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Nephrocalcinosis: A Diagnostic Conundrum

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Nephrocalcinosis: A Diagnostic Conundrum

Lalathaksha Kumbar and Jerry Yee

Clinical Presentation

A 26-year-old muscular man was referred for evaluation of elevated serum creatinine concentration of 4 mg/dL without attributable symptoms. The patient reported taking creatine supplements and ibuprofen, 800 mg, before exercise. He also regularly consumed protein shakes. Two years prior, during a physical examination required for athletic participation, an elevated serum creatinine concentration (1.87 mg/dL; from a baseline of 1.4 mg/dL) with proteinuria (2+) but no hematuria was noted. An ultrasound showed preserved kidney size with increased medullary echogenicity, suggesting medullary nephrocalcinosis. Kidney biopsy showed focal segmental glomerulosclerosis, severe interstitial fibrosis, and mild arteriosclerosis.

The patient's family history lacked any record of kidney disease. He had no known allergies and denied toxic alcohol ingestion or use of tobacco, anabolic steroids, or prescription medications. On examination, the patient was obese (body mass index, 32 kg/m^2) and hypertensive (blood pressure, 146/93 mm Hg). Urinalysis showed proteinuria with protein excretion > 300 mg/dL, and by microscopy, there were 2 to 3 red blood cells and 6 to 10 white blood cells per high-power field, with an occasional granular cast. Laboratory data are presented in Table 1. Chest radiograph showed the usual cardiomediastinal silhouette and pulmonary vasculature. Repeat ultrasound showed shrunken kidneys with echogenic cortices and hyperechoic pyramids consistent with medullary nephrocalcinosis (Fig 1), but findings from computed tomography (CT) were unremarkable.

- **What are the diagnostic challenges in a patient with chronic kidney disease and nephrocalcinosis?**
- **What is the pathophysiologic explanation of calcium deposition in kidney?**
- **What is the most likely cause of nephrocalcinosis in this patient?**

Discussion

What are the diagnostic challenges in a patient with chronic kidney disease and nephrocalcinosis?

Nephrocalcinosis is defined as generalized deposition of calcium phosphate and/or calcium oxalate in the kidney, predominantly in the interstitium.[1] Calcifications in renal pyramids, characteristic of medullary nephrocalcinosis, are seen in 98% of nephrocalcinosis cases.[1] Clinical presentation and course are not dependent on the severity of nephrocalcinosis. The critical feature noted in nephrocalcinosis is hypercalciuria with or without hypercalcemia. The presence or absence of hypercalcemia aids in the evaluation of newly diagnosed nephrocalcinosis. Conditions with hypercalcemia and hypercalciuria are systemic disorders, such as primary hyperparathyroidism, sarcoidosis, hypervitaminosis D, and milk-alkali syndrome. Hypercalciuria without hypercalcemia is associated with dysregulation of renal handling of calcium from a variety of conditions, including distal tubular acidosis, medullary sponge kidney, and inherited tubulopathies such as Dent disease.

Our unusual case of a young man with nephrocalcinosis with advanced chronic kidney disease (CKD) presented with a unique set of challenges in identifying the underlying cause. The elevated serum creatinine concentration was unexplained, and he had mild hypercalcemia without hypercalciuria. Nephrocalcinosis was identified on renal ultrasound on 2 different occasions during a 2-year period, but kidney biopsy and CT of the abdomen failed to show calcifications.

The overall frequency of nephrocalcinosis in a native kidney biopsy is very low (0.4%).[2] An autopsy study identified 2 distinct histopathologic patterns of nephrocalcinosis by light microscopy. The group with hypercalcemia or hypercalciuria due to malignant tumors, hyperparathyroidism, sarcoidosis, Dent disease, or parcelin 1 mutations had finely granular or clumpy calcium deposits. The group with hyperphosphaturia (as seen with phosphate-based bowel preparation, nephrotic syndrome in children, and inherited disorders of renal phosphate wasting) had shell-like or globular deposits, likely with a phosphate-rich core surrounded by a thin layer of calcium phosphate. In both groups, calcifications were seen in both the cortical and medullary regions.

Our patient had hypovitaminosis D with hypercalcemia without hypercalciuria or hyperphosphaturia. In an average adult, a 24-hour urine sample is expected to contain 100 to 250 mg of calcium, which varies with dietary sodium intake. Hypercalciuria is a prominent feature in nephrocalcinosis and diseases such as Dent disease until worsening kidney function limits calcium excretion. Pre-existing CKD in our patient, with an estimated glomerular filtration rate of 44 mL/min/1.73 m^2 by the CKD-EPI (CKD Epidemiology Collaboration) creatinine–cystatin C equation, likely explained the low urinary calcium excretion. Ultrasonographic examination of kidneys, with its inherent advantages of the lack of radiation, ease of use, and wide availability, is the preferred initial test. Magnetic resonance imaging

Table 1. Laboratory Findings

Parameter	Values		
	Prior	Initial	Repeat
Serum			
Creatinine, mg/dL	1.87	3.58	3.7
Calcium, mg/dL	9.8	9.4	9.7
Albumin, g/dL	3.2	3.7	3.6
Vitamin D, ng/mL		22	29
ANA		ND	
iPTH, pg/mL		76	
Urine			
Total protein-creatinine ratio, mg/dL		4.3	
Albumin-creatinine ratio, mg/dL		1.5	
RBP-creatinine ratio, μg/g		827	
A1M-creatinine ratio, mg/g		21	
β_2-Microglobulin, mg/L		2.37	
24-h urine calcium, mg		38	57
24-h urine phosphorus, g		1.1	
OCRL1 and *CLCN5* mutation screen		ND	

Abbreviations: A1M, α_1-microglobulin; ANA, antinuclear antibody; iPTH, intact parathyroid hormone; ND, not detected; RBP, retinol-binding protein.

is not sensitive for identification of calcification. In a limited study, ultrasonography alone had sensitivity of 85% to 90%, whereas CT had sensitivity between 81% and 86%. Combined ultrasonography with CT had higher sensitivity (92%) and specificity of 89%, but there was lower concordance between CT and ultrasonography, making the radiologic diagnosis of nephrocalcinosis a challenge.[3]

What is the pathophysiologic explanation of calcium deposition in the kidney?

The exact pathogenesis of calcium deposition in nephrocalcinosis remains unclear. Every day, nearly 99% of ~10 g of diffusible calcium gets reabsorbed in the kidneys.[4] The proximal tubule reabsorbs ~65% of the filtered load, with the thick ascending limb of Henle accounting for 20% to 25%.[5] Distal tubule reabsorption of calcium accounts for 8% to 10%. In this segment, calcium reabsorption is against a transtubular electrochemical gradient. Any precipitation of calcium is intricately related to phosphorus and/or oxalate transport. Calcium precipitation noted in the interstitium could be a de novo phenomenon or a transtubular migration of intratubular calcium precipitate. A complex dysregulation between calcification inhibitors and promoters might play a pivotal role in interstitial precipitation.[6]

What is the most likely cause of nephrocalcinosis in this patient?

Inherited tubulopathies and renal tubular acidosis are essential conditions leading to nephrocalcinosis. In our patient, renal tubular acidosis was less likely given the negative aminoaciduria screen with acidic urine pH. Elevated retinol-binding protein, β_2-microglobulin, and α_1-microglobulin concentrations confirmed low-molecular-weight proteinuria, suggesting proximal tubulopathy. The patient's clinical presentation and lack of specific metabolic abnormalities excluded Bartter and Gitelman syndromes.

Dent disease is a familial X-linked recessive disorder of the proximal tubules that features nephrocalcinosis, hypercalciuria, low-molecular-weight proteinuria, kidney failure, and metabolic bone disease.[7] Dent disease has no known high-risk populations, but has a marked male dominance. Although 25% of Dent disease cases constitute a heterogeneous genetic group with classic phenotype but lacking known mutations,[8,9] three-quarters of Dent disease cases are of 1 of 2 types. Dent type 1, found in 60%, has mutations in Xp11.22 leading to inactivation of the voltage-gated chloride transporter, CLC5, which is expressed in the kidney.[10] This product of the *CLCN5* gene is a chloride/proton

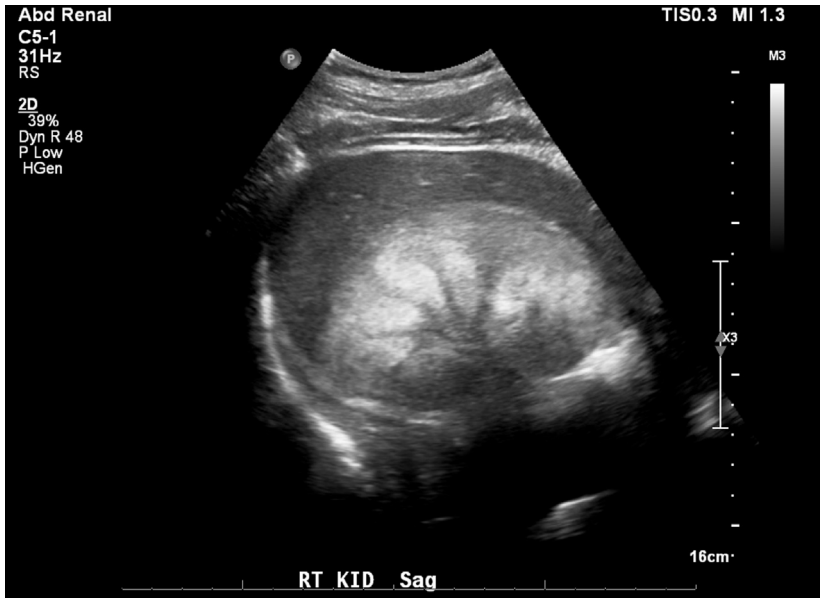

Figure 1. Ultrasound image of the right kidney with medullary hyperechogenicity indicating medullary nephrocalcinosis.

exchanger that facilitates acidification of endosomes in proximal tubular cells. When CLC5 is inactivated by mutation (>85 different mutations have been identified[9]), the disrupted endosomal acidification causes a failure to process adsorbed low-molecular-weight proteins, leading to proteinuria.[11] Dent type 2 is characterized by *OCRL1* gene mutations (mutations in this gene are also seen in the oculocerebrorenal syndrome of Lowe[9,12]) and accounts for another 15%. The phosphatase encoded by the *OCRL1* gene has overlapping function with the CLC5 protein in endosomal trafficking, which explains the similar phenotype as Dent disease type 1.[8] In Dent disease, hypercalciuria appears to be due to hyperabsorption of calcium from the gastrointestinal tract. The hyperphosphaturia and greater 1α-hydroxylation seen in Dent disease and related conditions may be partially because parathyroid hormone, being a low-molecular-weight protein, has impaired proximal tubular reabsorption, which in turn leads to increased activation of parathyroid hormone receptors in the late proximal tubule.

Evaluation for Dent disease is a must in any male patient with low-molecular-weight proteinuria, hypercalciuria, and at least 1 of the following: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, and CKD. The characteristic triad of low-molecular-weight proteinuria, hypercalciuria, and nephrocalcinosis can identify >85% of *CLCN5* mutations.[9] Hypercalciuria may be absent if decreased glomerular filtration rate is found. A positive family history and mutations in *CLCN5* or *OCRL1* confirm the diagnosis, but the negative genetic test result is not exclusionary. Focal global glomerulosclerosis, which is noted in 85% of Dent disease, is the predominant histopathologic finding, followed by effacement of foot processes.[13] Atypical presentations as seen in our patient have been reported with focal global glomerulosclerosis.[14] Making an accurate diagnosis of Dent disease is important to help avoid potentially toxic immunosuppressive medications.

Final Diagnosis

The constellation of findings of focal global glomerulosclerosis with nephrocalcinosis, low-molecular-weight proteinuria, and CKD suggested the possibility of Dent disease. Gene sequencing of *OCRL1* and *CLCN5* did not detect pathogenic variants. The characteristic phenotype with the apparent absence of mutations in known genes confirmed the diagnosis of non-*CLCN5* non-*OCRL1* Dent disease.

Article Information

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