Case Report / Olgu Sunumu

DOI: 10.4274/tod.galenos.2023.75317
Turk J Osteoporos 2024;30:64-7

Alendronate-associated Polyarticular Synovitis: A Case Report

Alendronat İlişkili Poliartiküler Sinovit: Olgu Sunumu

Büşra Şirin, Fatma Nur Kesiktaş

İstanbul Physical Medicine and Rehabilitation Training and Research Hospital, İstanbul, Turkey

Abstract

Osteoporosis is a commonly observed systemic metabolic disease characterized by a decrease in bone mineral density and an increased risk of fractures worldwide. Bisphosphonates are commonly preferred for its prevention and treatment. Among the side effects of bisphosphonates used orally and parenterally are gastrointestinal symptoms, musculoskeletal pains, flu-like syndrome, and an increase in acute-phase reactants. In this case report, a rare side effect observed during alendronate treatment, polyarticular synovitis, will be presented.
Keywords: Osteoporosis, synovitis, alendronate, bisphosphonate

Öz

Osteoporoz, dünya çapında yaygın olarak görülen, kemik mineral dansitesinde azalma ve kırık riskinde artış ile karakterize sistemik metabolik bir hastalıktır. Önlenmesi ve tedavisinde bifosfonatlar yaygın olarak tercih edilmektedir. Oral ve parenteral olarak kullanılan bifosfonatların yan etkileri arasında gastrointestinal semptomlar, kas iskelet sistemi ağrıları, flu-like sendrom, akut faz reaktanlarında artış bulunmaktadır. Bu olgu sunumunda, alendronat tedavisi sırasında nadir gözlenen bir yan etki olarak poliartiküler sinovit olgusu sunulacaktır.
Anahtar kelimeler: Osteoporoz, sinovit, alendronat, bifosfonat

Introduction

Osteoporosis is a common, systemic, metabolic disease that is a significant cause of morbidity and mortality in postmenopausal women and the elderly population (1). It is characterized by the deterioration of bone architecture and an increased risk of fractures (2). Fractures associated with osteoporosis are more likely to occur in the vertebrae and hips, and the prevalence of fractures in postmenopausal osteoporosis is quite high (3). Postmenopausal women are at risk of developing osteoporosis due to the known decrease in estrogen hormone levels, which limits bone resorption (4). Bisphosphonates are analogs of pyrophosphate with a high affinity for the bone mineral surface and are commonly used in the treatment of postmenopausal osteoporosis (5). They help increase bone mineral density (BMD) and reduce the risk of fractures by suppressing osteoclast activity and reducing bone resorption (6). Alendronate is among the oral bisphosphonates commonly used for the prevention (5 mg daily) and treatment (70 mg weekly or 10 mg daily) of postmenopausal osteoporosis. Alendronate and other oral bisphosphonates commonly cause gastrointestinal side effects (7). Additionally, muscle and joint pains can rarely occur (8). Intravenous bisphosphonate treatment can lead to a temporary acute-phase reaction in patients. Acute-phase reactions can rarely be observed after oral bisphosphonate treatment as well (9). Jaw osteonecrosis typically develops as a long-term side effect of high-dose intravenous bisphosphonate administration (10). In this case, a rare case of polyarticular synovitis that developed after the use of oral alendronate for postmenopausal osteoporosis treatment will be presented.

Case Report

A 62-year-old postmenopausal female patient presented to our clinic for an annual check-up. The informed consent form has been obtained from the patient. She had a medical history of hypertension and diabetes. Dual-energy X-ray absorptiometry (DEXA) and routine blood tests were requested. DEXA showed a lumbar spine BMD of 0.701 g/cm^2 (T-score: -3.2) and a femoral neck BMD of 0.605 g/cm^2 (T-score: -1.7). The patient was diagnosed with osteoporosis, and her blood tests revealed 25-hydroxyvitamin D level of 23.6 ng/mL, calcium level of 8.6 mg/dL, and C-reactive protein (CRP) of 6.6 mg/dL. She was started on weekly 70 mg alendronate, oral calcium (1 g/day), and vitamin D3 (880 IU/day) treatment.

Address for Correspondence/Yazışma Adresi: Büşra Şirin MD, İstanbul Physical Medicine and Rehabilitation Training and Research Hospital, İstanbul, Turkey
Phone: +90 554 448 04 18 **E-mail:** bsrn080@gmail.com **ORCID ID:** orcid.org/0000-0001-8519-1747
Received/Geliş Tarihi: 02.09.2023 **Accepted/Kabul Tarihi:** 06.11.2023

Twenty-four hours after starting treatment, she complained of weakness, fatigue, myalgia, subfebrile fever, swelling, and pain in the left ankle, as well as in the 2nd, 3rd, and 4th proximal interphalangeal and 2nd and 3rd distal interphalangeal joints of both hands (Figure 1). These joints were tender upon palpation, and joint movements were restricted due to pain. Blood tests at that time showed CRP of 11.6 mg/L, with a normal complete blood count. Symptomatic treatment with oral diclofenac sodium 75 mg/day was initiated. In the following days, the patient's symptoms improved, but after taking the second week's dose of alendronate 75 mg, her symptoms recurred on the 2nd day. Blood tests on the 9th day of alendronate treatment showed CRP of 25 mg/L, procalcitonin of 0.12 ng/mL, sedimentation rate of 22 mm, white blood cell (WBC) of 9.47, rheumatoid factor <10, antinuclear antibody indirect immunofluorescence assay 1/100 titer negative, and anti-cyclic citrullinated peptide antibody negative. Prednisolone 10 mg/day was added to diclofenac sodium as an adjunct treatment. On the 12th day, blood tests showed CRP of 62 mg/L, sedimentation rate of 43 mm, and WBC of 10.1. Since her symptoms did not improve, a bilateral hand, wrist, and left foot magnetic resonance imaging was performed. The foot imaging showed an increase in synovial fluid in the 1st metatarsophalangeal joint space, tenosynovitis around the peroneal muscle tendons, and focal bone marrow edema in the 2nd and 3rd metatarsal proximal metaphyses and intermediate and lateral cuneiform bones (Figure 2). The right wrist imaging revealed mild synovial fluid increase in the radiocarpal and intercarpal joint spaces, focal bone marrow edema in the lunate bone, subchondral edema areas near the proximal interphalangeal joints of the 1st, 2nd, and 4th fingers, and synovial fluid increase in the joint space. The left wrist imaging showed mild synovial fluid increase in the radiocarpal and intercarpal joint spaces, mild synovial fluid increase between the dorsal 1st and 2nd extensor tendons, and synovial fluid increase in the joint space between the 3rd and 4th fingers (Figure 3). The patient had no history of rheumatic diseases, and there were no findings suggestive of pyrophosphate arthropathy. Since her current symptoms were attributed to alendronate treatment and she had not experienced similar joint complaints or morning stiffness before, the treatment was discontinued. One week later, there was a significant improvement in her symptoms, and acute-phase reactants returned to normal. After three weeks, her symptoms had completely resolved. Follow-up blood tests one month later showed no pathological findings. The patient was prescribed denosumab treatment for osteoporosis, and she was followed up for eight months without recurrent arthritis symptoms. Therefore, rheumatological diagnoses were ruled out, and the polyarthritis that developed was considered a side effect of alendronate treatment.

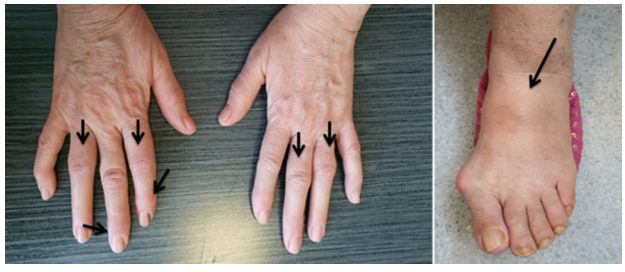

Figure 1. Swelling in the proximal and distal interphalangeal joints and dorsum of the left foot

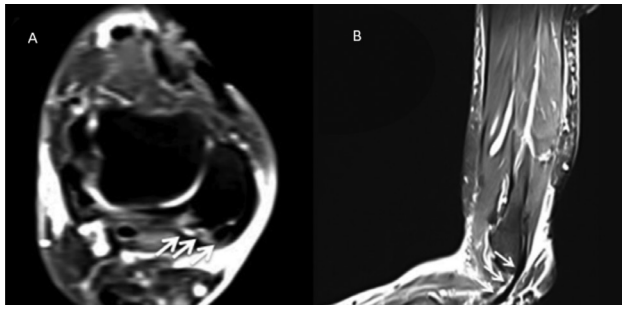

Figure 2. T2 weighted fat-sat axial (A) and sagittal (B) images show fluid increase in favor of tenosynovitis around peroneal tendons

Discussion

Bisphosphonates, synthetic pyrophosphate analogs, are potent inhibitors of osteoclastic bone resorption. They are successfully used in the prevention and treatment of osteoporosis and are well-tolerated (11). In the 1990s, it was discovered how bisphosphonates biochemically affect cells. Nitrogen-containing bisphosphonates (aminobisphosphonates) like alendronate, risedronate, ibandronate, and zoledronate inhibit the enzyme farnesyl pyrophosphate synthase, thereby suppressing osteoclast-mediated bone resorption. This enzyme is responsible for synthesizing farnesyl pyrophosphate from mevalonate and is a part of cholesterol biosynthesis. Reduced levels of farnesyl pyrophosphate prevent the prenylation of guanosine triphosphate binding proteins (such as ras, rab, rho), leading to dysfunction in osteoclasts. As a result, nitrogen-containing bisphosphonates, similar to statins, interfere with cholesterol biosynthesis (12). Nitrogen-free bisphosphonates (non-aminobisphosphonates) include etidronate and clodronate (13). Non-aminobisphosphonates inhibit the enzyme adenosine diphosphate/adenosine triphosphate (ATP) translocase, leading to the accumulation of non-hydrolyzed ATP analogs and, through

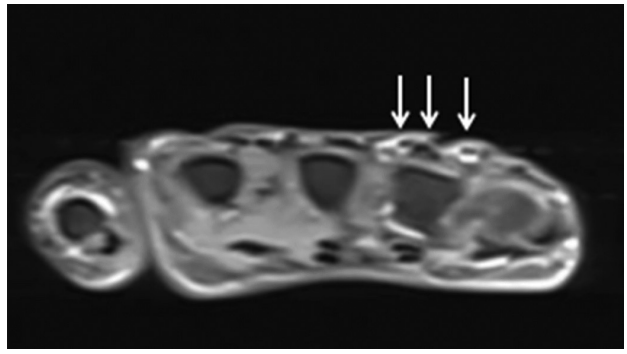

Figure 3. T2 weighted fat-sat coronal image shows fluid increase in favor of tenosynovitis around 3rd and 4th extansor tendons

this mechanism, inducing osteoclast apoptosis (14). Oral bisphosphonates most commonly cause upper gastrointestinal symptoms, including gastritis, esophagitis, and dyspepsia. One of the side effects seen in aminobisphosphonates is an acute-phase reaction characterized by fever, fatigue, an increase in erythrocyte sedimentation rate, CRP levels, myalgia, and arthralgia. This reaction is associated with the release of proinflammatory mediators and is more commonly observed after intravenous bisphosphonate therapy but can also rarely occur with oral bisphosphonate treatment (15).

Approximately 50-60% of the administered bisphosphonate is excreted unchanged through the kidneys. The use of non-steroidal anti-inflammatory drugs with potential nephrotoxicity, dehydration, and similar conditions can increase the risk of renal toxicity associated with intravenous bisphosphonates. Therefore, it is essential to ensure that the glomerular filtration rate is above 30 mL/min in patients starting intravenous bisphosphonate therapy (16). In the HORIZON study, atrial fibrillation was mentioned as one of the potential side effects of zoledronic acid treatment for the first time (17). However, subsequent studies have raised doubts about this association (18,19). Additionally, an association has been suggested between bisphosphonate use and conditions such as jaw osteonecrosis, esophageal cancer, and atypical femur fractures, although conclusive evidence has not been established (20). Bisphosphonate-associated synovitis was first reported in the literature in 2003 by the Uppsala Monitoring Centre with a case series of eight patients (21).

Gwynne Jones et al. (13) published a case series describing the development of synovitis in 7 postmenopausal osteoporosis patients who were treated with alendronate. In each of these cases, synovitis developed after alendronate treatment, similar to our case, and discontinuing the treatment led to the resolution of symptoms. Frederiksen et al. (22) reported a case presentation of a 62-year-old postmenopausal osteoporosis patient who developed polyarticular synovitis as a result of alendronate treatment. This patient continued to have residual synovitis despite low-dose prednisolone treatment during 14 months of follow-up. In a case reported by Gökkus et al. (23) in 2016, a postmenopausal osteoporosis patient developed polyarthritis starting on the 2nd day of alendronate treatment. Although more commonly seen with intravenous bisphosphonates, as in our case, this case also showed an increase in acute-phase reactants. Discontinuation of treatment resulted in the resolution of arthritis symptoms and the normalization of acute-phase reactants, similar to other cases and our case. When rheumatic diseases and potential etiologies like pyrophosphate arthropathy were excluded, the examined cases were considered as side effects of alendronate. Arthritis and synovitis are rarely observed among the side effects of bisphosphonates, and there are few cases reported in the literature. This case presentation aims to remind that although rare, bisphosphonate use can lead to the development of poly-synovitis and polyarthritis during the diagnosis and treatment process.

Ethics

Informed Consent: The informed consent form has been obtained from the patient.

Authorship Contributions

Concept: B.Ş. F.N.K., Design: B.Ş. F.N.K., Data Collection or Processing: B.Ş., Analysis or Interpretation: B.Ş. F.N.K., Literature Search: B.Ş., Writing: B.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Abboskhujaeva LS, Ismailov SI, Alikhanova NM. Efficacy of strontium ranelate in combination with a D-hormone analog for the treatment of postmenopausal osteoporosis. Drugs R D 2014;14:315-24.
2. Sambrook P, Cooper C. Osteoporosis. Lancet 2006;367:2010-8.
3. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556-61.
4. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol 2013;9:699-712.
5. Davison KS, Siminoski K, Adachi JD, Hanley DA, Goltzman D, Hodsman AB, et al. The effects of antifracture therapies on the components of bone strength: assessment of fracture risk today and in the future. Semin Arthritis Rheum 2006;36:10-21.
6. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008;148:197-213.
7. Bisphosphonates for osteoporosis. Drug Ther Bull 2001;39:68-72.
8. US Food and Drug Administration. Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa). 2009. Available from:s URL: https://wayback.archive-it.org/7993/20161022053007/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101551.htm Accessed May 29, 2009.
9. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 2010;95:4380-7.
10. Ruggiero SL. Bisphosphonate-related osteonecrosis of the jaw: an overview. Ann N Y Acad Sci 2011;1218:38-46.
11. Wang YK, Qin SQ, Ma T, Song W, Jiang RQ, Guo JB, et al. Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96:e6970.
12. Cremers S, Drake MT, Ebetino FH, Bilezikian JP, Russell RGG. Pharmacology of bisphosphonates. Br J Clin Pharmacol 2019;85:1052-62.
13. Gwynne Jones DP, Savage RL, Highton J. Alendronate-induced synovitis. J Rheumatol 2008;35:537-8.
14. Reid IR. Bisphosphonates: new indications and methods of administration. Curr Opin Rheumatol 2003;15:458-63.
15. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc 2009;84:632-7.
16. Khosla S, Bilezikian JP, Dempster DW, Lewiecki EM, Miller PD, Neer RM, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab 2012;97:2272-82.

17. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley CA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
18. U.S. Food and Drug Administration. Early communication of an ongoing safety review: bisphosphonates: alendronate (Fosamax, Fosamax plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel w/calcium), tiludronate (Skelid), and Zoledronic acid (reclast, zometa). Available from: s URL: https://wayback.archive-it.org/7993/20161022204214/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070303.htm Updated 2008. Accessed March 11, 2015.
19. Kim SY, Kim MJ, Cadarette SM, Solomon DH. Bisphosphonates and risk of atrial fibrillation: a meta-analysis. Arthritis Res Ther 2010;12:R30.
20. Pazianas M, Cooper C, Ebetino FH, Russell RG. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. Ther Clin Risk Manag 2010;6:325-43.
21. The Uppsala Monitoring Centre. Alendronic Acid and Synovitis. Signal, March 2003. (Restricted Document). Contact the Uppsala Monitoring Centre for Details. e-mail: info@who-umc.org.
22. Frederiksen L, Junker P, Brixen KT. Persisterende polyartikulaer synovitis efter behandling med alendronat [Persistent polyarticular synovitis after treatment with alendronate]. Ugeskr Laeger 2007;169:1583-4.
23. Gökkus K, Yazicioglu G, Sagtas E, Uyan A, Aydin AT. Possible alendronate-induced polyarticular synovitis. J Postgrad Med 2016;62:126-8.