Zoledronic acid-induced acute tubulointerstitial nephritis

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Abstract

The intravenous bisphosphonates widely used for treating osteoporosis and malignant hypercalcemia are potentially nephrotoxic drugs. They can be associated with acute tubular necrosis and focal and segmental glomerulosclerosis. We present the case of a 79-year-old woman who developed acute tubulointerstitial nephritis after intravenous administration of zoledronic acid to treat osteoporosis. This caused acute kidney injury requiring renal replacement therapy, with a good response to glucocorticoid treatment. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.4719).**

Keywords: *zoledronic acid, bisphosphonates, interstitial nephritis, tubulointerstitial nephritis, renal tubules.*

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Introduction

Intravenous bisphosphonates are widely used for treating osteoporosis and malignant hypercalcemia; they are considered effective and safe. Their renal effects have been extensively described, especially due to their high kidney excretion, which is why they are contraindicated in patients with glomerular filtration rates of less than 30 mL/min/1.73 m^2 (1).

Zoledronic acid is part of the intravenous bisphosphonate group. It has a half-life of 150-200 days and low plasma protein binding (56%) (1). It has proven useful in treating osteoporosis by inhibiting bone resorption; however, cases of renal toxicity associated with its use have been described (2). The most frequently reported histological patterns of kidney injury are acute tubular necrosis and focal and segmental glomerulosclerosis. Below, we describe the case of a patient who received intravenous zoledronic acid and subsequently developed acute tubulointerstitial nephritis.

Case report

This was a female patient in her 70s with a history of hypertension, non-insulin-dependent type 2 diabetes, seropositive rheumatoid arthritis and osteoporosis, being treated with irbesartan, amlodipine, carvedilol, metformin, calcium citrate, vitamin D and 17.5 mg of methotrexate per week.

The patient reported that she had received an initial dose of 5 mg of intravenous zoledronic acid to treat her osteoporosis and, since then, had experienced a runny nose, quantified febrile episodes, self-limited skin erythema, chills, fatigue and headache. The symptoms persisted over the following three days, and she had multiple loose, apparently bloody, stools associated with dysuria, urinary urgency, and abdominal pain, which is why she decided to go to the hospital.

On admission, she was in fair general condition, with no evident abnormalities on complete physical exam, a blood pressure of 104/62 mmHg, heart rate of 106 beats per minute and oxygen saturation of 90% on room air.

Her laboratory tests (Table 1) were remarkable for a complete blood count showing bicytopenia due to leukopenia and normocytic anemia, elevated nitrogen, hyperkalemia and arterial gases indicating metabolic acidemia, without abnormal oxygenation. The urinalysis reported proteinuria, glucosuria, leukocyturia, hematuria and bacteriuria.

Since the patient had tests a month before showing a creatinine level of 0.9 mg/dL, she was diagnosed with KDIGO 3 acute kidney injury with criteria for urgent dialysis, and renal replacement therapy was started on her first day in the hospital.

Over the following hours, her clinical condition deteriorated, with distributive shock. A septic source was found in a urinary tract infection, and empirical antibiotic treatment was started with piperacillin/tazobactam. On her fourth day in the hospital, vasopressor support was discontinued and her clinical condition showed improvement.

Due to her bicytopenia and prior use of methotrexate without folic acid supplementation, the cytopenias were considered to be secondary to the medication. She was given intravenous folinic acid, which completely resolved the cytopenias and normalized the cell lines.

A kidney and urinary tract ultrasound showed normal-sized kidneys with increased echogenicity bilaterally and a cortical thickness of 1.2 cm. She had normal calcium,

phosphorus, uric acid and magnesium levels; her proteinuria was in the subnephrotic range (665 mg in 24 hours) and she had a negative viral panel (HIV test, non-treponemal test and hepatotropes).

Considering the above, the nephrology service suspected that acute kidney failure could be secondary to acute tubulointerstitial nephritis. Given the lack of improvement in nitrogen compound clearance and the ongoing need for hemodialysis (Figure 1), a kidney biopsy was performed on her sixth hospital day, which showed acute tubulointerstitial nephritis changes (Figure 2).

With the infection resolved, glucocorticoid treatment began on hospital day 19: 250 mg of intravenous methylprednisolone every 24 hours, for three doses, followed by prednisolone at 1 mg/kg/day (50 mg). She had a favorable clinical response and did not require further hemodialysis sessions after hospital day 23, with sustained nitrogen compound reduction. She was discharged from the hospital with a glucocorticoid taper and nephrology follow-up.

In this case, the most likely cause of acute tubulointerstitial nephritis was the use of zoledronic acid, especially given the acute symptoms beginning with its administration and rapid kidney function deterioration in a patient with previously normal nitrogen compounds.

Discussion

Zoledronic acid is a powerful long-acting bisphosphonate used extensively for treating malignant hypercalcemia and osteoporosis. When administered intravenously, it is not metabolized; 27 to 62% of the medication binds to the mineral bone, while the rest is excreted through the kidney, mainly in the first hours after infusion (3). The renal excretion mechanisms are mainly glomerular filtration and active transport in the proximal tubule cells (4).

Zoledronic acid-induced acute kidney injury is a rare complication associated with multiple nephrotoxic pathophysiological processes. Acute tubular necrosis has been mainly reported (5), but also focal and segmental glomerulosclerosis, Fanconi syndrome, and, less frequently, acute tubulointerstitial nephritis (3).

The proposed mechanisms include direct tubular cell damage, inducing apoptosis through the mevalonate pathway, similar to its effects on osteoclasts (6). It has also been proposed that tubular damage from the internalization of bisphosphonates in proximal tubular cells causes brush border loss and, therefore, acute tubular necrosis with antigen exposure to the immune system (7).

Risk factors for zoledronic acid-induced nephrotoxicity include advanced cancer, chronic kidney disease, diabetes mellitus, hypertension, severe dehydration, concomitant use of other nephrotoxic agents and rapid infusion (in less than 15 minutes) (8).

Acute tubulointerstitial nephritis is not frequently described as a kidney injury mechanism; there are few cases in the literature, some of which are associated with Fanconi syndrome (6, 9, 10). It has been hypothesized that farnesyl diphosphate inhibition causes mitochondrial and podocyte injury, with decreased levels of prenylated proteins in the proximal tubule and direct toxicity of the parietal epithelium (10).

In our case, the patient did not have Fanconi syndrome, and the kidney biopsy findings only showed acute tubulointerstitial nephritis, this being the first case with these characteristics reported in the literature.

While we cannot determine for sure that zoledronic acid was the cause of acute tubulointerstitial nephritis in our patient, certain clinical characteristics increase suspicion, including the onset of flu-like symptoms immediately after its infusion (11), as well as the timing of the increased nitrogen

Table 1. *Laboratory tests on admission.*

Laboratory tests	Values	Laboratory tests	Values
Leukocytes	930/mm^3	Creatinine	6.1 mg/dL
Hemoglobin	10.1 gr/dL	Urea nitrogen	54 mg/dL
Platelets	206,000/mm^3	C-reactive protein	24 mg/dL
Urinalysis	pH 8, specific gravity 1.007, protein 25, glucose 50, nitrites (+)	Sodium Potassium Chloride	136 mmol/L 5.1 mmol/L 111 mmol/L
Urine sediment	Erythrocytes 11-20 per HPF, leukocytes 30-35 per HPF, abundant bacteria	Uric acid Phosphorus	3.5 mmol/L 4.6 mmol/L
Protein in 24-hour urine	665 mg	Uric acid in 24-hour urine	165 mg
Phosphorus in 24-hour urine	0.09 gr	C3 C4	92 mg/dL 19 mg/dL
Arterial blood gases	pH: 7.19 $PaCO_2$: 20 mmHg $PaCO_2$: 80 mmHg HCO_3^-: 7.6 mmol/L		

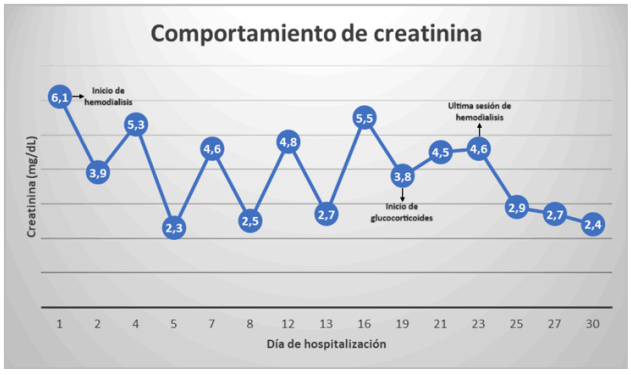

Figure 1. *Creatinine behavior during hospitalization.*

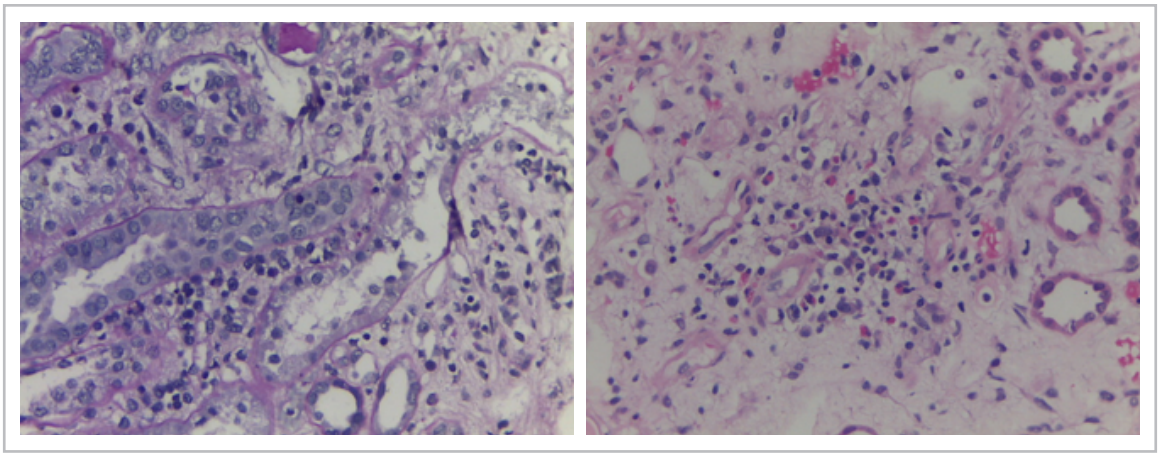

Figure 2. *Kidney biopsy. Kidney biopsy: hematoxylin-eosin stain at 200x. Moderate interstitial inflammatory infiltrate along with eosinophils and tubulitis. Degenerative epithelial changes are evident in many tubules, such as brush border loss, epithelial flattening and lumen dilation with hyaline casts. Interstitial fibrosis and tubular atrophy in 10% of the cortex examined. Findings compatible with acute tubulointerstitial nephritis with mild chronic changes. (These images are the property of the Department of Pathology at Universidad de Antioquia and are reproduced in this article with their permission.)*

compound levels, considering that her glomerular filtration rate was normal the month before.

As far as we know, this is the first case of zoledronic acid-induced acute tubulointerstitial nephritis without concomitant Fanconi syndrome.

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