonatlar: Romatolojik Hastalıklarla Mücadelede Dost mu, Düşman mı? İki Olgu Raporu

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Abstract

Due to their primary and well-known antiresorptive activity, bisphosphonate (BPs) are commonly prescribed as first-line drugs for osteoporosis treatment. Some reports suggest that they may also possess immunomodulatory and anti-inflammatory properties, along with potential benefits in preventing structural joint damage in inflammatory rheumatic diseases. However, despite the promising outcomes observed with BP use in treating rheumatic disorders, numerous reports have implicated these drugs as potential contributors to the development of arthritis. In this case report, two female patients aged 71 and 55 years who developed arthritis in the wrist and dactylitis in the finger after zoledronic acid infusion are presented. This study is significant because, to our knowledge, one of our patients is the first to have been diagnosed with dactylitis, and the other case is one of the few cases in the literature presenting oligoarticular involvement of joints after zoledronic acid administration.

Keywords: Arthritis, biphosphonates, dactylitis

Öz

Bisfosfonatlar (BP'ler), iyi bilinen anti-rezorptif etkileri nedeniyle, osteoporoz tedavisinde tercih edilen ilk ilaçlardandır. Bazı çalışmalara göre, immün modülasyon, anti-enflamatuvar etki ile romatolojik hastalıklarda yapısal eklem hasarının önlemede de işlev görebilecekleri bildirilmiştir. BP'lerin romatolojik hastalıkların tedavisinde kullanılabileceğine dair bu umut verici sonuçlara rağmen, çok sayıda rapor, ilaçların artrit gelişimine katkıda bulunan bir faktör olduğuna işaret etmektedir. Zoledronik asit kullanımına bağlı el bilek artriti ve parmağında daktilit gelişen sırasıyla 71 ve 55 yaşında iki hasta sunulacaktır. Bu çalışma, hastamızın zoledronik asit uygulaması sonrası daktilit tanısı alan ilk olgu olması ve diğer olgumuzun da literatürde zoledronik asit uygulaması sonrası oligoartiküler eklem tutulumu görülen birkaç olgudan biri olması nedeniyle önemlidir.

Anahtar kelimeler: Artrit, bifosfonatlar, daktilit

Introduction

Bisphosphonates (BPs) are considered the primary medications for treating osteoporosis because of their well-established antiresorptive function. Additionally, certain publications suggest their potential role in immunomodulation, anti-inflammation, and preventing structural joint damage in inflammatory rheumatic diseases (1).

Research into the immunomodulatory effects of BPs has concentrated on understanding the mechanisms associated with the acute-phase response triggered by their administration. This includes the stimulation of pro-inflammatory cytokines via the mevalonate pathway, activation of T-cells, and reduction in cytotoxic T-lymphocyte antigen-4 (CTLA-4). In terms of the predominant rheumatologic conditions, significant emphasis has been placed on their potential to mitigate structural damage in inflammatory joint diseases and their role in modulating immune responses within bone lesions (1).

While studies suggest that BPs can be included as part of combination therapy, numerous musculoskeletal side effects have been reported following their use, contrary to previous

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indications. The most common among these is musculoskeletal pain, listed as a potential side effect on the label of all BPs. Between 1995 and 2005, the United States Food and Drug Administration received 117 reports of individuals experiencing severe musculoskeletal pain while taking BPs, including discomfort in bones, joints, and/or muscles (2,3). Atypical femoral fractures and medication-related osteonecrosis of the jaw are two more severe but rare musculoskeletal side effects associated with BP use (4). The expected annual incidence of BP-related jaw osteonecrosis is 0.7 per 100,000 individuals (5). The age-adjusted incidence rate of atypical femoral fracture due to BP use ranges from 1.8 to 113 instances per 100,000 person-years for durations of less than 2 years to 8-10 years, respectively (6). Another infrequently reported side effect of BP use is arthritis and synovitis, which are documented sporadically in the literature on a case-by-case basis.

In this case report, a 71-year-old patient experienced wrist joint pain and swelling attributed to zoledronic acid use, with symptoms managed using steroids over an 8-week period. Additionally, a 55-year-old woman presented with dactylitis, developing over 3-4 days. This report is noteworthy as it documents the first recorded instance of dactylitis in one of our patients and one of the infrequent cases of oligoarticular involvement following zoledronic acid administration documented in the literature for the other patient.

Case Report

Case 1

A 71-year-old woman diagnosed with post-menopausal osteoporosis was initiated on zoledronic acid once a year due to a T-score of -3.3 in bone density assessment. One week after administration, the patient presented to the outpatient clinic complaining of pain and swelling in both hands. She reported no history of trauma or recent excessive hand use. Medical history revealed diabetes mellitus and hypertension but no rheumatologic disease. Moreover, there were no signs or symptoms suggestive of rheumatological disorders such as aphthous or genital ulcers, dermatologic eruptions, eye involvement, dry eyes and mouth, fever, abdominal or chest pain, or inflammatory back pain. There was no family history of rheumatologic disease. Laboratory investigations showed elevated levels of C-reactive protein (CRP) (138.4 mg/L, N: 0-5), sedimentation rate (51 mm/hour), and white blood cell (WBC) count (10,200), with neutrophil count at 8140 and lymphocyte count at 1330. ENA profile, RF, and CCP were all negative. Magnetic resonance imaging (MRI) and ultrasonographic examinations revealed synovial effusion in both wrist joints and tenosynovitis in the extensor tendons (Figure 1). Treatment began with 5 mg of prednisolone, leading to significant pain relief at the one-week follow-up. However, due to persistent fluid accumulation on ultrasonographic images, the prednisolone dosage was increased to 10 mg. By the fourth week, the patient's clinical condition improved, with acute phase reactants showing regression (CRP: 7 mg/L, sedimentation 40 mm/hour, WBC: 9800, neutrophil: 7600, lymphocyte: 1200). Consequently, the prednisolone dose was tapered by 5 mg over two weeks and discontinued by the eighth week. At the one-year follow-up, there were no arthritis exacerbations observed.

Case 2

A 55-year-old patient presented to the outpatient clinic with right knee pain and swelling that developed after falling down stairs a year prior. MRI investigation revealed avascular necrosis in the lateral femoral condyle. Zoledronic acid infusion was recommended following orthopedic consultation. One day after receiving zoledronic acid, the patient returned to the clinic with pain and erythematous swelling in the middle finger of the left hand, diagnosed as dactylitis (Figure 2). She denied recent trauma or excessive hand use. The patient had no history of rheumatologic or dermatologic diseases such as psoriasis. Moreover, there were no signs or symptoms suggestive of rheumatological disorders, including aphthous or genital ulcers,

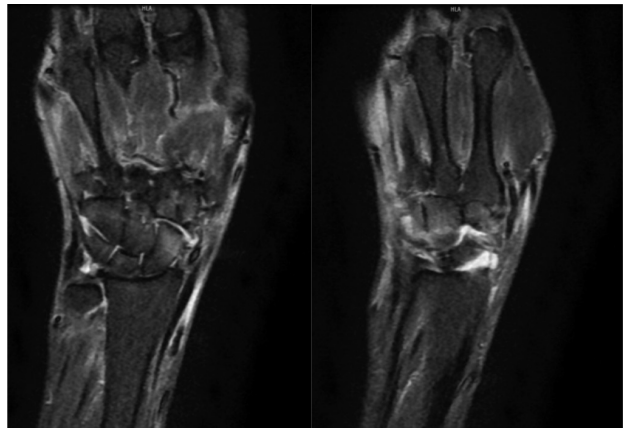

Figure 1. MRI of wrist joint. In MRI investigation, synovial effusion in both wrist joint and tenosynovitis of extensor tendons were detected
MRI: Magnetic resonance imaging

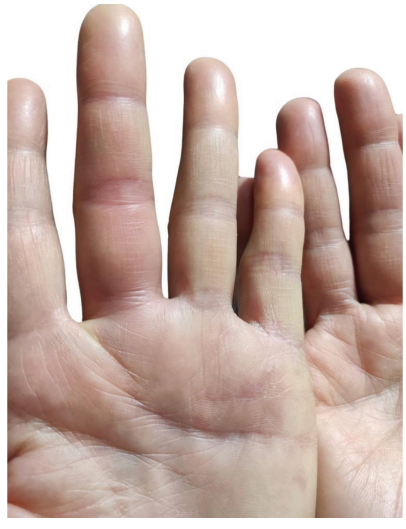

Figure 2. Dactylitis of the middle finger. Erythematous swelling is seen in middle finger of left hand accepted as dactylitis due to BP use
BP: Bisphosphonate

dermatologic eruptions, nail pathologies, eye involvement, dry eyes and mouth, recurrent fever, abdominal or chest pain, or inflammatory back pain. Laboratory investigations, including complete blood count, sedimentation rate, CRP, ENA profile, RF, CCP, and HLA B27, were all within normal ranges. Treatment commenced with non-steroidal anti-inflammatory medication, resulting in symptom resolution within 3-4 days. During the one-year follow-up, no exacerbations were noted.

Written consent was obtained from both patients for publication.

Discussion

In addition to their established mechanisms in osteoporosis treatment, some articles have proposed that BPs might possess immunomodulatory effects, anti-inflammatory properties, and the potential to mitigate structural joint damage in inflammatory rheumatic disorders (1).

One of the most recognized immunomodulatory reactions associated with BPs is the transient acute phase response (7). Studies have shown that zoledronate can modulate CTLA-4, which is elevated in various autoimmune diseases (8). Furthermore, researchers have observed a decrease in CTLA-4 expression after 3 and 5 days, suggesting that zoledronate inhibits this regulator of T-cell responses (7).

Numerous studies have illustrated how BPs halt bone degradation in rheumatologic patients. Specifically, zoledronate, especially at higher doses, has been shown to reduce bone erosion scores on histological assessments and decrease joint damage on radiological investigations in rats with collagen-induced arthritis. These findings are in line with zoledronate's capacity to inhibit osteoclastic bone resorption (9-11).

Despite the promising outcomes observed with the use of BPs in managing rheumatic diseases, there are numerous reports suggesting that BPs may act as a causative agent in the development of arthritis.

There are several case reports demonstrating that BPs can induce pseudogout attacks (12-14). Additionally, instances of arthritis without crystal detection in synovial fluid analysis have been documented in the literature. Numerous reports have also described transient or persistent arthritis following the use of alendronate (15-19).

Cases of arthritis have also been reported with other BPs besides alendronate. For instance, a patient who developed arthritis 48 hours after receiving the second dose of oral risedronate has been documented. Although her symptoms subsided quickly with rest, they returned one week later when the patient was administered another dose (20).

A patient with metastatic breast cancer developed bilateral knee pain and effusions that left her bedridden for almost four weeks within 48 hours of taking zoledronic acid (21). Another patient experienced a flare-up of hand osteoarthritis following zoledronic acid infusions (22). Additionally, a third case involved acute and severely debilitating polyarthritis induced by zoledronic acid, requiring an extended hospital stay in a frail older patient with multiple co-morbidities (23).

In this case report, a 71-year-old patient experienced wrist joint pain and swelling associated with zoledronic acid use, managed with steroids over an 8-week period, while a 55-year-old woman presented with dactylitis lasting 3-4 days. The absence of a diagnosed rheumatological disease, lack of infection or rheumatological findings upon systemic examination, normal laboratory tests for rheumatological diseases, and the temporal association with drug use all suggest the development of arthritis following BP administration. This report is significant as, to our knowledge, one patient represents the first recorded case of dactylitis following BP use, while the other case is among the few instances documented in the literature of oligoarticular involvement after zoledronic acid administration.

It is undeniable that studies have demonstrated the effectiveness of BPs in preventing structural bone damage and their immunomodulatory effects in treating rheumatological diseases. However, numerous cases, including those presented in our study, have been described in the literature following BP use, indicating potential adverse effects that cannot be overlooked. Despite the well-known side effects of BPs, reports of this nature are relatively scarce in the literature. We believe this may be due to doctors potentially underestimating the prevalence of this condition, possibly due to lack of awareness. Our report aims to draw attention to the possibility of this uncommon side effect of BPs and emphasizes the importance of considering it in the differential diagnosis of acute arthritis or synovitis in patients receiving these medications.

Ethics

Informed Consent: Written consent was obtained from both patients for publication.

Authorship Contributions

Concept: S.S.Ö., B.G., E.U.K., N.M., D.G.K., Design: S.S.Ö., B.G., E.U.K., N.M., D.G.K., Data Collection or Processing: S.S.Ö., B.G., E.U.K., Analysis or Interpretation: S.S.Ö., N.M., D.G.K., Literature Search: S.S.Ö., N.M., D.G.K., Writing: S.S.Ö., B.G., E.U.K.

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