ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

An Unknown Side Effect of Zoledronic Acid: Acute Pancreatitis

CASE REPORT
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ABSTRACT

Bisphosphonates are widely used to treat several clinical conditions. Zoledronic acid is one of these classes, commonly used for the treatment and prevention of osteoporosis, hypercalcemia of malignancy, Paget's disease, and multiple myeloma. Side effects associated with zoledronic acid include fever, fatigue, arthralgia, myalgia, nausea, and bone pain. Liver damage caused by bisphosphonate is rare. No cases of acute pancreatitis have been described in the literature. We describe a 74-year-old woman who presented with features of acute pancreatitis 3 days following the first dose of intravenous zoledronic acid infusion administered to treat postmenopausal osteoporosis. Supportive treatment was given for 5 days. She was discharged without any problems.

Keywords: Osteoporosis, bisphosphonate zoledronic acid, pancreatitis

Introduction

Osteoporosis is a progressive metabolic bone disease characterized by reduced bone mass and the deterioration of bone tissue microarchitecture. Bisphosphonates, such as zoledronic acid, are utilized in treating postmenopausal osteoporosis, multiple myeloma, and hypercalcemia of malignancy. Zoledronic acid, a derivative of bisphosphonates, is administered intravenously at a dosage of 5 mg annually for osteoporosis treatment. It exerts an antiresorptive effect by binding to hydroxyapatite crystals in bone and inhibiting osteoclast function and proliferation.[1]

Zoledronic acid is typically a safe and well-tolerated medication, with common side effects including fever, fatigue, arthralgia, myalgia, nausea, and bone pain. While bisphosphonate-induced liver damage is rare, there have been no reported cases of acute pancreatitis associated with its use. The most common causes of acute pancreatitis are gallstones (accounting for 40% to 70% of cases) and alcohol consumption (responsible for approximately 25% to 35% of cases in the United States). Drug-induced pancreatitis is rare, comprising less than 5% of cases. This report describes a case of acute pancreatitis that occurred 3 days after the administration of intravenous zoledronic acid for the treatment of secondary osteoporosis after ruling out other potential causes.[2]

Case Presentation

A 74-year-old female patient with known diagnoses of type 2 diabetes mellitus, osteoporosis, and spondyloarthropathy has been using prednisolone 2.5 mg due to spondyloarthropathy since October 2021. In January 2022, the patient's bone mineral densitometry, femur T score, and Z score were normal. The steroid dose used by the patient was not considered a risk factor because it was a low dose for the risk of secondary osteoporosis. Therefore, bisphosphonate treatment was not considered. Calcium and vitamin D supplements were given to the patient in the postmenopausal period. During his annual routine check-ups, the bone mineral density test revealed a femoral neck T score of −2.7. The patient did not have severe back pain or fractures. She smoked 10 packs of cigarettes per year and had not smoked for 17 years. She had no history of alcohol use. There was no family history of osteoporosis. Physical examination was normal. On March 10, 2023, 5 mg of zoledronic acid was given in 100 mL of normal saline as an intravenous infusion for 15 minutes. Myalgia and arthralgia developed 3 days after the infusion. She applied to the outpatient clinic because his pain continued despite the use of nonsteroidal anti-inflammatory drugs. In blood tests, C-reactive protein (CRP) increased to 108.6 mg/L (normal range 0-5 mg/L, aspartate aminotransferase (AST) 29 U/L, alanine

Ayça Demirel[1]
Mustafa Şentürk[1]
Özlem İyidir Turhan[2]
Neslihan Başçıl Tütüncü[2]

[1]*Department of Internal Medicine, Başkent University Faculty of Medicine, Ankara, Türkiye*
[2]*Department of Endocrinology, Başkent University Faculty of Medicine, Ankara, Türkiye*

Corresponding author:
Ayça Demirel
✉ aycademirel96@gmail.com

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Table 1. Follow-up of Liver Function Tests, Amylase, and Lipase Values Following Zoledronic Acid Infusion

Date	AST (U/L)	ALT (U/L)	GGT (U/L)	Amylase (U/L)	Lipase (U/L)	CRP (mg/L)	Leukocyte $10^3/mm^3$
February 17	23	15	25	61	32	3.8	3.95
March 14	29	31	30	99	178	108.6	9.2
March 14	53	59	77	322	511	181	10.3
March 18	40	51	95	153	272	190.2	7.53
March 19	31	39	86	112	184	135.9	7.21
March 20	25	38	79	62	90	82.9	6.53
March 22	20	32	75	40	72	53.5	5.3

CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

aminotransferase (ALT) 31 U/L, gamma-glutamyltransferase (GGT) was 30 U/L, and alkaline phosphatase (ALP) was 56 U/L. Amylase was 99 U/L; Lipase was 178 U/L (Table 1). The patient was hospitalized. The next day, amylase 322, lipase 511, AST 53 U/L, ALT 59 U/L, ALP 75 U/L, GGT 77 U/L, and CRP 181 mg/L (Table 1) was detected. The patient whose amylase and lipase levels were more than 3 times elevated was investigated for acute pancreatitis. Abdominal computer tomography revealed an appearance suggestive of acute focal pancreatitis in the tail of the pancreas and edema around it (Figure 1). There was no abdominal pain during the physical examination. The patient's regimen was stopped, and fluid and analgesia treatment was given to the patient, who was evaluated as having acute pancreatitis. In the tests performed to clarify the etiology, the patient's corrected calcium value was 8.8 mg/dL, triglyceride - 120 mg/dL, influenza A-B virus antigen for viral etiology (–), severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR) (–), respiratory syncytial virus (–), anti HIV (–), rubella IgM (–), Epstein–Barr virus (EBV) viral capsular antigen (VCA) IgM (–), mumps IgM (–), varicella zoster IgM (–), and hepatitis markers negative. Upon detection of cytomegalovirus (CMV) IgM 2.21 (index value <0.85 index : negative 0.85-0.99 index : borderline positive >=1 positive), CMV PCR was run and found to be negative. Cytomegalovirus infection was not considered after consulting infectious diseases. Abdominal USG was performed for biliary pathology. Gallbladder dimensions and wall thickness were normal; no stones or masses were observed within the lumen. Intra and extrahepatic bile ducts were normal. Liver function tests and lipase monitoring were performed daily. The patient started enteral nutrition on March 20, did not develop any additional complaints during follow-up, and was discharged on March 22, 2023.

MAIN POINTS

- Zoledronic acid is one of these classes, commonly used for the treatment and prevention of osteoporosis, hypercalcemia of malignancy, Paget's disease, and multiple myeloma.
- Side effects associated with zoledronic acid include fever, fatigue, arthralgia, myalgia, nausea and bone pain, and they rarely cause liver damage.
- Clinicians should be aware that acute pancreatitis may develop after zoledronic acid infusion.

Discussion

Intravenous bisphosphonates used in the treatment of postmenopausal osteoporosis have been associated with adverse effects such as acute phase response, hypocalcemia and secondary hyperparathyroidism, musculoskeletal pain, renal toxicity, osteonecrosis of the jaw, and ocular events. Although rare, transient hepatotoxicity has been reported in a few cases after zoledronic acid infusion. Hepatotoxicity was confirmed by biopsy after zoledronic acid in the study of Dieterle et al[3] in 2007 and Polyzos et al[4] in 2011. Additionally, Halabe et al;[5] Carrére et al;[6] Yanık et al;[7] and Phillips[8] published several cases of hepatitis that developed and resolved within a few months of stopping bisphosphonates. However, when the literature was searched, no cases of acute pancreatitis were reported after zoledronic acid infusion. In the study conducted by Brewer et al[9] in 2022, in which

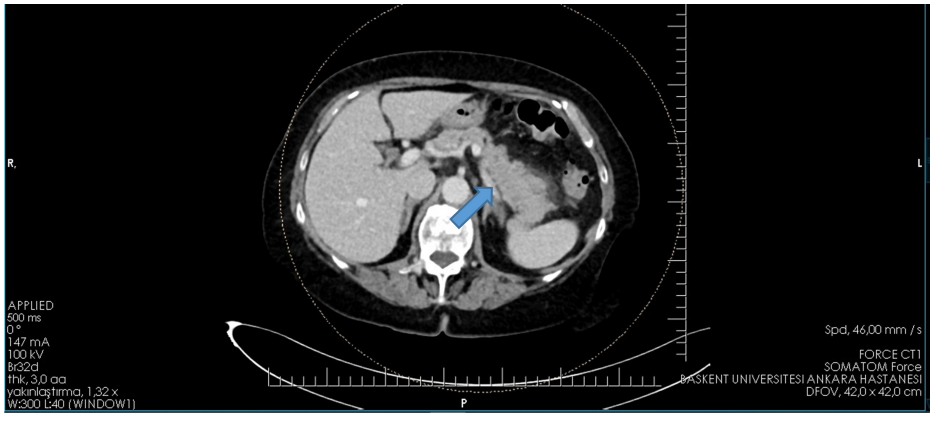

Figure 1. Abdomen computed tomography examination, an appearance suggestive of acute focal pancreatitis in the tail of the pancreas and surrounding edema.

they analyzed the side effects following zoledronic acid treatment on 95 dogs, 13 adverse events were recorded in 10 dogs and acute pancreatitis was detected in 1.

The literature does not currently provide any data regarding the underlying causes of acute pancreatitis related to zoledronic acid. After excluding other potential causes of pancreatitis, it was hypothesized that the condition might be related to the drug. Further research is required to clarify the pathophysiological mechanisms involved.

In our case, we present a case of acute pancreatitis that developed after zoledronic acid infusion and after excluding other etiological factors. The aim of this case is to remind us that acute pancreatitis may develop after zoledronic acid infusion. More prospective data is needed regarding the relationship between zoledronic acid and acute pancreatitis.

Availability of Data and Materials: Dataset regarding the patient's evaluation may be obtained from the corresponding author upon reasonable request.

Informed Consent: Verbal informed consent was obtained from the patient who agreed to take part in the study.

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