Alendronate-associated Polyarticular Synovitis: A Case Report

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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

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/cm² (T-score: -3.2) and a femoral neck BMD of 0.605 g/cm² (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.
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.

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 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

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


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.
