A Case of Renal Medullary Cystic Disease with Proximal Tubular Dysfunction

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A 50-year-old man with sporadic renal medullary cystic disease associated with moderate renal failure, severe anemia, dehydration and osteodystrophy, and without edema, hypertension or remarkable urine sediment was studied. Hyperchloremic acidosis and hypokalemia were found in this patient, which could be explained as a consequence of proximal renal tubular acidosis, since, during the normalization of plasma bicarbonate level by the administration of sodium bicarbonate, urinary potassium excretion was increased and urinary pH was further increased to 8.1. In addition, he had generalized aminoaciduria and increased clearance of phosphate and uric acid. Particularly the lysozyme clearance (C_{ly}/C_{cr}) in this patient was significantly higher than in patients with chronic glomerulonephritis, and equal to the value of Fanconi's syndrome. The presence of salt-wasting, hyperchloremic metabolic acidosis, aminoaciduria, hyperuricosuria and "tubular proteinuria" suggests that the patient with medullary cystic disease is associated with multiple proximal tubular dysfunction. The finding of renal biopsy is presented which suggests that this disorder represents a toxic nephropathy.

Key Words: Toxic nephropathy, Renal tubular acidosis, Tubular proteinuria, Aminoaciduria, Osteodystrophy.

Medullary cystic disease is a term used to describe a renal disorder characterized by the insidious onset of uremia and severe anemia without edema, hypertension or remarkable urine sediment^{1,2)}. In Japan, there have been reported very few cases of this disorder¹⁶⁾. In general, there occurs the clinically important phenomenon of renal salt wasting and distal tubular dysfunction, but notably absent is a proximal tubular dysfunction^{3,4)}. We have encountered a patient with medullary cystic disease associated with hyperchloremic metabolic acidosis, hypokalemia, hyperuricosuria, and "tubular proteinuria", possibly as a consequence of proximal renal tubular dysfunction. Moreover, we describe that

this disorder is clinically and histologically similar to a toxic nephropathy

CASE REPORT

A 50 year old Japanese man was first admitted to Kawasaki City Ida Hospital for the investigation of his anemia and renal failure in March, 1974. At age 40 he was asymptomatic when first seen by a physician for evaluation of proteinuria and glycosuria. For the previous three years he had been unwell with increasing pallor, polydipsia and polyuria. There had been no episodes of loin pain, edema hematuria, or hypertension. None of his family were known to have renal disease. Physical examination revealed a chronically ill man

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with poor turgor of the skin and pronounced pallor of mucous membranes. He was 170cm tall and weighed 54 Kg. Blood pressure, with the patient in the supine position, was 94/60mmHg; upon standing it quickly decreased to 80/50mmHg without symptoms. A grade 2 systolic murmur was heard at the apical and the left sternal border areas. There was neither hepatosplenomegaly nor lymphadenopathy. Fundoscopic examination showed arteriolar narrowing and tortuosity, comparable to a grade I of Keith-Wagner's classification. Laboratory examination showed a red cell count of $267 \times 10^4/\text{mm}^3$, hemoglobin level of 9.0g/100ml, white blood cell count of 4,600/ mm^3 and platelets 246,000/ mm^3 . Bone marrow showed reduced erythropoiesis. Serum sodium was 137mEq/l, chloride 118mEq/l, potassium 2.8mEq/l and bicarbonate 17.4mEq/l. Serum creatinine was 3.2mg/100ml, blood urea nitrogen 72.4mg/100ml, calcium 7.8mg/100ml, phosphorus 2.2mg/100ml, uric acid 1.5mg/100ml, fasting blood sugar 92mg/100ml, iron 102 $\mu\text{g}/100\text{ml}$, and total protein was 7.4g/100ml with 4.6g/100ml of albumin. Urine volume was 2.0 to 3.5 liter, daily, and pH ranged between 6.0 and 7.0. Urinalysis revealed a fixed specific gravity of 1.008 to 1.010, +proteinuria, +glycosuria, and a normal sediment. Endogenous creatinine clearance was 28.8 and 32.2ml/min/1.48m². The fractional uric acid clearance ($C_{\text{UA}}/C_{\text{Cr}}$) was increased 1.2 (normal: 0.05-0.20). As shown in Fig. 1, the fractional lysozyme clearance ($C_{\text{Ly}}/C_{\text{Cr}}$) in this patient (9.5%) was as high as the values of Fanconi's syndrome (8.2 and 10.5%), compared to those in patients with chronic glomerulonephritis (0.02 $\pm$ 0.01%, mean $\pm$ SE), suggesting a proteinuria of the "tubular" type. Percent TRP was decreased to 62. Analysis of 24-hour urinary amino acids demonstrated generalized aminoaciduria. Plasma renin activity (radioimmunoassay) was elevated to 8.0ng/ml/hour (normal, 0.5-2.0ng/ml/hour) and urinary aldosterone excretion was also increased to 20 $\mu\text{g}/\text{day}$ (normal,

Fig. 1. Fractional lysozyme clearance in 16 patients with chronic glomerulonephritis with various degree of GFR above 20ml/min, in 6 patients with chronic glomerulonephritis with various degree of GFR below 20ml/min, in two patients with Fanconi's syndrome, and in this patient with medullary cystic disease. Lysozyme was measured by the lyso-plate method of Osserman et al (17). Fractional lysozyme clearance (%) was calculated by 100X lysozyme clearance/creatinine clearance.

Fig. 2. Tubular Dysfunction in this patient.

5-10 μ g/day). A skeletal survey showed renal osteodystrophy with moderate changes of hyperparathyroidism and osteomalacia, but there was neither calcification on soft tissues nor any bone fracture. There was delayed and incomplete visualization on intravenous pyelogram.

He was treated with intravenous saline and sodium bicarbonate, and his blood urea nitrogen fell to a minimum of 35mg/100ml, but urinary potassium excretion was increased from 62 to 80mEq/day on a constant diet 120mEq sodium and 70mEq potassium, aggravating the hypokalemia with serum potassium level into 2.1mEq/l, and urinary pH was increased further to 8.1, possibly resulting from massive bicarbonaturia. Subsequently, he needed a high fluid intake, a diet restricted in protein, and an oral supplement of sodium bicarbonate and potassium chloride, because of the tendency of "salt-wasting". He was discharged with the temporary diagnosis

of a "tubular disease" to follow on an Outpatient basis. Fig. 2 shows "tubular dysfunction" seen in this patient.

Over the next two years the BUN level was increased to 130mg/100ml, although he had taken a well-restricted diet, and the patient developed signs and symptoms of uremia. Chronic hemodialysis was begun. To clarify the diagnosis of this curious tubular disease, we have investigated the radiological and histological studies in this patient.

Retrograde pyelogram showed unremarkable changes, although usually there are pelvocalceal defects in polycystic kidney. Renal arteriograms demonstrated the small kidneys with very thin cortex. During the nephrogram phase, renal cysts could be radiologically identified at the inner cortex and medulla (Fig. 4). The interlobar and arcuate arteries were tapered and stretched by these large cysts (Fig. 3)

An open renal biopsy was performed. The kidney was very hard but smooth in the surface. Microscopic examination re-

Fig. 3. Left renal arteriogram shows tapering and stretching of the interlobar arteries (arrows).

Fig. 4. The nephrogram shows multiple cysts (small arrows), and sparing of the outer cortical margin (large arrows).

Fig. 5. Microphotograph of the right kidney demonstrates the reduced cortical zone and several cysts at the corticomedullary junction. C: Capsule, M: Medulla (PAS stain, degree of magnification: 15 times).

Fig. 6. A Bowman's capsule cyst (Glomerular Cyst) with marked periglomerular fibrosis and interstitial lymphocytic infiltration and fibrosis. (Hematoxylin-eosin stain, degree of magnification: 96 times).

vealed the reduced cortical zone and several cysts at the corticomedullary junction (Fig. 5). The cysts lined by a regular low cubic epithelium, in most instances single-layered, suggesting dilatation of collecting ducts. There were some cysts composed of the dilated Bowman's capsule (Fig. 6). A ma-

jority of the glomeruli were completely hyalinized, but remaining glomeruli showed no abnormality, except for mild hyperplasia of juxtaglomerular apparatus. Severe interstitial fibrosis with lymphocytic infiltration was present. Most of the tubules were almost completely atrophied, and the rest

were hypertrophied. The basement membrane of some tubules was thickened, forming a collar around the tubules.

DISCUSSION

Both clinically and histologically, the patient showed typical of medullary cystic disease¹⁻⁴). Failure to conserve sodium and water, lack of hypertension, and the presence of renal osteodystrophy are all characteristic (2). With the use of renal angiography and renal biopsy, moreover, we obtained such a diagnostic finding as the presence of cysts at the corticomedullary junction.

This disease is a very rare disorder, usually in childhood or adolescence. Some reported cases of medullary cystic disease appeared with sporadic family incidence, suggesting autosomal recessive transmission^{2,3}) while others had frequent family involvement consistent with dominant transmission⁴). In Europe, on the other hand, they have used a term "familial juvenile nephronophthisis" which is a disorder of childhood with autosomal recessive genetic transmission, having a similar histological appearance except for occasional absence of cysts⁵). In 1964, Winberg

suggested that juvenile nephronophthisis and medullary cystic disease might be identical⁶). Subsequently, investigators generally have supported his opinion⁷). However, nephronophthisis has been reported in the young, while there has been a patient with medullary cystic disease who survived to fifty-six²). Therefore, a term "medullary cystic disease" seems to be rather suitable for our patient since his age was fifty and his kidney contained numerous cysts.

Medullary cystic disease is one of the renal cystic diseases. Clinically, it is difficult to differentiate it from the other cystic diseases such as polycystic kidney and medullary sponge kidney. However it is important to make a diagnosis, since medullary cystic disease has poor prognosis with severe complications such as anemia, dehydration and osteodystrophy, compared to the other two cystic diseases. In table 1, one can see the characteristic findings for the differential diagnosis between polycystic kidney, medullary sponge kidney, and medullary cystic disease. Polycystic kidney is often associated with hypertension and hematuria, but medullary cystic disease usually occurs without hypertension or he-

Table 1. Differences of Medullary Cystic Disease Against Polycystic Kidney and Medullary Sponge Kidney

	Polycystic Kidney (adult-type)	Medullary Sponge Kidney	Medullary Cystic Disease
Clinical changes			
Hematuria	+	+	-
Hypertension	+	-	-
Nephrolithiasis	-	+	-
Kidney size	enlarged	normal	small
Polycystic liver	+	-	-
Renal function			
Renal failure	+	-	+
Hyperchloremic acidosis	+	+	+
Sodium wasting	-	-	+
Tubular proteinuria	-	-	+
Prognosis	Fatal	Good	Fatal
Genetic transmission	autosomal dominant-sporadic	Sporadic	autosomal recessive dominant?
Diagnosed age	30 ~ 40	30 ~ 40	10 ~ 40
Urogram			
I.V.P.	occasionally invisible	pyramidal opacification	occasionally invisible
Retrograde P. Angiogram	pelvocalyceal defects large cysts	normal normal	normal small cysts
Pathological changes			
Cortex	cysts	normal	fibrosis
Medulla	cysts	ectasia	cysts

maturia. Moreover, retrograde pyelogram shows pelvocalceal defects in polycystic kidney, while in medullary cystic disease it shows normal appearances, as seen in this patient. Medullary sponge kidney should be differentiated from medullary cystic disease because they are different diseases, although in the past they have been confused with each other. The main differences are in the course of the disease, and the fact that the cysts in medullary cystic disease are at the corticomedullary junction, while those in sponge kidney are in the collecting tubules and are at the tips of the papillae. Most sponge kidney is not inherited and follows a benign course if uncomplicated. The diagnosis usually can be made by intravenous pyelography, on the basis of mildly dilated tubules and/or the clusters of small calculi in the renal papillae⁸⁾.

Medullary cystic disease is often not recognized until azotemia and anemia appears, because the early warning signs of renal disease, such as hypertension, hematuria, and abnormal urinary sediment are absent¹⁻⁴⁾. Therefore, it might be impossible to obtain a useful intravenous pyelogram in any case⁹⁾, since these patients are always uremic when first seen. However, it is necessary for a clinician to make a diagnosis and begin the treatment for osteodystrophy, acidosis and dehydration, as early as possible. Recently, Mena et al¹⁰⁾ reported that angiographic features in this disorder were specific and enabled differentiation from other conditions, such as sponge kidney, classical polycystic kidney and pyelonephritis. In 4 of 5 cases, cystic changes were radiologically seen. In addition, the peripheral cortical margins of the cysts were intact, while there was cortical interruption of cysts in polycystic kidney. In this patient, the correct angiographic diagnosis could be suggested on the basis of cystic changes and the lack of cortical interruption (Fig. 2, 3). Therefore, renal angiography may offer a safer and equally satisfactory approach in patients with me-

dullly cystic disease, even if they are uremic.

Herdman et al demonstrated such signs of distal damage as reduced ability to concentrate and acidify the urine but the absence of glycosuria and aminoaciduria, concluding that the proximal tubule was not affected in medullary cystic disease³⁾. However, our patient was associated with hyperchloremic metabolic acidosis, hypokalemia, and hyperreninemia, which could be explained as a consequence of proximal renal tubular acidosis (proximal RTA). Because renal potassium wasting became more severe when acidosis was corrected with a large amount of alkali, although in distal RTA correction of acidosis is predictably attended by a reduction in the urinary excretion rate of potassium¹¹⁾. In addition, the observation supported the presence of proximal RTA in this patient that the urinary pH was further increased to 8.1 when plasma pH became normal with the alkali¹²⁾. In this disorder of renal acidification, the impairment of bicarbonate reabsorption in the proximal tubule results not only in bicarbonate wasting, leading to hyperchloremic "alkali-resistant" acidosis, but in delivery to the distal tubules of such increased amounts of the relative impermeant bicarbonate anion that distal intraluminal electronegativity is increased, potassium secretion is thereby increased, and renal potassium wasting is promoted¹¹⁾. In addition, hypokalemia is partly due to secondary aldosteronism. He was associated with high plasma renin activity, hyperaldosteronism, and juxtaglomerular cell hyperplasia. These conditions might be caused from the depressed extracellular volume, because of the tendency of salt-wasting, which is apparently similar to the pathophysiology of Bartter's syndrome^{18,19)} (Fig. 2). The causes of renal osteodystrophy in this patient were not only renal failure but also proximal tubular dysfunction. Especially, osteomalacia is often found in medullary cystic disease, which may be due to the impaired reabsorption of phosphate and bicarbonate, via

hypophosphatemia and acidosis. Recently, it has become well known that in the kidney, particularly in the proximal tubular cells, vitamin D is activated by 1α -hydroxylase and that 1, 25-dihydroxycholecalciferol, an active vitamin D metabolite, is produced²⁰. Since the deficiency of 1, 25-dihydroxycholecalciferol may cause osteomalacia²¹, it should be considered as a cause of osteodystrophy in this patient.

In this patient, as well as patients reported by Giselson et al¹³, additional evidences of proximal tubular dysfunction were found such as glycosuria, lysozymuria and hyperuricosuria. Since lysozyme is a low-molecular-weight protein, it is freely filtered at the glomeruli and reabsorbed by the proximal tubule. Therefore, normally the urine contains its trace amounts. Increased excretion of lysozyme has been demonstrated in patients with proximal tubular damages such as cadmium poisoning^{14,15}. Most recently, we have reported that injection of maleic acid in the rats produced experimental Fanconi syndrome associated with massive lysozymuria²⁵. However, in the azotemic patients, serum lysozyme is increased and then lysozymuria can result from filtered loads of lysozyme exceeding the maximum transport capacity of the proximal tubule.

Since the fractional absorption of lysozyme is relatively constant over a wide range of plasma concentrations, we have measured the fractional lysozyme clearance. Consequently, the value in this patient is significantly higher than in chronic glomerulonephritis, and equal to that of Fanconi's syndrome which is a typical disease causing proximal RTA. Evidence presented suggests that the patient with medullary cystic disease is associated with proximal tubular dysfunction.

The pathogenesis of this disease remains obscure. Mongeau et al have suggested that medullary cystic disease results from the action on the kidney of a nephrotoxic substance, which accumulates because of an inborn metabolic error²². Their suggestion has some basis in the experimental fact that rats fed diphenylamine develop medullary cysts in their kidney^{23,24}. It is well known that most patients with chronic intoxication of a heavy metal e.g. cadmium or lead, might suffer from proximal tubular dysfunction, prior to the disturbance of glomerular function¹⁵. The course of this disorder with tubular damage early and silent progression to renal insufficiency is similar to that seen in a number of toxic nephropathies. Moreover, the resemblance to toxic nephropathy is also seen in the

Fig. 7. The pathogenesis of medullary cystic disease and juvenile nephronophthisis.

appearance of the kidney. In this patient, as reported in most cases of medullary cystic disease, the basement membrane of some tubules was concentrically thickened, forming a collar around the tubules. Some tubules were dilated and a large Bowman's space was present around the glomeruli (Fig. 5). Evidence presented suggests that the development of the cysts is a secondary process in which a localized thickening of the basement membrane leads to partial obstruction of the urine flow in a nephron with well functioning glomerulus, in turn a rise in intratubular pressure resulting in cystic dilatation of the tubule, leading to tubular dysfunction, and in a large Bowman's space (Fig. 7). As a result, juvenile nephronophthisis is the early state that cysts are not yet developed, probably progressing to medullary cystic disease. Therefore, it seems to be an attractive theory that a toxin, causing damage to renal tissue, accumulates because of a metabolic error in medullary cystic disease, although any nephrotoxic substance has not been identified.

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