Collapsing Focal Segmental Glomerulosclerosis Following Treatment with High-Dose Pamidronate

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Abstract. Collapsing focal segmental glomerulosclerosis (FSGS) is a distinct clinicopathologic entity seen most commonly in young African American patients who present with renal insufficiency and nephrotic syndrome. The only epidemiologic factor previously linked to collapsing FSGS is HIV infection. Here clinicopathologic findings are reported for a distinctive population of seven patients, who were older, Caucasian, and HIV negative and developed collapsing FSGS during active treatment of malignancy (multiple myeloma in six patients and metastatic breast carcinoma in one). Although oncologic treatment regimens included vincristine for four patients, doxorubicin for five patients, cisplatin for two patients, and total-body irradiation for one patient, the only agent common to all patients was pamidronate (Aredia). All patients had normal renal function before the administration of pamidronate. Patients began therapy with pamidronate at or below the recommended dose of 90 mg, intravenously, monthly, which was increased to 180 mg monthly in two patients and 360 mg monthly in three patients. Patients received pamidronate for 15 to 48 mo before presentation with renal insufficiency (mean serum creatinine, 3.6 mg/dl) and full nephrotic syndrome (mean 24-h urinary protein excretion, 12.4 g/d). Pamidronate, which is a member of the class of bisphosphonates, is widely used in the treatment of hypercalcemia of malignancy and osteolytic metastases. At the recommended dose of 90 mg, intravenously, monthly, renal toxicity is infrequent; however, higher doses have produced nephrotoxicity in animal models. The temporal association between pamidronate therapy and the development of renal insufficiency, the use of escalating doses that exceed recommended levels, and the distinctive pattern of glomerular and tubular injury strongly suggest a mechanism of drug-associated podocyte and tubular toxicity. These data provide the first association of collapsing FSGS with toxicity to a therapeutic agent.

Focal segmental glomerulosclerosis (FSGS) is the most frequent pattern of idiopathic nephrotic syndrome in African Americans, and its incidence in all races has increased in recent years (1–4). Within the clinicopathologic spectrum of FSGS, collapsing FSGS has been defined as a distinct morphologic variant characterized by marked wrinkling and “collapse” of the glomerular basement membranes and hypertrophy and hyperplasia of overlying podocytes (5,6). This dramatic pattern of disease was first reported in patients with HIV-associated nephropathy (7) but has since been recognized as a morphologic variant of idiopathic FSGS as well (5,6). In both conditions, collapsing FSGS is identified most commonly in young African American patients and typically presents with nephrotic syndrome and renal insufficiency (5,6,8). Compared with the usual form of FSGS with discrete segmental scars, collapsing FSGS is distinguished by more severe nephrotic syndrome, greater resistance to immunosuppressive therapy, and an accelerated course to renal failure (5,6,8). Although the pathogenesis of collapsing FSGS remains unknown, evidence suggests a primary injury to the podocyte, leading to altered cell cycle regulation and reversion to an immature cellular phenotype (9).

With the exception of HIV infection, no common epidemiologic features or toxic exposures have been linked to the development of collapsing FSGS. We report the first association of collapsing FSGS with toxicity to a therapeutic agent. The demographic profile of this cohort differs from that for idiopathic collapsing FSGS in that all seven patients were older, Caucasian, and HIV negative and developed collapsing FSGS in the course of active treatment for malignancy. Although the majority of patients had multiple myeloma and...
received varying types of chemotherapy, with or without radiotherapy, the single unifying factor was prolonged intravenous treatment with high-dose pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ). Supporting the possibility of dose-related toxicity is the observation that, in most cases, renal disease developed only after doses in excess of the standard recommended dose (90 mg, intravenously [IV], each month) were administered for many months.

Clinical Histories

Patient 1

A 63-yr-old Caucasian man was diagnosed with multiple myeloma in 1993, after resection of a left rib plasmacytoma. The patient was treated with melphalan and prednisone, followed by tandem stem cell transplantation with total-body irradiation in late 1995 and again in early 1996. The myeloma remitted for 1 yr until a relapse in January 1997, which was treated with four cycles of cyclophosphamide, dexamethasone, etoposide, and cisplatin, followed by five cycles of cyclophosphamide, vincristine, doxorubicin, and dexamethasone. This chemotherapeutic regimen was discontinued in August 1998, and the patient then was maintained on escalating doses of thalidomide (up to 800 mg/d). The patient had a baseline serum creatinine of 1.2 mg/dl in April 1997. Pamidronate therapy was initiated in May 1997, at a dose of 90 mg IV every 3 wk; this dose was increased to 180 mg IV every 2 wk in February 1998. The serum creatinine increased to 2.0 mg/dl in August 1998 and to 4.0 mg/dl in December 1998. In December 1998, the patient became fully nephrotic, with 24-h urinary protein excretion of 26 g/d, peripheral edema, and serum albumin of 2.7 g/dl. A renal biopsy was performed in December 1998. One mo later, the patient continued to receive pamidronate, had serum creatinine of 8.4 mg/dl, and required hemodialysis.

Patient 2

A 71-yr-old Caucasian woman was diagnosed with multiple myeloma in 1993, after resection of a left rib plasmacytoma. The patient was treated with melphalan and prednisone from late 1997 to early 1998. The patient never received varying types of chemotherapy, with or without radiotherapy, the single unifying factor was prolonged intravenous treatment with high-dose pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ). Supporting the possibility of dose-related toxicity is the observation that, in most cases, renal disease developed only after doses in excess of the standard recommended dose (90 mg, intravenously [IV], each month) were administered for many months.

Patient 3

A 50-yr-old Caucasian woman was diagnosed with multiple myeloma in 1996 and received three cycles of vincristine, doxorubicin, and dexamethasone, followed by tandem stem cell transplantation. The patient was treated with a short course of interferon-α in early 1997 but never received total-body irradiation or thalidomide. In July 1996, she was started on pamidronate at 90 mg IV monthly; this dose was increased to 180 mg IV monthly in January 1998. In October 1999, the patient had a serum creatinine of 0.5 mg/dl, and pamidronate therapy was increased to 180 mg IV bimonthly. Subsequently, the creatinine increased to 2.3 mg/dl in December 1999 and to 2.8 mg/dl in January 2000. At that time, the patient developed full nephrotic syndrome, with 24-h urinary protein excretion of 5.8 g/dl, albumin of 2.8 g/dl, and peripheral edema. A renal biopsy was performed in January 2000. After 3 mo of follow-up monitoring, the patient continued to receive pamidronate, had a serum creatinine of 7.5 mg/dl, and began hemodialysis.

Patient 4

A 53-yr-old Caucasian woman was diagnosed with multiple myeloma and was given a short course of radiotherapy to treat a plasmacytoma of her seventh thoracic vertebra in September 1997. She then received vincristine, doxorubicin, dexamethasone, cyclophosphamide, and melphalan, followed by tandem autologous stem cell transplants in March 1998 and July 1998. The patient did not receive total-body irradiation. Pamidronate therapy was initiated in March 1998, at a dose of 90 mg IV monthly; the dose was increased to 180 mg monthly in July 1998. In November 1999, the patient developed renal insufficiency (creatinine, 3.0 mg/dl) and nephrotic syndrome, with 24-h urinary protein excretion of 14.8 g/dl, albumin of 2.5 g/dl, cholesterol of 725 mg/dl, and peripheral edema. The multiple myeloma was believed to be in clinical remission at that time, and the patient subsequently was maintained on thalidomide (400 mg/dl, started in November 1999) and pamidronate (180 mg monthly) only. A renal biopsy was performed in April 2000. After the biopsy, pamidronate therapy was discontinued and the patient was treated with prednisone. Seven mo later, she had a serum creatinine of 4.3 mg/dl and remained fully nephrotic.

Patient 5

A 49-yr-old Caucasian woman was diagnosed with infiltrating ductal carcinoma of the right breast in 1992 and underwent a modified radical mastectomy and axillary dissection, with no evidence of metastasis. The patient received three courses of chemotherapy with doxorubicin and cyclophosphamide, ending in February 1993. She was free of disease until May 1997, when she was diagnosed with infiltrating ductal carcinoma of the left breast. Despite the discovery of multiple bone metastases, the patient elected to undergo a modified radical left mastectomy. In June 1997, she had a serum creatinine of 0.6 mg/dl and was started on pamidronate (90 mg IV monthly). In December 1997, she underwent bilateral oophorectomy for estrogen depletion, followed by sequential hormonal therapies,
including tamoxifen, fulvestrant, and anastrazole. In October 1998, the pamidronate dose was increased to 180 mg IV monthly. In January 1999, Herceptin (Genentech, South San Francisco, CA) therapy at 110 mg IV every week was initiated. In June 1999, dura-based brain metastases necessitated gamma knife surgery and whole-brain irradiation. In May 2000, the patient developed nephrotic syndrome and renal insufficiency, with 24-h urinary protein excretion of 15 g/d, albumin of 1.9 g/dl, severe peripheral edema, and serum creatinine of 4.8 mg/dl. A renal biopsy was performed in May 2000. Subsequently, the pamidronate therapy was discontinued and the patient was treated with prednisone. Five mo later, she remained fully nephrotic, with a serum creatinine of 4.2 mg/dl.

**Patient 6**
A 76-yr-old Caucasian woman was diagnosed with multiple myeloma in 1982. She was treated with melphalan, prednisone, and vincristine from 1982 to 1983 and with melphalan and prednisone from 1987 to 1988 and again from 1992 to 1993. The patient also received local irradiation to her thoracic and lumbar spine in 1983 and to her left hip in 1989. She never received a bone marrow transplant, total-body irradiation, or thalidomide therapy. In June 1998, the patient had a serum creatinine of 1.2 mg/dl and was started on pamidronate at 90 mg IV monthly. Her creatinine subsequently increased to 1.5 mg/dl in December 1998, to 2.4 mg/dl in June 1999, and to 5.0 mg/dl in September 1999. In September 1999, the patient became fully nephrotic, with 24-h urinary protein excretion of 8 g/dl, albumin of 3.6 g/dl, cholesterol of 334 mg/dl, and peripheral edema. A renal biopsy was performed in September 1999. Despite discontinuation of pamidronate therapy and treatment with steroids, 1 mo later the patient had a creatinine of 8 mg/dl and began hemodialysis.

**Patient 7**
A 77-yr-old Caucasian man was diagnosed with multiple myeloma in 1995, after back pain and discovery of lytic lesions in the T5 vertebra and left rib. He was treated with localized irradiation and one course of chemotherapy with prednisone and cyclophosphamide. The patient never received a bone marrow transplant or total-body irradiation. In July 1996, the patient was started on pamidronate at 60 mg IV monthly. He had a baseline serum creatinine of 1.2 mg/dl and was started on pamidronate at 90 mg IV monthly. He had a baseline serum creatinine of 1.2 mg/dl in July 1996 and again in January 2000. In July 2000, the patient developed renal insufficiency and full nephrotic syndrome, with a serum creatinine of 1.6 mg/dl, 24-h urinary protein excretion of 5.4 g/dl, serum albumin of 3.5 g/dl, and peripheral edema. A renal biopsy was performed in August 2000. After the biopsy, pamidronate therapy was discontinued. After 3 mo of follow-up monitoring, the patient remained nephrotic, with a creatinine of 1.4 mg/dl.

**Materials and Methods**
All seven patients were diagnosed with and treated for malignancy at six different institutions, located in New Jersey (two patients), Delaware, Pennsylvania, Texas, South Carolina, and New York. Five renal biopsies were processed at Columbia Presbyterian Medical Center (those for patients 1, 2, 3, 6, and 7), and two were processed elsewhere and reviewed in consultation. Renal biopsies were processed for light microscopy, immunofluorescence, and electron microscopy according to standard techniques. At least 11 serial sections (3-μm thick) were stained with hematoxylin and eosin, periodic-acid Schiff stain, Masson trichrome stain, and Jones methenamine silver stain. Routine immunofluorescence analyses were performed on 3-μm cryostat sections, using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, κ, λ, fibrinogen, and albumin (Dako Corp., Carpinteria, CA). In six of the seven cases, glomerular tissue was available for ultrastructural evaluation.

Paraffin-embedded tissue was available for immunohistochemical analysis for the five biopsies processed at Columbia Presbyterian Medical Center. For synaptopodin staining, sections were heated in a microwave oven and then overlaid sequentially with 10% normal horse serum (Vector Laboratories, Burlingame, CA), synaptopodin-specific antibody (1:1: Maine Biotechnology, Portland, ME), and biotinylated horse anti-mouse antibody (1:100; Vector Laboratories), followed by avidin-biotin complex (Vector Laboratories) and diamobenzidine, as described previously (9). Staining for Ki-67 (1:400; Immunotech, France) was performed with a Dako autostainer, using the Dako Envision Plus detection system (Carpinteria, CA), horseradish peroxidase, and diaminobenzidine substrate.

Patients’ charts were reviewed for age, gender, race, type of malignancy, detailed history of oncologic treatments, and parameters of renal function. Nephrotic syndrome was defined by the presence of proteinuria of >3.5 g/dl, hypoalbuminemia (<3.5 g/dl), and peripheral edema. In each case, an attempt was made to document and correlate the time course of the development of renal insufficiency and nephrotic syndrome with different forms of oncologic treatment.

**Results**
Table 1 summarizes the clinical features of the seven patients. All seven patients were Caucasian adults, with a mean age of 62.7 yr (range, 49 to 77 yr). The group consisted of five women and two men. All patients had a history of malignancy, including six patients with multiple myeloma and one patient with metastatic breast carcinoma. No patient was HIV positive. Three patients underwent stem cell transplantation and, although multiple patients received localized radiotherapy, with radiation ports well away from renal sites, only one patient received total-body irradiation. Chemotherapeutic regimens included vincristine for four patients, doxorubicin for five patients, thalidomide for three patients, and cisplatin for two patients.

All seven patients were treated with pamidronate for 15 to 48 mo before renal biopsy. Although all began therapy at or below the recommended dose of 90 mg IV monthly (10,11) (for a mean 16.9 mo), the dose subsequently was increased for five of the seven patients, to 180 mg monthly in two patients and to 360 mg monthly in three patients. In these five patients, the elevated dose was administered for a mean of 14.8 mo before renal biopsy. One patient received the standard dose of 90 mg IV monthly for 15 mo, whereas another received 60 mg IV monthly for 48 mo. No patient had a serum creatinine of >1.2 mg/dl before the initiation of pamidronate therapy, and all developed renal insufficiency and nephrotic syndrome while they were maintained on continuous, monthly, IV pam-
idronate therapy. Of note, the pamidronate dosage was not altered during the progression of renal insufficiency.

At the time of renal biopsy, all patients had evidence of renal insufficiency and full nephrotic syndrome (Table 1). The mean serum creatinine was 3.6 mg/dl (range, 1.6 to 5.0 mg/dl), and the mean 24-h urinary protein excretion was 12.4 g/d (range, 5.4 to 26 g/d). All patients were hypoalbuminemic, and all had peripheral edema.

After renal biopsy, one patient (patient 2) immediately began dialysis and three additional patients (patients 1, 3, and 6) required dialysis within 1 to 3 mo. Of note, two of the three patients who experienced disease progression continued to receive pamidronate; one patient also was treated with a course of prednisone. In contrast, pamidronate therapy was discontinued in the remaining three patients (patients 4, 5, and 7), of whom two had decreases in serum creatinine over the course of 3 to 7 mo and none required renal replacement therapy.

The renal biopsy findings in patients with pamidronate-associated collapsing FSGS are highlighted in Table 2. All seven biopsies displayed lesions of collapsing FSGS characterized by implosive retraction of the glomerular basement membranes and hyperplasia of the overlying podocytes, some of which contained intracytoplasmic protein resorption droplets (Figure 1, A and B). Diffuse podocyte swelling was frequently noted in glomeruli without FSGS lesions. The mean number of glomeruli sampled was 17.1 (range, 4 to 35), and the mean number of glomeruli with FSGS lesions was 3.4 (range, 2 to 5). All biopsies displayed diffuse severe tubular degenerative changes, including luminal ectasia, epithelial simplification, loss of the brush border, nuclear pleomorphism with prominent nucleoli, cytoplasmic vacuolization, and focal apoptosis (Figure 1C). The degree of tubular atrophy and interstitial fibrosis ranged from mild to severe, with focal tubular microcyst formation.

In electron microscopic studies, the podocytes displayed diffuse loss of their highly differentiated cytoarchitecture, including the disappearance of primary processes and extensive foot process effacement over a mean of 84% (range, 60 to 100%) of the glomerular capillary surface area (Figure 1D). Many podocytes had increased organelar content, including numerous small mitochondria. The proximal tubular epithelium also displayed extensive degenerative changes, including epithelial simplification, loss of the apical brush border, and dilation of the endoplasmic reticulum (Figure 1E). A rare

Table 1. Clinical parameters for patients with pamidronate-associated FSGS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
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<td>F</td>
<td>F</td>
<td>F</td>
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<td>M</td>
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<td>C</td>
<td>C</td>
<td>C</td>
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<td>MM</td>
<td>MM</td>
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<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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<td>4</td>
<td>16</td>
<td>15</td>
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<td>time (mo) at &gt;90 mg/mo</td>
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<td>180</td>
<td>90</td>
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<td>3</td>
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<td>Yes</td>
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a M, male; F, female; C, Caucasian; MM, multiple myeloma; Br Ca, carcinoma of breast; HD, hemodialysis; FSGS, focal segmental glomerulosclerosis; NA, not available.
b Patient 7 never received >60 mg/mo of pamidronate.
c Before pamidronate administration.
d Patient 2 began to undergo dialysis immediately after biopsy.
Table 2. Pathologic findings for patients with pamidronate-associated FSGS

<table>
<thead>
<tr>
<th>Finding</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
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<td>17</td>
<td>28</td>
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<td>EM, foot process fusion (%)</td>
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<td>100</td>
<td>90</td>
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a GS, glomerulosclerosis; TA and IF, tubular atrophy and interstitial fibrosis; PCD, plasma cell dyscrasia; EM, electron microscopy; NA, not available.

Discussion

Pamidronate disodium (Aredia), a member of the bisphosphonate class of drugs, is an inhibitor of bone resorption. Its mechanism of action is thought to involve direct binding to calcium phosphate crystals within the bone matrix, with resultant inhibition of osteoclastic activity. Established indications for the use of pamidronate include hypercalcemia (e.g., hypercalcemia of malignancy), Paget’s disease, and osteolytic metastases (e.g., in patients with multiple myeloma or carcinoma of the breast) (12).

The efficacy of pamidronate in patients with osteolytic metastases has been established. In a large, placebo-controlled study of 392 patients with stage III multiple myeloma, nine monthly cycles of 90 mg IV of pamidronate were shown to reduce skeletal complications and bone pain and to improve quality of life (10). When the study was extended to 21 monthly cycles of therapy, similar results were obtained (13). Of note, four of the 198 patients who received pamidronate were removed from the trial because of worsening renal insufficiency, although data on renal histologic evaluation were not provided (13). Similarly, a large, placebo-controlled study was performed on 382 women with stage IV breast cancer and osteolytic metastases (11). The study population received up to 24 cycles of 90 mg of pamidronate, administered IV, every 3 to 4 wk and experienced a significant decrease in skeletal complications. In that study, a single patient discontinued pamidronate treatment because of renal failure, which was believed to be “possibly related to the study drug” (11).

After reaching the systemic circulation, bisphosphonates either bind to bone or are excreted unchanged via the kidneys. Animal models have shown that the clearance of bisphosphonates can exceed the GFR, suggesting active tubular secretion. This observation provides the basis for slow intravenous infusion of pamidronate over several hours, in an attempt to prevent toxic concentrations from being reached at the level of the proximal tubule (14). Despite slow infusion, human studies demonstrated a 1 to 8% incidence of elevation in serum creatinine after administration of bisphosphonates (15). Those studies also suggested that the newer, more potent bisphosphonates are effective at lower doses, thereby producing less renal toxicity (i.e., 2% for pamidronate) (15).

Multiple lines of evidence point to pamidronate as the etiologic agent producing collapsing FSGS in our cohort of patients. First is the previously established, albeit infrequent, renal toxicity associated with this agent (11,13,15). The recommended dose of pamidronate in humans is 0.4 to 1.5 mg/kg, based in part on rat studies that showed no nephrotoxicity at comparable levels of up to 1.5 mg/kg (16). However, dose-dependent nephrotoxicity was observed in rats given higher doses (5.0 to 50.0 mg/kg) (16). Although a short-term study on 12 patients treated with pamidronate at 90 mg IV weekly for 4 consecutive weeks revealed no evidence of nephrotoxicity...
(17), no studies have addressed the potential nephrotoxicity of long-term use at higher-than-standard doses. As inferred from data in rats, pamidronate dosing schedules that are 2 to 4 times greater than recommended are likely to increase the risk of renal toxicity. The renal biopsy findings of sparse interstitial inflammatory infiltrates, without inflammation within tubules...
“tubulitis”) or eosinophils, and the lack of demonstrable antibodies in immunofluorescence analyses suggest that pamidronate acts as an epithelial toxin that targets both the podocyte and the tubular epithelium, rather than via an immunologic or allergic mechanism.

The clinical profiles of our patients also provide strong evidence of high-dose pamidronate being the etiologic agent in collapsing FSGS. The occurrence of the distinctive pattern of collapsing FSGS in a cohort of predominantly older and exclusively Caucasian individuals, all with a history of malignancy, is striking and is in sharp contrast to the predominantly young, African-American population among whom idiopathic collapsing FSGS typically is observed. No patient had evidence of multiple myeloma-associated nephropathy (e.g., amyloidosis, light chain deposition disease), radiotherapy- or chemotherapy-associated thrombotic microangiopathy, or urate nephropathy (tumor lysis syndrome). Although patients were exposed to a variety of potent nephrotoxins, including total-body irradiation and cisplatin, the only potential nephrotoxin common to all patients was pamidronate. Furthermore, the typical patterns of nephrotoxicity observed with these other agents are thrombotic microangiopathy (total-body irradiation) and acute tubular injury without glomerular pathologic features (cisplatin). The only chemotherapeutic agent that has been implicated in FSGS is interferon-α, which was administered to only one of the seven patients and which has not been associated with the collapsing form of FSGS (18).

Temporally, the development of proteinuria and renal insufficiency closely paralleled the administration of pamidronate in escalating doses that exceeded the recommended levels. All seven patients had normal renal function before the start of pamidronate therapy. Renal insufficiency and nephrotic syndrome did not develop until the dosage was increased to 180 mg/mo in patients 4 and 5 and to 360 mg/mo in patients 1, 2, and 3. Two patients (patients 6 and 7) never received pamidronate at greater than the recommended dose of 90 mg/mo. Furthermore, two of the three patients in whom pamidronate was discontinued after biopsy had decreases in serum creatinine at 3 and 5 mo; all three patients have not yet required dialysis.

The concept of a drug-induced form of FSGS is not unique; in animal models, FSGS can be induced by treatment with

Figure 2. (A) Immunohistochemical staining for proliferation marker Ki-67, showing numerous cell cycle-engaged tubular epithelial cells (patient 2). (B) Immunohistochemical staining for Ki-67 in a glomerulus from patient 7, showing numerous cycling podocytes overlying an area of collapse and a rare positive parietal epithelial cell. (C) Glomerulus from a normal adult control subject, showing intense global immunoreactivity for synaptopodin at the base of the podocytes. (D) Representative glomerulus from patient 2, showing global reduction and segmental loss of podocyte staining for synaptopodin. Magnifications: ×200 in A; ×500 in B; ×400 in C and D.
doxorubicin (19,20) or puromycin aminonucleoside (21). In rats, a single intravenous dose of puromycin aminonucleoside produces a glomerulopathy that initially resembles minimal-change disease but evolves into FSGS with time (21). In contrast, a single injection of doxorubicin can produce an animal model of FSGS (20), although this effect is more consistently observed after two successive doxorubicin administrations (20).

In humans, drug-induced nephrotic syndrome related to minimal-change disease or FSGS is uncommon but has been reported with interferon-α, nonsteroidal anti-inflammatory drugs, and lithium. In none of those cases have collapsing FSGS lesions been observed (18,22). Within the spectrum of FSGS, collapsing FSGS represents the most severe morphologic expression. Evidence from both HIV-associated and idiopathic forms indicates a direct podocyte injury, whereby podocytes enter the cell cycle and lose their differentiated phenotype, with reduced expression of maturity markers such as Wilm’s tumor protein WT-1, common acute lymphoblastic leukemia antigen, podocalyxin, and synaptopodin (9). The same findings of increased podocytic proliferation index and reduced expression of synaptopodin observed in our patients with collapsing FSGS after high-dose pamidronate therapy suggest a direct podocyte effect. Although tubular toxicity was proposed previously for high-dose pamidronate, tubular injury alone is insufficient to account for the collapsing FSGS and nephrotic syndrome. The severe tubular and glomerular alterations observed after high-dose pamidronate therapy suggest combined tubular epithelial and podocyte toxicity. Similar broad renal epithelial toxicity has been observed in HIV-associated nephropathy, in both human and transgenic models (23,24).

The potential mechanism of renal epithelial toxicity may involve cellular effects similar to those documented in osteoclasts. A major action of bisphosphonates is to mimic the calcium-chelating property of inorganic pyrophosphate, an endogenous regulator of bone mineralization, thereby inhibiting the lipid modification of hydroxyapatite of the bone matrix (25). However, in addition to these physicochemical properties, bisphosphonates are internalized by osteoclasts and exert a number of cellular effects. The nitrogen-containing bisphosphonates, such as pamidronate, can inhibit the intracellular mevalonate pathway required for the posttranslational lipid modification (i.e., prenylation) of small GTPases (26). By anchoring the GTPases in cell membranes, lipid prenyl groups ensure the correct subcellular compartmentalization and functioning of GTPases in a variety of cellular processes, including integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis (25,27–30). Through incorporation into ATP analogues, bisphosphonates also can impair cell energetics via inhibition of ATP-dependent metabolic pathways (31). At nontoxic doses, bisphosphonates have been shown to disrupt the osteoclast cytoskeleton by inhibiting the assembly of actin rings, leading to loss of the osteoclast ruffled border (32). The unique cytoarchitecture of osteoclasts and podocytes (both of which have a highly differentiated cytoskeleton with specialized processes and motility), coupled with the high drug levels attained in bone and kidney, may explain the cell-specific toxicities observed. Finally, via their homology to certain T-cell ligands, bisphosphonates have been reported to stimulate γδ T cells, leading to increased production of interferon-γ and other cytokines (33). A potential mechanism of podocyte injury by T-cell–derived lymphokines or “permeability factors” has been proposed for idiopathic FSGS (34,35).

Pamidronate is a widely used and important therapeutic agent in the treatment of hypercalcemia of malignancy and osteolytic metastases. Large-scale, long-term studies are necessary to establish the safety of this agent when it is used at doses that exceed the recommended levels, especially in patients with renal insufficiency. Because of the possible direct podocyte toxicity of this drug, periodic evaluations for proteinuria, in addition to measurements of renal function, may provide a useful means to monitor patients at risk for developing pamidronate nephrotoxicity.

High-dose pamidronate administration seems to be the first drug-related cause of collapsing FSGS, and pamidronate joins interferon-α and lithium as potential inducers of FSGS. In patients with multiple myeloma, renal biopsies often are performed to assess the pathogenesis of proteinuria and/or renal insufficiency. Although chemotherapeutic agents may be associated with acute tubular injury or thrombotic microangiopathy, they do not produce nephrotic syndrome. In contrast, the presence of full nephrotic syndrome in this clinical setting usually heralds the development of amyloidosis or light chain deposition disease. The causes of nephrotic syndrome in this patient population now may be expanded to include collapsing FSGS after treatment with high-dose pamidronate.

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References


