Podocyte disease following treatment with intravenous ibandronate in an older patient

Podocyte disease associated with ibandronate

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ABSTRACT

Bisphosphonates are commonly used to treat osteoporosis. While renal toxicity is common with pamidronate and zoledronate, few ibandronate-related cases are reported. We describe a rare case of ibandronate-associated nephrotoxicity.

An 88-year-old woman was admitted for edema. She had been receiving intravenous ibandronate treatment for postmenopausal osteoporosis and had no other diagnosed diseases. She was presented with proteinuria, hypoalbuminemia (1.9 g/dL), and an elevated serum creatinine level (1.8 mg/dL).

Renal biopsy revealed podocyte disease, favoring a diagnosis of focal segmental glomerulosclerosis.

She was treated with diuretics, tacrolimus, and fimasartan. Steroids were avoided due to severe osteoporosis. Three months later, the edema had subsided and the laboratory findings had improved (serum albumin 3.5 g/dL, serum creatinine 0.97 mg/dL).

This case emphasizes the importance of careful monitoring of proteinuria and renal function during ibandronate treatment. In older adult patients, kidney biopsy and immunosuppressive treatment may be considered based on physical activity and underlying diseases.

Key Words: Ibandronic acid, Osteoporosis, Postmenopausal, Nephrotic syndrome
INTRODUCTION

Bisphosphonates have been used as key treatments for osteoporosis for over two decades. In the US, alendronate, ibandronate, risedronate, and zoledronate are approved for the prevention and treatment of postmenopausal osteoporosis (PMO). Several studies have demonstrated the effectiveness of these medications as antiresorptive agents, which reduce fracture risk by 40–70%.\(^1\)

Intravenous bisphosphonates show improved patient compliance compared with oral therapy. However, intravenous bisphosphonates have a greater probability of adverse effects, including post-infusion pyrexia, flu-like symptoms, hypocalcemia, mandibular osteonecrosis, and nephrotoxicity, than oral agents.

Bisphosphonates can induce several types of nephrotoxicity. The mechanism by which bisphosphonates induce nephrotoxicity is unknown, but pathological findings suggest certain tendencies. Many reports of pamidronate-associated glomerular diseases, such as focal segmental glomerulosclerosis and zoledronate-associated acute tubular necrosis, appear in the literature.

Unlike pamidronate and zoledronate, recent clinical studies have indicated that intravenous ibandronate does not cause significant kidney damage and is well-tolerated, even in patients with underlying kidney disease.\(^2\) Thus, reports of ibandronate-associated nephrotoxicity are limited.

Herein, we describe a case with podocyte disease accompanied by azotemia following the intravenous administration of ibandronate.

CASE REPORT

An 88-year-old woman was referred to the emergency room because of generalized edema that had developed one month previously. She had been diagnosed with osteoporosis approximately 20 years before. Twenty months earlier, she received a quarterly intravenous administration of ibandronate (3 mg). The last treatment had been administered two weeks before. One month before admission, she noticed edema in both lower extremities that had gradually worsened. At the time of admission, she had gained 7 kg.

After the diagnosis of PMO, calcium and vitamin D were administered for the first 10 years. Subsequently, she took oral ibandronate once monthly for three years and continued calcium and vitamin D without ibandronate for five years. Finally, the patient had received intravenous ibandronate for 20 months before hospitalization.

The patient had no diagnosis of diseases other than hyperlipidemia and osteoporosis. She had been taking statins, calcium, and vitamin D as oral medications, but no new medications had been recently added.

The patient had no family history of renal disease. A physical examination revealed generalized grade 4 edema in both lower extremities. The initial blood pressure and urine volume were 146/81 mmHg and 1,800 mL/day, respectively.
Laboratory tests revealed proteinuria with a urine protein/creatinine ratio (uPCR) of 32 and hypoalbuminemia (1.9 g/dL). The serum creatinine level was elevated (1.8 mg/dL) compared to baseline (0.8 mg/dL). Other serum findings (electrolytes, liver function tests, uric acid, glucose, and complete blood count) were within normal ranges. Serological evaluations for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), antibodies to nuclear antigens, rheumatoid factor, and antineutrophil cytoplasmic antibodies (anti-PR3 and anti-MPO) were all negative. Serum complement (C3 and C4), protein electrophoresis, and immunofixation results were within the normal ranges. Thyroid function test results were normal, and we observed no evidence of cardiogenic problems; the pro-brain natriuretic peptide (BNP) and troponin levels were within the normal range, and chest radiography showed no cardiomegaly. Additionally, renal ultrasonography showed no abnormal findings. We diagnosed the patient with nephrotic syndrome based on the test results.

A renal biopsy was performed to determine the pathological type. Light microscopy revealed mild mesangial hypercellularity and segmental amorphous collagen deposition in the glomeruli (Fig. 1A). The tubules showed marked focal atrophy and interstitial fibrosis (Fig. 1B). The immunofluorescence findings were unremarkable. Electron microscopy revealed diffuse effacement of the foot processes and no electron-dense deposits (Fig. 1C), consistent with podocyte disease favoring focal segmental glomerulosclerosis (FSGS).

Diuretic therapy was initiated to treat the edema. We administered angiotensin receptor blockers and tacrolimus, with adjustment of the tacrolimus dosage according to the target serum level (5–10 ng/mL). Steroids were not administered due to the severe osteoporosis.

A physical examination performed three months later revealed that the edema had resolved. The laboratory findings had improved (uPCR 2, serum albumin 3.5 g/dL, serum creatinine 0.97 mg/dL). Six months later, proteinuria and serum albumin levels had improved to near-normal levels (uPCR 0.64, serum albumin 4.28 g/dL).

**DISCUSSION**

Many drugs and chemicals can cause structural damage to the glomerulus, thereby increasing its permeability to large molecules. This condition often manifests as proteinuria or nephrotic syndrome. Hence, if common causes of proteinuria, and nephrotic syndrome, such as hypertension, diabetes, infection, and autoimmune disease, are excluded, the drug history must be checked. In this case, various etiologies were considered to be the cause of nephrotic syndrome. However, these were excluded through examination; therefore, the use of ibandronate was the most likely cause.

Compared to pamidronate and zoledronate, ibandronate is more protein-bound and has a significantly shorter renal tissue half-life, which might explain the rarity of ibandronate-associated nephrotoxicity. Several studies have demonstrated the renal safety of ibandronate. For example, a study involving >3000 patients with PMO who received 2–12 mg of...
intravenous ibandronate annually observed no adverse renal effects or renal failure, demonstrating a favorable renal safety profile. In this analysis, the mean decline of estimated glomerular filtration in patients exposed to 12 mg of intravenous ibandronate (-0.72 mL/min) was similar to that of patients treated with 2.5 mg of oral ibandronate (-0.28 mL/min).²

Despite the renal safety of ibandronate, one case of nephrotoxicity associated with its oral form has been reported. Jia et al. reported a case of FSGS in a patient with breast cancer after long-term oral ibandronate treatment (50 mg once daily for 29 months).³ In this case, the patient had normal serum creatinine levels but exhibited clinical features of nephrotic syndrome, including edema, heavy proteinuria, and hypoalbuminemia. A renal biopsy revealed collapsing FSGS with significant podocyte injury. When reviewing cases of nephrotoxicity associated with other bisphosphonates, pamidronate primarily targets podocytes, whereas zoledronate primarily affects the tubular epithelium. However, a few cases have reported the opposite pattern.² Contrary to these cases of bisphosphonate nephropathies, our patient showed simultaneous podocyte disease and tubule damage.

Inhibitors of the renin-angiotensin-aldosterone system (RAAS), steroids, and immunosuppressants are commonly used to treat focal segmental glomerulosclerosis. Older adult patients are often hesitant to initiate immunosuppressive treatment. Severe infection is a major side effect of immunosuppressive treatment and contributes to increased mortality, especially in patients of advanced age. In this case, we administered an immunosuppressant (tacrolimus), considering the patient’s underlying disease and level of functional ability. Consequently, proteinuria and renal function improved. The patient remains alive without any treatment-related side effects.

We reported a relatively rare case of nephrotic syndrome associated with ibandronate treatment. Proteinuria and renal function can be reversed with immunosuppressive treatment if the syndrome is diagnosed early and ibandronate use is discontinued. We recommend monitoring proteinuria and renal function for the early detection of nephrotoxicity in patients treated with ibandronate. In older adult patients, the procedural risk of renal biopsy is not significantly high, and treatment outcomes can be anticipated.⁷ Therefore, even in older patients, renal biopsy may be necessary, and immunosuppressive treatment can be started considering the level of physical activity and underlying disease.

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Conflict of interest
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