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Focal segmental glomerulosclerosis, proteinuria and nephrocalcinosis associated with renal tubular acidosis

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Introduction

Patients with renal tubular acidosis (RTA) usually have 'tubular' or low molecular weight proteinuria. We report the case of a patient with autosomal dominant hereditary distal RTA (dRTA), nephrocalcinosis, and characteristic glomerular lesions of focal segmental glomerulosclerosis that are likely to be responsible for her near nephrotic range proteinuria.

Case

A 31-year-old female with hereditary dRTA, diagnosed at age 14, and associated recurrent symptomatic urolithiasis was referred to a nephrologist in an attempt to curtail her formation of new stones. Over the previous 15 years she had recurrent urinary tract infections including right-sided pyelonephritis, chronic bilateral flank pain and multiple urological interventions including extracorporeal shock wave lithotripsy, cystoscopy and ureteroscopy with ureteral stent placement. A past history of peptic ulcer disease and 'heavy narcotic' use for chronic flank pain and headaches was noted. Her medications at that time included 10 mg amlodipine daily, 25 mg amytriptyline twice daily, 20 mg omeprazole twice daily, 5/500 mg hydrocodone/acetaminophen twice daily and 8–10 tablets sodium bicarbonate (7.8 mEq) daily. There had been no long-term non-steroidal anti-inflammatory drug use. Her father and paternal grandfather were known to have had dRTA and her sister was diagnosed with the same disease in childhood and has had recurrent urinary tract infections and nephrolithiasis.

Physical examination showed a young, well-nourished female with blood pressure of 112/68 mmHg, pulse rate of 84 beats/min and pale conjunctivae. Lung fields were clear and heart examination was within normal limits. Abdomen was soft with mild costovertebral angle tenderness. She had no peripheral oedema.

Laboratory findings

Urine dipstick showed a specific gravity of 1.010, pH of 7, positive leukocyte esterase, trace protein, negative glucose, and 2+ blood; microscopic examination showed 4–7 white blood cells per high power field (hpf) and 0–2 red blood cells/hpf. Her serum creatinine was 3.6 mg/dl, blood urea nitrogen 39 mg/dl, bicarbonate 17 mEq/l and serum potassium 4.2 mEq/l. Serum albumin was 3.6 g/dl and total cholesterol was 313 mg/dl. Stone analysis: 10% calcium oxalate and 90% calcium phosphate. Radiological studies are shown (Figures 1, 2 and 3).

Over the next 7 months, her renal function deteriorated rapidly in the absence of obstructing stones or urinary tract infection. Her serum creatinine increased to 7.1 mg/dl, blood urea nitrogen 52 mg/dl, bicarbonate 22 mEq/l and serum potassium 5.6 mEq/l. Urine analysis now showed 3+ proteinuria by dipstick, 24-h urine collection contained 2.9 g of protein and creatinine clearance was 7 ml/min.

She started chronic haemodialysis treatment and shortly thereafter had a right nephrectomy, the first stage of a planned bilateral nephrectomy for intractable pain and recurrent pyelonephritis in anticipation of renal transplantation.

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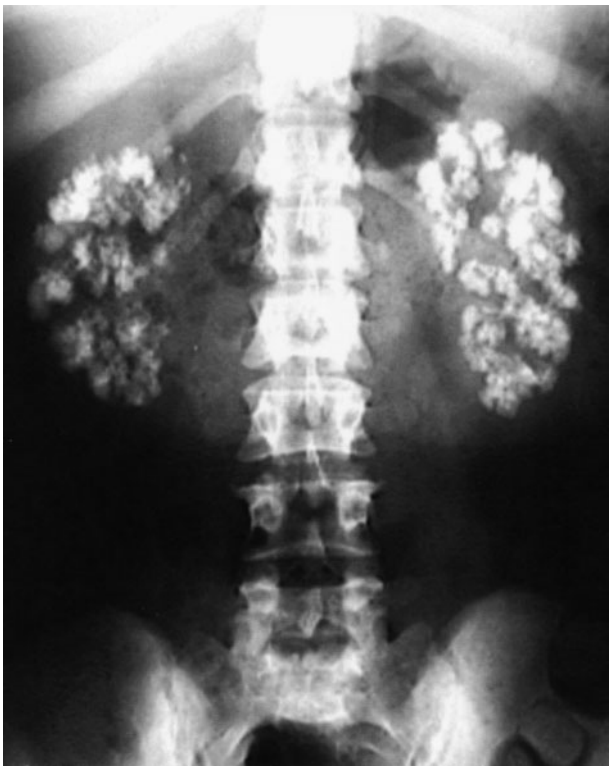

Fig. 1. Plain X-ray of the kidneys, bladder and ureters showing severe nephrocalcinosis.

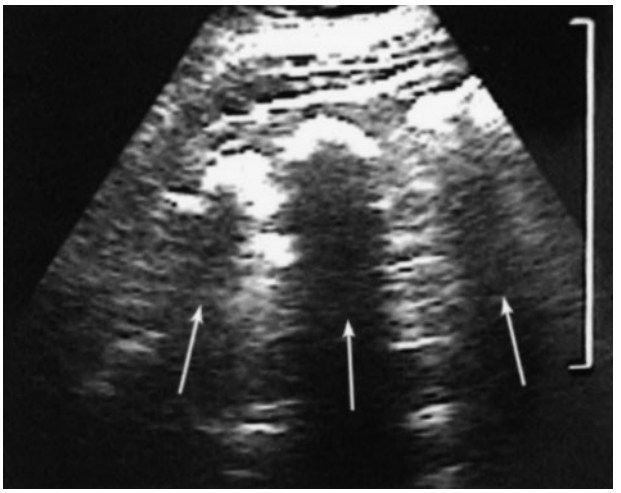

Fig. 2. Renal ultrasound showing abnormally echogenic medullary region and acoustic shadows (arrows) beyond the calcifications.

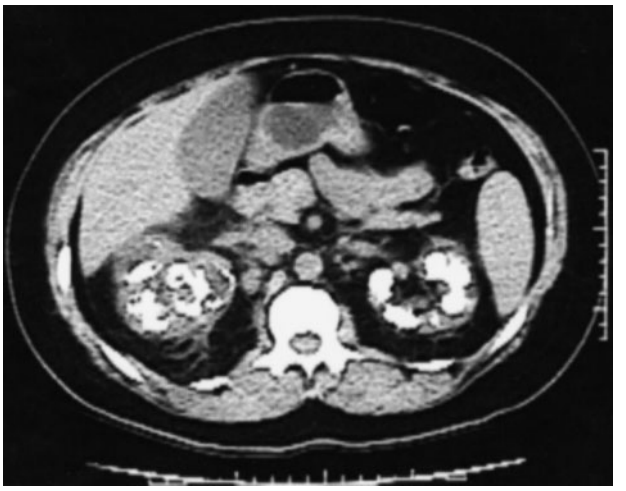

Fig. 3. Computed tomographic scan confirming medullary calcifications.

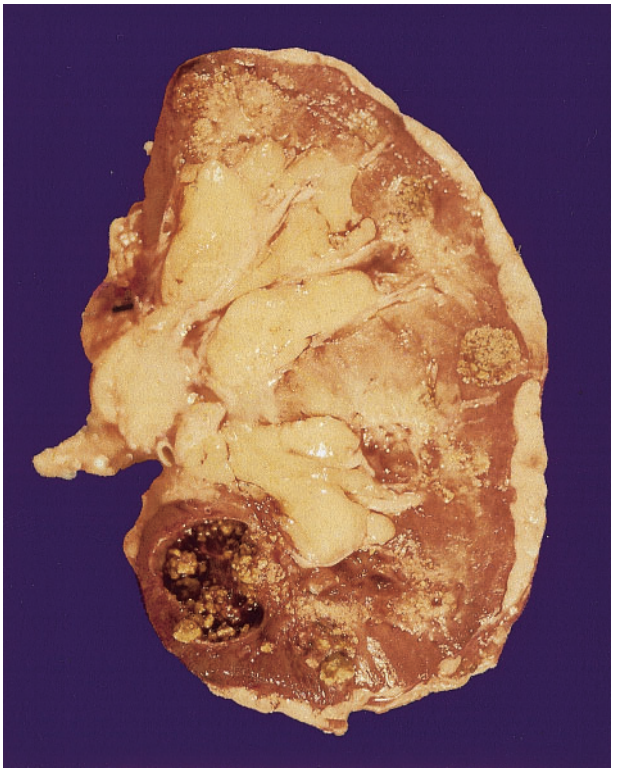

Fig. 4. Nephrectomy specimen showing nodular and cystic calcific masses preferentially involving the renal medulla and calyces. Irregular parenchymal fibrosis is also present.

Pathology

Her nephrectomy findings are as shown (Figures 4, 5 and 6). On gross examination the specimen weighed 192 g and the renal parenchyma was heavily calcified making sectioning extremely difficult. There was gross focal nodular and fine diffuse grainy calcification of parenchymal tissue affecting the medullary tissues most severely. A cystic lesion containing numerous calculi, (presumably an obstructed and dilated calyx) was noted (Figure 4). Following decalcification procedures, tissue sections of the calcified masses showed numerous concentrically lamellar concretions with intervening fibrous stroma (Figure 5). Renal cortical parenchyma that was grossly less diseased showed characteristic lesions of focal segmental glomerulosclerosis (Figure 6).

Immunofluorescence showed IgM and C3 positivity for the focal and segmentally distributed hyalinosis type deposits. Electron microscopy showed segmental

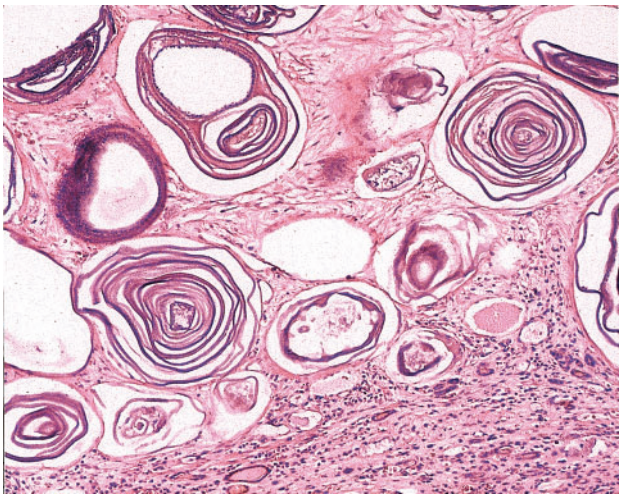

Fig. 5. Histology of calcific parenchymal mass (from Figure 4) shows many concentrically lamellar concretions with fibroblastic stromal reaction. Decalcified tissue. Haematoxylin and eosin stain (original magnification ×100).

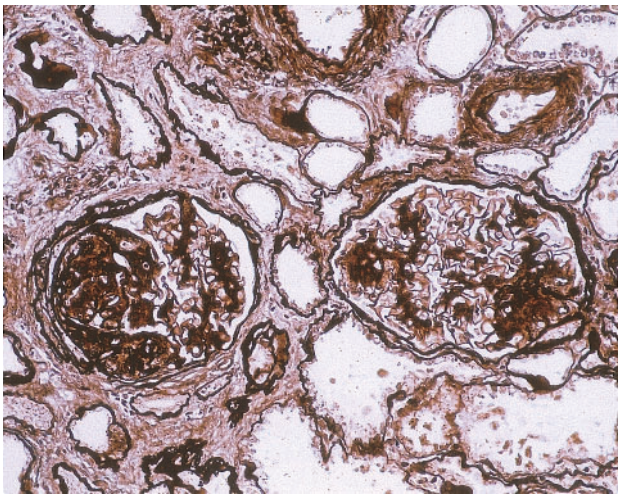

Fig. 6. Two glomeruli showing segmental sclerosis. Periodic acid methenamine silver stain (original magnification ×200).

sclerotic lesions and mild mesangial expansion without immune complex type dense deposits or fibrillary deposits.

Discussion

The proteinuria associated with primary focal segmental glomerulosclerosis (FSGS) can be in the non-nephrotic range [1]. Secondary FSGS with non-nephrotic range proteinuria and without hypoalbuminaemia or severe oedema has been reported in patients with massive obesity, vesicoureteral reflux, or renal mass reduction [2,3].

dRTA has a known association with medullary nephrocalcinosis either as cause or effect [4]. Proteinuria in patients with RTA is frequently regarded as 'tubular' with excretion of mainly low molecular weight proteins (less than 40 000 Da) [5–7]. However, in patients with dRTA, Norden *et al.* [8] showed that low molecular proteinuria was less marked than in other tubular defects and albuminuria was noted to be common, although highly variable in intensity.

The recorded three-generation presence of dRTA in this case suggests an autosomal dominant pattern of inheritance. This occurs with mutation of the AE1 gene which codes for the Cl^-/HCO_3^- exchanger in the basolateral membrane of the renal collecting ducts [9,10]. Scheinman's review of the X-linked hypercalciuric nephrolithiasis syndromes associated with proximal tubular dysfunction notes a subset of these patients with biopsy-proven glomerular sclerosis and increased albuminuria [11].

This case of hereditary distal RTA shows nephrocalcinosis, FSGS lesions and associated rapid worsening of proteinuria. FSGS in the glomeruli with the least gross abnormality and proteinuria greater than 0.5–2 g/day [11] is highly suggestive of a major glomerular origin of the proteinuria. dRTA may be one of the causes of secondary FSGS and proteinuria of glomerular origin.

References

1. Falk JF, Jennette JC, Nachman PH. Glomerular diseases that cause nephrotic syndrome. In: Brenner B, ed. *Brenner & Rector's The Kidney*, 6th Edn. W. B. Saunders Company, Philadelphia: 2000; 1277
2. Praga M, Morales E, Herrero JC *et al.* Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. *Am J Kidney Dis* 1999; 33: 52–58
3. Praga M, Borstein B, Andres A *et al.* Nephrotic proteinuria without hypoalbuminemia: clinical characteristics and response to angiotensin-converting enzyme inhibition. *Am J Kidney Dis* 1991; 17: 330–338
4. Simoes A, Domingos F, Prata MM. Nephrocalcinosis induced by furosemide in an adult patient with incomplete renal tubular acidosis. *Nephrol Dial Transplant* 2001; 16: 1073–1074
5. Igarashi T. Renal tubular acidosis (RTA). *Nippon Rinsho* 1996; 54: 794–800
6. Juncos LI, Muino JC, Garcia NH *et al.* Renal tubular acidosis and vasculitis associated with IgE deposits in the kidney and small vessels. *Am J Kidney Dis* 2000; 35: 941–949
7. Igarashi T, Kawato H, Kamoshita S. Reversible low-molecular-weight proteinuria in patients with distal renal tubular acidosis. *Pediatr Nephrol* 1990; 4: 593–596
8. Norden AG, Scheinman SJ, Deschodt-Lanckman, *et al.* Tubular proteinuria defined by a study of Dent's (CLCN5 mutation) and other tubular diseases. *Kidney Int* 2000; 57: 240–249
9. Jarolim P, Shayakul C, Prabakaran D *et al.* Autosomal dominant distal renal tubular acidosis is associated in three families with heterozygosity for the R589H mutation in the AE1 (band 3) Cl^-/HCO_3^- exchanger. *J Biol Chem* 1998; 273: 6380–6388
10. Shayakul C, Alper SL. Inherited renal tubular acidosis. *Curr Opin Nephrol Hypertens* 2000; 9: 541–546
11. Scheinman SJ. X-linked hypercalciuric nephrolithiasis: clinical syndromes and chloride channel mutations. *Kidney Int* 1998; 53: 3–17