Collapsing glomerulopathy induced by long-term treatment with standard-dose pamidronate in a myeloma patient

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Introduction

Bisphosphonates currently are important antiresorptive agents used in the treatment of metabolic bone diseases, including tumour-associated osteolysis and hypercalcaemia, Paget’s disease and osteoporosis. These drugs cause a loss of the osteoclast ruffled border, disruption of the osteoclast cytoskeleton and inhibition of actin ring formation, sufficient to prevent bone resorption [1]. Several studies have demonstrated that high concentrations of bisphosphonates can cause apoptotic cell death of mouse, rat and rabbit osteoclasts in vitro and in vivo by inhibiting the mevalonate pathway and protein prenylation [2]. Bisphosphonates are excreted unchanged via the kidneys. The high drug levels attained in the kidney may cause renal toxicity through a mechanism similar to that described in osteoclasts.

Short-term [3] and long-term [4–6] tubular toxicity of pamidronate were reported in humans. Recently, an association between collapsing glomerulopathy and prolonged intravenous treatment with high-dose pamidronate was reported in patients with malignancy [4,5]. We describe a patient with multiple myeloma in remission who developed collapsing glomerulopathy without significant tubular damage after long-term treatment with standard-dose pamidronate.

Case

A 52-year-old woman was referred to the haematology out-patient clinic with anaemia and lytic vertebral lesions. Monoclonal serum IgG fraction and urine lambda light chain were found. Bone marrow aspiration showed 90% plasma cells and multiple myeloma was diagnosed. The patient was treated with three cycles of vincristine, doxorubicin and dexamethasone, followed by autologous stem cell transplantation and a short course of interferon-alpha. Later, she received two courses of pulse dexamethasone and thalidomide was started. Pamidronate therapy for the bone lesions was initiated soon after the diagnosis of multiple myeloma was made. A dose of 90 mg over 150–180 min every 4 weeks was given. After a year and a half of treatment, urinary and serum paraprotein were undetectable, the level of beta2-microglobulin was 0.0037 g/l (normal range 0–0.003 g/l), and there was no plasmacytosis in bone marrow. While in remission, serum creatinine rose progressively from 88.4 to 203.3 μmol/l. The patient developed nephrotic syndrome with a 24 h urinary protein excretion of 17 g, serum albumin of 27 g/l, cholesterol of 9.54 mmol/l and peripheral oedema. Autoimmune and viral serological evaluation that included antibodies to HIV and parvovirus B19 was negative. At that time, serum paraprotein was undetected and the urinary Bence Jones proteins level was non-significant. A renal biopsy was performed and seven glomeruli were examined (Figure 1). Light microscopy showed that the glomeruli were normocellular and no thickening of the glomerular capillary wall was seen. One glomerulus showed global collapse of the glomerular tuft with hypertrophy and hyperplasia of epithelial cells and adhesions to Bowman’s capsule (Figure 2). The glomerulus was surrounded by atrophic tubules and interstitial fibrosis (Figure 3). There were well preserved tubules in other parts of the biopsy specimen. Immunofluorescence staining for IgA, IgG, IgM, kappa was negative. Electron microscopy showed glomerular collapse with wrinkling and folding of the basal lamina, foot process effacement of the glomerular podocytes. No electron dense deposits were present. The pathological findings were consistent with collapsing glomerulopathy. Pamidronate was stopped. Oral treatment with 1 mg/kg/day prednisone

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was initiated. Treatment was discontinued after 3 months because of lack of response and severe side effects. Serum creatinine continued to rise and a month later haemodialysis was started. The total number of injections of pamidronate the patient had received was 40 over 3.5 years. The total dose of the drug during the whole period of treatment was \( \sim 3.2 \text{ g.} \)

**Discussion**

Collapsing glomerulopathy is a distinct morphologic variant of focal segmental glomerulosclerosis (FSGS) characterised by marked wrinkling and 'collapse' of the glomerular basement membrane and hypertrophy and hyperplasia of overlying podocytes [7,8]. Compared with classic FSGS, the collapsing variant is distinguished by a more severe nephrotic syndrome, greater resistance to immunosuppressive therapy, rapid progression to end-stage renal failure and predominant occurrence in African American patients [7,8]. Collapsing glomerulopathy was reported in patients with HIV-associated nephropathy [9]. Additionally, an idiopathic variant of collapsing glomerulopathy has been defined [8]. An increased incidence of parvovirus B19 DNA in renal biopsies of patients with non-HIV collapsing glomerulopathy was reported [10,11]. Li et al. [12] found evidence of Simian virus 40 replication in human kidney and suggested that this virus may contribute to the pathogenesis of FSGS.

Recently, Markowitz et al. [4] described seven patients with collapsing glomerulopathy and severe tubular degenerative changes in all those cases and related the disease to treatment with high-dose pamidronate. Another case report described a patient with multiple myeloma who was treated with high-dose pamidronate and developed nephrotic syndrome due to collapsing glomerulopathy, with subsequent fluctuations in proteinuria in parallel with discontinuation and reintroduction of the drug [5].

Our patient was white, HIV and parvovirus B19 negative. She was treated with a standard dose of pamidronate (90 mg/month) for more than 40 months, developed severe nephrotic syndrome and rapidly deteriorated to end-stage renal failure despite discontinuation of the drug and treatment with steroids. Renal biopsy showed glomerular injury consistent with collapsing glomerulopathy and relatively well preserved tubules and interstitium. There was no evidence of cast...
nephropathy, amyloidosis or light chain deposition disease.

It appears that the potential mechanism of renal pamidronate toxicity on glomerular epithelial cells as well as tubular cells involved cellular effects similar to those described in osteoclasts. Therefore, apoptosis of podocytes may be responsible for the nephrotoxicity developed in our patient.

Studies in primary and recurrent FSGS implicate podocytes injury in the pathogenesis of segmental glomerular scarring [13]. Evidence from the HIV-associated and non-HIV collapsing forms also supports the concept of primary podocytes injury, resulting in a loss of differentiation markers and a dysregulated podocytes phenotype [14]. Shankland et al. [15] have demonstrated that human podocytes differentiation and proliferation depends on the levels of specific cyclin-dependent kinase inhibitors. An important consequence of podocytes dysregulation is the induction of apoptotic cell death. Apoptosis may constitute a direct pathogenic mechanism for loss of podocytes in FSGS [16] or, alternatively, it may represent a physiological process for the elimination of sublethally injured or excessively proliferating podocytes [17].

Our case of pamidronate-induced collapsing glomerulopathy showed well preserved tubules and interstitium. The biopsies of patients with HIV-related glomerulopathy [9] and previously reported cases of pamidronate-induced collapsing glomerulopathy [4,5] displayed diffuse severe degenerative changes in tubules and tubular microcyst formation. Banerjee et al. [3] described a patient with biopsy-proven acute tubular necrosis from pamidronate with a reversible renal failure due to solely tubular damage. The mechanism of tubular toxicity of pamidronate is probably similar to that of glomerular lesions: induction of apoptosis in tubular cells. An alternative explanation for tubular injury may be tubular epithelial cell damage by transdifferentiated podocytes having acquired macrophagic epitopes and migrating from the tuft to Bowman’s space or drifting within the tubular lumens as was described in progressive glomerulonephritides [18] and collapsing glomerulopathy [19].

In the previously reported [4,5] and our cases of pamidronate-induced glomerulopathy, the total dose of the drug administrated ranged from 1.3 to 8.6 g. This wide range indicates that additional factors may influence the patient susceptibility to renal injury, such as the duration of intravenous infusion of the drug or underlying diseases like malignancy.

In conclusion, pamidronate-induced glomerulopathy can occur at recommended doses although long-term treatment is needed. Therefore, pamidronate-treated patients should be monitored for changes in renal function and proteinuria. The development of nephrotic syndrome and renal failure during remission of multiple myeloma should raise the possibility of collapsing glomerulopathy due to pamidronate.

Thus, pamidronate represents a new, toxic cause in the aetiology of collapsing glomerulopathy in human. Apoptosis is a possible mechanism for podocyte injury in this entity.

Conflict of interest statement. None declared.

References


Fig. 3. Renal biopsy shows glomerulus with global collapse of the glomerular tuft with surrounding tubules exhibiting atrophy. Interstitial fibrosis is also present (silver methenamine stain ×200).


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