A Severe Acute Kidney Injury Following Zoledronic Acid Therapy Leading to Chronic Hemodialysis Treatment: A Case Report

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KEY WORDS: acute interstitial nephritis, acute tubular necrosis, hemodialysis, osteoporosis, zoledronic acid

IMAJ 2023; 25: 828–829

Higher potency bisphosphonates, typically intravenous formulations, are given at lower doses for postmenopausal women. The treatment has improved compliance compared to daily oral therapy. Since bisphosphonates are exclusively excreted via the kidneys, intravenous formulation has been associated with deterioration of renal function, specifically in the setting of preexisting renal disease or concomitant use of nephrotoxic agents [1].

Bisphosphonate nephrotoxicity can be avoided by adhering to guidelines for monitoring serum creatinine prior to each treatment, temporarily withholding therapy in the setting of renal insufficiency cases, and adjusting doses in patients with pre-existing chronic kidney disease. Patterns of nephrotoxicity described with these agents include acute tubular necrosis (ATN) and collapsing focal segmental glomerulosclerosis (FSGS) [1].

Osteoporosis is a common condition that affects millions of people globally. Zoledronic acid is a potent antiresorptive medication from the bisphosphonate class. It is given intravenously for the treatment of osteoporosis and is effective in improving bone mass density and reducing vertebral and non-vertebral fracture risk. There are other indications for the use of bisphosphonate, including multiple myeloma (MM), Paget's disease, hypercalcemia of malignancy, and metastatic bone disease [2].

PATIENT DESCRIPTION

A 78-year-old Caucasian female presented with a past medical history of ischemic heart disease, osteoporosis with several previous fractures, and rheumatoid arthritis, which was well controlled and treated with leflunomide and abatacept once monthly.

She presented to the emergency department with complaints of general weakness for the week prior and a fall incident due to dizziness and fatigue. Recent medical therapy included new pregabalin use, with side effects of dizziness and drowsiness, and a dose of intravenous zoledronic acid 5 mg a week prior to her admission. She had previously received bisphosphonates, including risedronate therapy for 3 years, which was stopped 10 years prior to the current presentation. This treatment was followed by yearly intravenous zoledronic acid administered 2, 3, and 6 years prior to her admission.

On arrival, her vital signs were normal. Her temperature was 37.0°C and blood pressure was 124/74 mmHg. Her physical examination was without anomalies. She denied any symptoms of vomiting or diarrhea, urinary complaints, or coughing or breathing difficulties.

Blood tests on admission included leukocytosis 14.6 K/µl, highly elevated C-reactive protein 28 mg/dl, acute kidney injury with creatinine level of 3.4 mg/dl (from base line of 0.9 mg/dl a month prior to admission), urea 88 mg/dl, and mildly elevated liver enzymes (aspartate aminotransferase 45 U/L, alanine transaminase 83 U/L). Chest X-ray was normal. Blood and urine cultures were obtained, and urine catheter was inserted. Ceftriaxone therapy was initiated for a potential infection.

After her admission, she was anuric despite the intravenous fluids and high dose of furosemide she received. Kidney ultrasound was normal. Urine analysis demonstrated proteinuria of 1 gram/24 hours with white and red blood cell casts. Since the patient remained oligoanuric, it was not possible to progress to hemodialysis. Blood and urine cultures were negative. A total body computed tomography was performed. No remarkable abnormalities led to antibiotic cessation.

Based on previous case reports of systemic inflammatory response after zoledronic acid infusion, we

suspected acute interstitial nephritis (AIN) as a leading cause of acute kidney injury (AKI) in our patient. We initiated pulse therapy with methylprednisolone 0.5 grams/day for 3 days followed by oral prednisone therapy (0.5 mg/kg).

Kidney biopsy revealed interstitial nephritis dominantly with lymphocyte and eosinophil infiltration and a few plasma cells with widespread tubular damage, tubular widening, and epithelial flattening. Atherosclerosis was found in blood vessels. Immunofluorescence staining was negative for immunoglobulin G (IgG), IgA, C3, and C4. These features were compatible with AIN with ATN. Under steroid treatment the patient's symptoms improved considerably but she remained on chronic hemodialysis.

COMMENT

The efficacy and prevalence of bisphosphonates for the reduction of fractures in patients with osteoporosis has been shown in many large controlled clinical trials. All bisphosphonates are associated with short-term adverse effects including upper gastrointestinal nausea, dyspepsia, abdominal pain, and acute phase reactions including fever, myalgia, and arthralgia occurring within 24 to 72 hours. Other long-term side effects include osteonecrosis of the jaw, sub-trochanteric femoral fractures, and severe suppression of bone turnover [1].

Renal complications secondary to bisphosphonate are rare but have been described, especially after intravenous infusion.

In a large cohort of patients in the United States, Chang et al. [3] underlined the multifactorial causes of zoledronate-associated toxic renal failure including advanced cancer, MM, preexisting renal failure, diabetes, hypertension, and concomitant use of nephrotoxic drugs. The exact role of zoledronic acid therapy was difficult to determine in the presence of these other contributing factors. Other risk factors included previous bisphosphonate therapy, chemotherapy, and severe dehydration.

Markowitz and colleagues [4] reported on four men and two women, mean age 69.2 years, who developed AKI following treatment with zoledronic acid. Five patients had a history of MM and one had Paget's disease. The mean baseline serum creatinine was 1.4 mg/dl. Patients received once monthly zoledronate at the recommended dose and infusion time. They were found to have AKI with a mean serum creatinine of 3.4 mg/dl with sub-nephrotic proteinuria following a mean of 4.7 months of treatment. A renal biopsy in all patients revealed toxic ATN, without evidence of collapsing FSGN. Discontinuation of zoledronate led to improvement in renal function, with a mean serum creatinine of 2.3 mg/dl at a mean of 3.2 months following renal biopsy [4].

A literature review of 10 case reports of acute kidney injury due to zoledronic acid, Rahbari-Oskoui et al. [5] also emphasized the risk in MM followed by Paget's disease and other malignancies. Their review presented similar changes in creatinine values after infusion, and a decline after therapy was discontinued. However, two cases progressed to end-stage renal disease with the need for chronic hemodialysis. Therefore, the presence of previous reversible episodes of mild AKI should be considered as a risk factor for occurrence of severe injury due to the toxic cumulative dose of zoledronic acid, which may prolong recovery time [5].

CONCLUSIONS

Our patient had normal levels of creatinine at baseline. She had no diagnosis of MM, Paget's disease, or other malignant disease and no use of nephrotoxic medication. Her indication for bisphosphonate therapy was osteoporosis, which was treated with previous repeated doses of bisphosphonates for many years with no fluctuating creatinine value after previous drug transfusion. The kidney biopsy presented a combined feature of acute interstitial nephritis with acute tubular necrosis. Our patient needed chronic hemodialysis. Hence, our case highlights a unique effect of zoledronic acid with severe kidney injury. Special awareness of this potential complication should be noted.

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