KIDNEY BIOPSY TEACHING CASE

Nephrotic-Range Proteinuria Following Pamidronate Therapy in a Patient With Metastatic Breast Cancer: Mitochondrial Toxicity as a Pathogenetic Concept?

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INDEX WORDS: Pamidronate; nephrotic syndrome; focal segmental glomerulosclerosis; mitochondrial toxicity.

THE DOSE-DEPENDENT nephrotoxicity of pamidronate was reported several times in humans with malignant disease. In particular, collapsing focal segmental glomerulosclerosis (FSGS) after treatment with high-dose pamidronate was described. Lockridge et al[1] reported another variant of pamidronate renal toxicity in a patient with Langerhans histiocytosis treated with monthly pamidronate. Renal biopsy showed severe acute tubular injury and minimal change disease. Electron microscopy (EM) showed extensive degenerative changes in tubules, but no EM changes in glomeruli were reported.[1] In a study of patients with myeloma who were administered pamidronate, Desikan et al[2] reported FSGS in 2 patients. Barri et al[3] reported a series of 5 patients who developed nephrotic syndrome after pamidronate therapy. Biopsy findings in light microscopy varied from minimal change disease (1 patient) to FSGS (2 patients), collapsing FSGS (1 patient), and global sclerosis (1 patient). Podocyte injury (in various degrees) was the common finding by EM (when performed).[3] Markowitz et al[4] reported similar findings and noted mitochondrial changes in association with pamidronate treatment in 1 biopsy specimen.

We report the case of a patient who developed nephrotic-range proteinuria after treatment with pamidronate for osteolytic bone metastases from an infiltrating ductal carcinoma of the breast.

CASE REPORT

Clinical History

Infiltrating ductal carcinoma of the left breast was diagnosed in a 63-year-old white woman in 1989, and she underwent a modified radical mastectomy and axillary dissection, with no evidence of metastasis. She was free of disease until February 1991, when local relapse of the ductal carcinoma was diagnosed. The tumor was excised, and the patient underwent radiation therapy. In 2002, osteolytic bone metastases were discovered. Because of severe skeletal pain, she was treated with palliative radiotherapy and pamidronate was infused at an interval of 4 weeks (90 mg as a 90-minute infusion). In total, she was treated with pamidronate for more than 3 years, ie, a total dose of about 2.7 g of pamidronate.

Before the pamidronate infusions, she had a serum creatinine level of 0.8 mg/dL (71 μmol/L), which subsequently increased to 1.4 mg/dL (124 μmol/L) in December 2004 and 1.6 (141 μmol/L) in May 2005. In June 2005, the patient was referred to our outpatient clinic with signs of nephrotic syndrome. Blood pressure was 120/80 mm Hg, and pulse was 82 beats/min. Heart, lung, and abdominal examinations were unremarkable. The patient showed edema of both ankles. No skin rash, petechiae, or purpura were present. Medications included simvastatin (40 mg/d), bisoprolol (5 mg/d), letrozol (2.5 mg/d), and thyroxine substitution (75 μg/d). Twenty-four–hour urinary protein excretion was 8 g, serum albumin level was 2.8 g/dL (28 g/L), cholesterol level was 392 mg/dL (10.14 mmol/L), blood urea nitrogen level was 25 mg/dL (8.9 mmol/L), and serum creatinine level was 1.8 mg/dL (159 μmol/L). White blood cell count (6.8 × 1,000 μL), hematocrit (35%), and lactic dehydrogenase (205 U/L) values were normal. Microscopic examination of urine sediment showed 7 white blood cell count, no red blood cells, and some granular casts.

Renal Biopsy

A renal biopsy was performed, and the specimen was analyzed by using light microscopy and EM. Three-micron thick paraffin-embedded sections were cut and stained with periodic acid–Schiff reagent. Immunohistochemical staining for Ki-67

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Received November 22, 2005; accepted in revised form February 21, 2006.

Originally published online as doi:10.1053/j.ajkd.2006.02.189 on April 26, 2006.

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0272-6386/06/4706-0017$32.00/0

doi:10.1053/j.ajkd.2006.02.189

was performed by using the alkaline phosphatase anti-alkaline phosphatase method described in Porubsky et al.[5] For EM, tissue was embedded in araldite. Ultrathin sections were stained with lead citrate and viewed with a transmission electron microscope (Zeiss 900; Zeiss, Germany).

By light microscopy, 11 glomeruli were evaluated, of which 1 was completely sclerosed and 3 were partially sclerosed. The remaining glomeruli showed an edematous endothelium and slight mesangial matrix widening. Visceral epithelial cells did not show proliferation. Occasional adhesions of glomerular capillaries to Bowman capsule could be discerned (Fig 1). Preglomerular arteries were unremarkable. Tubuli showed thickened basement membranes with flattened focally dedifferentiated epithelium and periodic acid–Schiff–positive intraluminal material. The interstitium showed a focal mononuclear cell infiltrate and chronic tubulointerstitial damage of approximately 25%. When stained for the cell proliferation marker Ki-67, solely interstitial macrophages and tubular cells showed occasional positive signals. Proliferative activity could not be detected in glomeruli (Fig 1C). In immunohistochemical staining, immunoglobulin A was positive in protein drops of proximal tubules and negative in glomerular structures. Immunoglobulin G was negative in glomeruli, and immunoglobulin M was positive in the mesangium, as well as in preglomerular arterioles. C1q and fibrinogen was lightly positive in the mesangium.

EM showed expansion of mesangial matrix without proliferation of mesangial cells. The glomerular basement membrane was thickened and wrinkled, but without osmiophilic deposits (Fig 2A). Podocytes showed disturbed architecture with foot-process effacement and pronounced increase in number of mitochondria. Mitochondria varied considerably in shape and size. High-power view showed focal degenerative changes in mitochondrial ultrastructure, with vacuolization and loss of cristae (Fig 2A, inlay). Prominent proliferation of mitochondria also was seen in tubuli (Fig 2B). For comparison, no mitochondrial changes were present in a biopsy specimen from a patient with nephrotic syndrome secondary to minimal change disease (Fig 2C and D).

Follow-Up

After the biopsy, pamidronate therapy was discontinued, and the patient was treated with an angiotensin-receptor-1 (AT1) antagonist (losartan, 50 mg/d). Five months after biopsy, serum creatinine level was 1.3 mg/dL (115 μmol/L), and estimated protein excretion was 1.5 g/g creatinine.

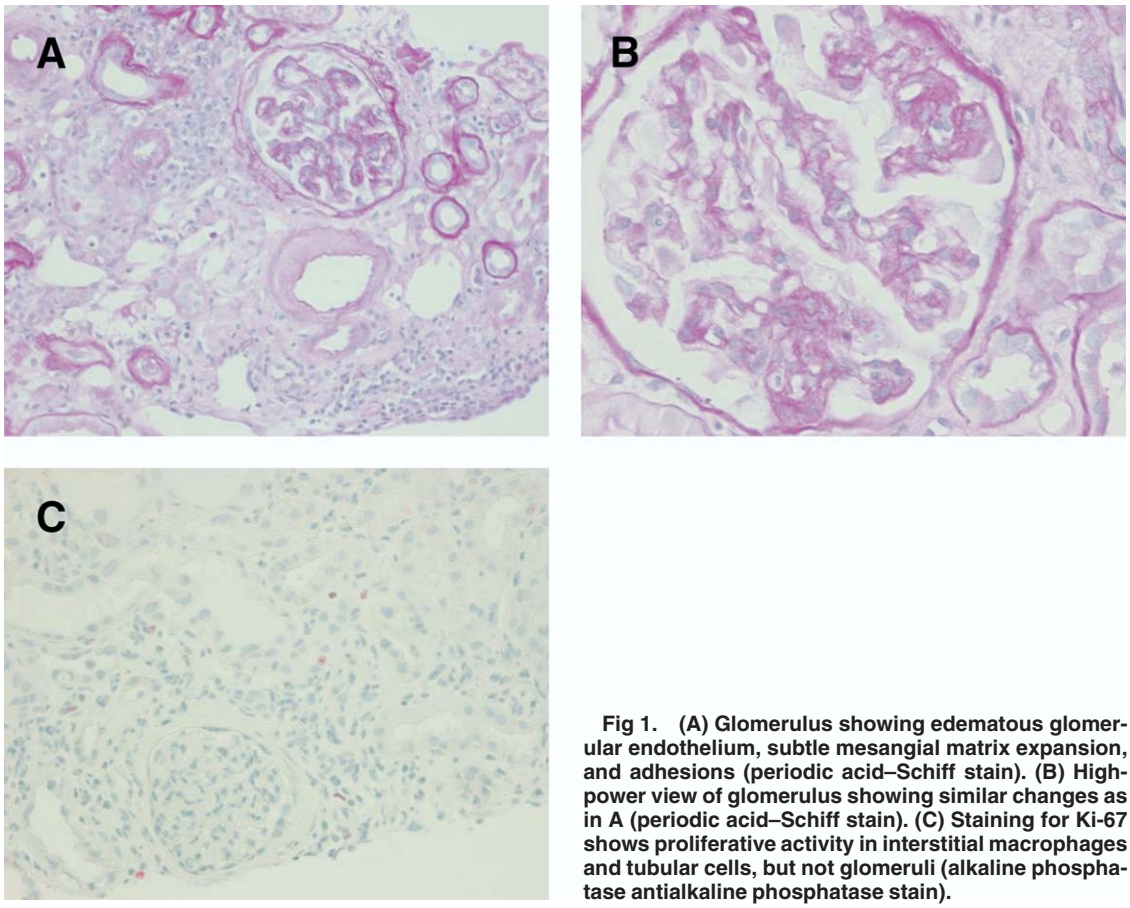

Fig 1. (A) Glomerulus showing edematous glomerular endothelium, subtle mesangial matrix expansion, and adhesions (periodic acid–Schiff stain). (B) High-power view of glomerulus showing similar changes as in A (periodic acid–Schiff stain). (C) Staining for Ki-67 shows proliferative activity in interstitial macrophages and tubular cells, but not glomeruli (alkaline phosphatase antialkaline phosphatase stain).