

CASE REPORT

Glomerular and Tubular Basement Membrane Calcinosis: Case Report and Literature Review

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• Nephrocalcinosis most commonly manifests as renal calculi or deposition within the tubulointerstitial compartment. Conversely, calcium deposition within glomeruli is extremely rare. We present the case of a 50-year-old man with multiple medical problems, including hepatitis C, diabetes, hypertension, proteinuria, and chronic renal failure. Renal biopsy showed impressive calcium deposits along glomerular basement membranes and tubular basement membranes, within intracellular organelles, and in the interstitium in the setting of a normal serum calcium level. Seven months after biopsy, the patient is on hemodialysis therapy. Although serological and medical examination failed to show a treatable cause for this patient's glomerular calcinosis, individual case reports in the literature have described resolution of calcinosis-associated nephrotic syndrome with treatment of the primary cause of hypercalcemia. *Am J Kidney Dis* 47:E23-E26.

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NEPHROCALCINOSIS most commonly affects the tubulointerstitial compartment of the kidney in cases of systemic hypercalcemia due to a variety of conditions, including hyperparathyroidism, multiple myeloma, other malignancy, hypervitaminosis D, or sarcoidosis.¹ Glomerulosclerosis is frequently seen in such cases, but most often is considered secondary to tubulointerstitial or vascular disease. Calcium deposition within glomeruli, including along glomerular basement membranes and within the mesangium, has been reported in rare individual cases.²⁻⁶ We describe a case of nephrocalcinosis involving glomerular basement membranes and mesangial areas, together with tubular basement membranes and interstitium, in a patient with multiple medical problems.

CASE REPORT

A 50-year-old man had hepatitis C, hypertension, diabetes mellitus type 2, and a history of intravenous drug use. Approximately 4 years before biopsy, he had bacterial endocarditis, resulting in cardiac valve replacement, and was treated transiently with hemodialysis. At the time of the present biopsy, the patient had chronic renal insufficiency, with serum creatinine values of 4.6 to 5.7 mg/dL (407 to 504 $\mu\text{mol/L}$), a calculated glomerular filtration rate of 14 mL/min (0.23 mL/s), and 3 to 4 g/24 h proteinuria. Spot urinalysis showed 100 mg/dL (1.0 g/L) of protein, 50⁺ white blood cells, and 3 to 4 red blood cells/high-power field, with other parameters negative or normal. Multiple serum chemistry values during the 5 months before biopsy were as follows: normal sodium at 138 to 141 mEq/L (138 to 141 mmol/L), hyperkalemia with potassium at 6.0 to 6.4 mEq/L (6.0 to 6.4 mmol/L), hyperchloremia with chloride at 113 to 120 mEq/L (113 to 120 mmol/L), and low bicarbonate, with blood carbon dioxide of 12 to 17 mEq/L (12 to 17 mmol/L). Serum glucose level was as high as 164 mg/dL (9.1 mmol/L),

but liver function test results, including total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase, were within normal limits. Serum albumin level was within the low-normal range. The patient was anemic, with a hemoglobin level of 9.6 to 10 g/dL (96 to 100 g/L) and hematocrit of 28% to 29%; platelet count also was low at 52 to 87 $\times 10^3/\mu\text{L}$ (52 to 87 $\times 10^9/\text{L}$). The patient's serum calcium value was within normal limits at all time points tested, ranging from 8.5 to 8.9 mg/dL (2.12 to 2.22 mmol/L; normal range, 8.5 to 10.5 mg/dL [2.12 to 2.62 mmol/L]). Serum phosphorus concentration was elevated 1 month before biopsy at 6.5 mg/dL (2.10 mmol/L; normal range, 2.4 to 4.7 mg/dL [0.77 to 1.52 mmol/L]). Serum parathyroid hormone concentration subsequent to biopsy was elevated at 116 to 120 pg/mL (116 to 120 ng/L; normal range, 6 to 40 pg/mL [6 to 40 ng/L]). Renal ultrasound showed kidneys of 11 and 12 cm in size, without hydronephrosis and with slightly echogenic cortices. Chest radiograph was unremarkable.

Renal biopsy tissue was submitted for light, immunofluorescence, and electron microscopic evaluation. The light microscopy portion of the specimen consisted of a single subcapsular core of renal cortex containing 10 glomeruli. All had patent capillaries, but were markedly abnormal (Fig 1). Hematoxylin and eosin- and periodic acid-Schiff-stained sections showed glomerular ischemia, including periglomerular fibrosis and

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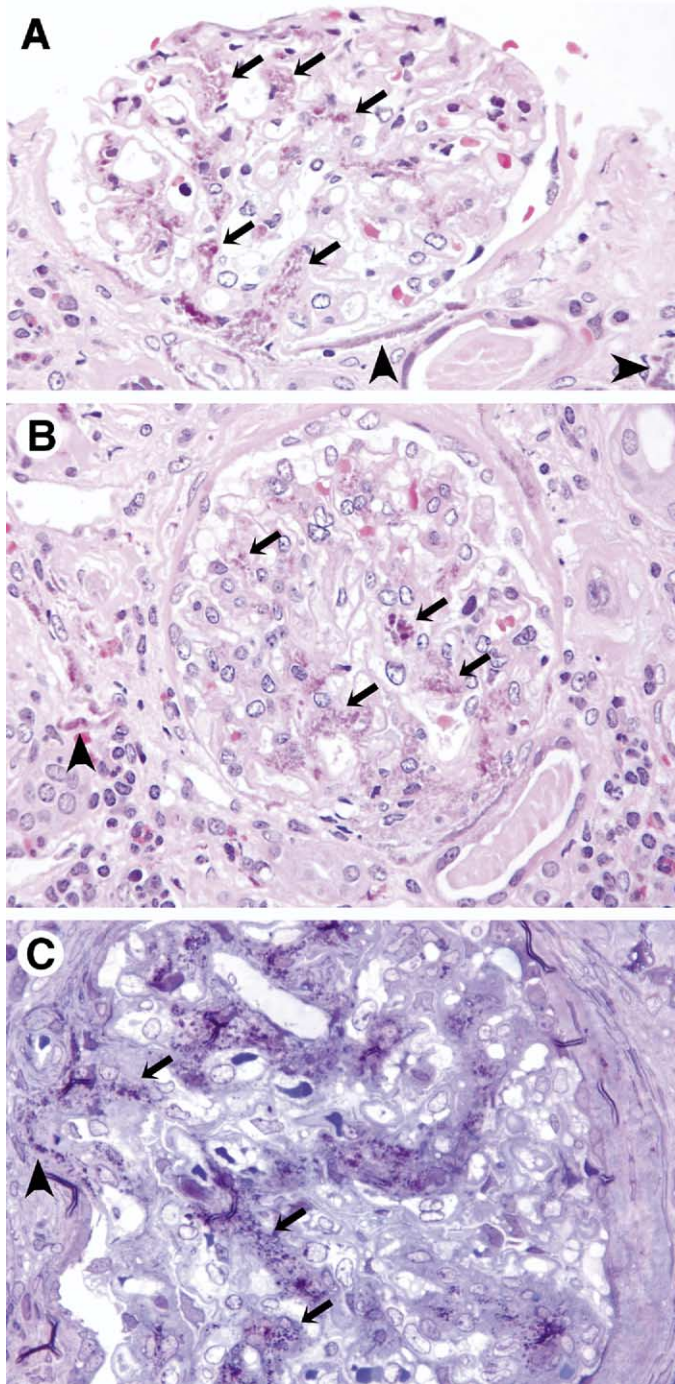


Fig 1. Light microscopic images. (A, B) Hematoxylin and eosin–stained sections show amphophilic granular calcification within glomerular mesangial areas (arrows), Bowman capsule, and tubular basement membranes (arrowheads), along with tubulointerstitial nephritis. (C) Toluidine blue–stained plastic sections show deep blue staining calcification in mesangial areas (arrows) and Bowman capsule (arrowhead). (Original magnification: [A, B] $\times 500$, [C] $\times 600$.)

wrinkling and retraction of capillary tufts. There was no evidence of segmental or global glomerulosclerosis, crescents, necrosis, or karyorrhexis. Glomerular basement membranes appeared to have nearly normal thickness, although this was difficult to assess in the setting of ischemia. Mesangial areas were mildly expanded. The most striking finding was the granular amphophilic material deposited within mesangial ar-

eas, along glomerular and tubular basement membranes, and in the interstitium. Hematoxylin and eosin staining characteristics were consistent with metastatic calcification. In addition, the granular material appeared periodic acid–Schiff positive; von Kossa and Alizarin red staining were attempted, but were unsuccessful due to Zenker’s fixation and minimal remaining tissue. Tubular basement membranes were markedly thickened,

surrounding atrophic tubules. The kidney appeared end stage, and atrophy was estimated to involve 80% to 90% of tubules. There was lymphocytic interstitial inflammatory infiltrate, with admixed eosinophils and neutrophils, concentrated in the sub-capsular area. Tamm-Horsfall protein casts were present within tubules, as was a rare neutrophil. Small- or medium-sized arteries were not present in the biopsy specimen.

Immunofluorescence microscopy was performed on a fragment of cortex containing 2 open, but ischemic, glomeruli. Direct immunofluorescence studies for C3, immunoglobulin G, immunoglobulin M, immunoglobulin A, fibrinogen, and C1q were negative (not shown). Staining for κ and λ light chains was attempted, but was uninterpretable because of tissue loss.

Tissue submitted for electron microscopy contained 4 ischemic glomeruli. Toluidine blue-stained thick sections showed prominent aggregates of darkly staining material within mildly expanded mesangial areas, as well as along glomerular and tubular basement membranes (Fig 1). Electron microscopic examination showed that the particulate material was of extremely high electron density, with granular ultrastructure, again consistent with calcium deposition. Electron-dense material was concentrated within mesangial areas, but sparse particles were seen along glomerular basement membranes. There was heavy deposition within Bowman capsule and tubular basement membranes. Calcification of mitochondria and other intracellular organelles also was seen (Fig 2). Amyloid fibrils or evidence of monoclonal immunoglobulin deposition disease was not identified. Glomerular basement membranes were wrinkled and of variable thickness, including some loops at 400 nm (within normal limits) and other loops with glomerular basement membrane thickness of 600 to 700 nm (mildly increased). Mesangial matrix was increased, with swelling of mesangial and endothelial cell cytoplasm. Podocyte foot processes showed partial effacement.

Given the end-stage appearance of the renal biopsy tissue, further serological or electrolyte workup was not pursued. Dialysis therapy was initiated approximately 7 months after biopsy, given a serum creatinine level of 7 mg/dL (534 μ mol/L) and significant edema. At that time, there was 2 to 3 g/24 h proteinuria, whereas serum calcium level was still within normal range at 8.0 mg/dL (2.00 mmol/L), serum phosphorus concentration remained elevated at 6.0 mg/dL (1.94 mmol/L), and parathyroid hormone concentration increased to 290 pg/mL (290 ng/L).

DISCUSSION

Rare case reports of metastatic calcinosis involving glomeruli have been published in the literature.²⁻⁶ This phenomenon was described by Mulligan² in 1947 in a review of metastatic calcification; of 23 patients with metastatic calcification attributed to renal disease, 10 had "significant calcification" of the kidney localized to tubules and interstitium, with "glomeruli and the basement membranes of tubules less frequently involved."² In 1969, Ross and Wing³ reported a dramatic case of calcium deposition within glo-

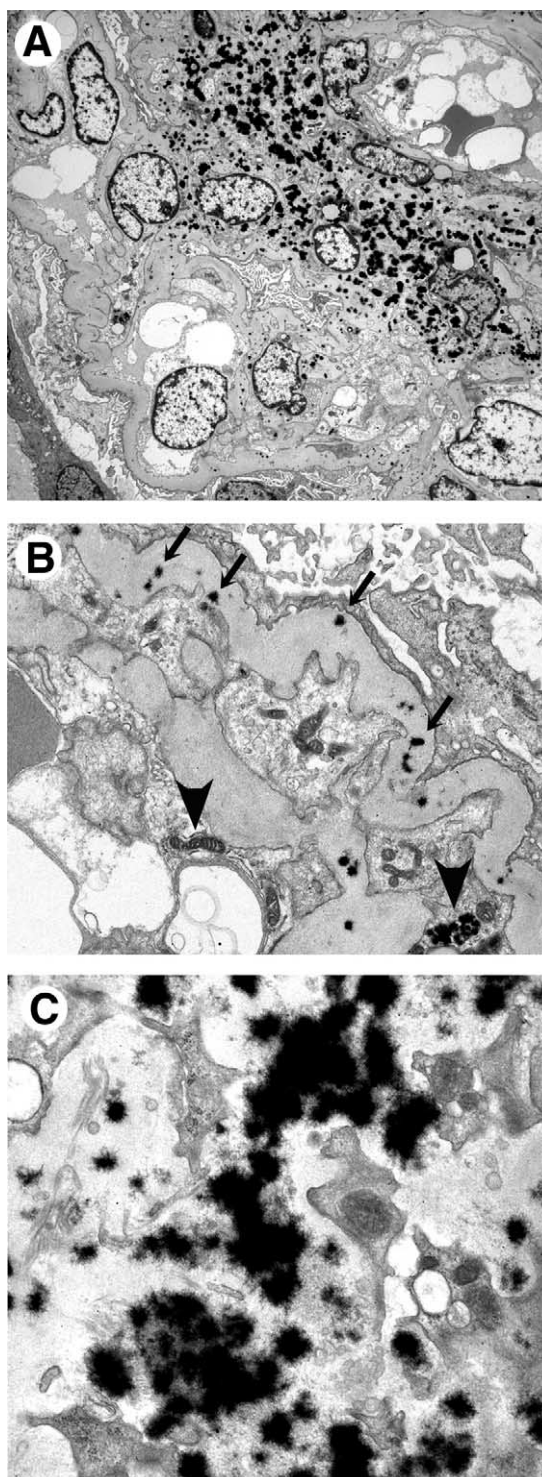


Fig 2. Electron microscopic images. (A) Extremely electron-dense granular material is concentrated in mesangial areas, but also present along basement membranes. (B) Sparse granules within basement membrane (arrows) and calcification of mitochondria and other intracellular organelles (arrowheads) are seen. (C) High-power view of electron densities. (Original magnification: [A] $\times 2,700$, [B] $\times 11,000$, [C] $\times 23,000$.)

meruli in a pattern strikingly similar to the present case, in a patient with multiple myeloma, osteolysis, and a serum calcium level of 14.6 mg/dL (3.64 mmol/L). This patient also showed calcification of renal tubular basement membranes, in the walls of medium-sized arteries, as well as in alveolar septa of the lung.³

Trillo et al⁵ reported a series of 5 renal biopsy specimens from 4 patients with sarcoidosis. Only 3 of 4 patients had elevated serum calcium levels, and the normocalcemic patient underwent biopsy twice (their case 2). In addition to classic features of renal sarcoidosis, including granulomas, interstitial calcification was seen in all cases and segmental sclerosis was seen in 3 cases. "Calcific microspherules" were observed in glomeruli of 4 of 5 specimens, including the normocalcemic patient, with histomorphological features similar to the present case. However, ultrastructural examination showed some lamellation to the particles, slightly different than seen in the present case.⁵

Fellner and Spargo⁴ presented a case of glomerular calcification in a patient with hyperparathyroidism resulting in markedly elevated serum calcium levels. Interestingly, this patient presented with nephrotic syndrome and the following laboratory values: 24-hour urine protein as high as 3.7 g; serum albumin as low as 2.0 g/dL (20.0 g/L); serum creatinine, 3.1 mg/dL (236 μ mol/L); and creatinine clearance, 23 to 26 mL/min (0.38 to 0.43 mL/s). Despite the presence of segmental glomerular sclerosis, removal of a parathyroid adenoma resulted in dramatic improvement in the patient's proteinuria (protein < 0.23 g/24 h), with improved serum creatinine and creatinine clearance (1.9 mg/dL [145 μ mol/L] and 65 mL/min [1.08 mL/s], respectively), although a repeat renal biopsy at 6 months showed marginally decreased tissue calcification, with aggregation of calcium particles within mesangial areas.⁴

A recent report by Henegar et al⁶ described 2 additional cases with extremely high serum calcium levels and tubulointerstitial, as well as glomerular, calcification. One of these patients presented with proteinuria with protein in the range of 3 g/24 h. Like the patient reported by Fellner and Spargo,⁴ proteinuria resolved with treatment of the primary cause of hypercalcemia (T-cell lymphoma), although segmental sclerosis was seen on renal biopsy material.⁶

The case reported here shares striking morphological and ultrastructural features of glomerular calcinosis with previously reported cases, but the clinical

presentation is unique. Although our patient had elevated serum parathyroid levels, these most likely are explained as secondary hyperparathyroidism related to the patient's renal failure and high serum phosphorus levels. Despite elevated serum parathyroid hormone levels, our patient presented with normal serum calcium levels, confirmed on multiple serial measurements, similar to case 2 of Trillo et al.⁵ The cause of our patient's nephrocalcinosis remains undetermined, although sequelae related to the patient's history of hemodialysis, intravenous drug use, and prior calcium overload related to these or other unknown factors should be considered. At 50 years of age, the patient is at some risk for multiple myeloma or other malignancies involving bone; however, there was no clinical indication of bony pain or lesions. Moreover, sarcoidosis is an unlikely possibility given the lack of pulmonary symptoms and normal chest radiograph. In addition, there was no indication of renal sarcoid on biopsy. Like patients reported by Fellner and Spargo,⁴ as well as Henegar et al,⁶ our patient shows nearly nephrotic-range proteinuria (protein of \sim 3 g/24 h). However, our patient did not share the favorable outcome reported in some of these previous studies, given the lack of a treatable proximal cause of his metastatic calcification and, most importantly, the presence of diffuse ischemia, as well as end-stage tubulointerstitial damage.

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