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Glomerulocystic kidney disease (GCKD) and tubulointerstitial fibrosis in a patient with recurrent acute kidney injure

Torbielowatość kłębuszków nerkowych z towarzyszącym włóknieniem śródmiąższu nerek u pacjentki z nawrotową ich niewydolnością

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Summary

We present a case of glomerular cystic kidney disease, most probably sporadic, revealed on renal biopsy performed to diagnose the deteriorating renal function in a 23 years old female. Surprisingly, the GCKD was accompanied by mild tubolointerstitial fibrosis, which is unusual and has been reported sporadically. Any farmacological intervention inevitably led to acute kidney injury (AKIN I-II). We hypothesize, that this could have happened also prior to diagnosis and the previous recurrent AKI episodes resulted in interstitial fibrosis. The inappropriately increased plasma uric acid concentrations could indicate the disturbance in uromodulin synthesis/secretion, which is typical to other ciliopathies. The unusual findings on renal biopsy and clinical course of GCKD in patient suggests direct link between ciliopathies and susceptibility to acute kidney injury, which can result in interstitial fibrosis and possibly, accelerated kidney failure progression.

Key words: glomerulocystic kidney disease, ciliopathy, recurrent acute kidney injury

Streszczenie

Przedstawiamy przypadek 23-letniej kobiety, u której w biopsji nerki, wykonanej z powodu narastającej niewydolności nerek, uwidoczniono cechy torbielowatości kłębuszków nerkowych z towarzyszącym miernie rozległym włóknieniem zrębu i zanikiem cewek, co w koincydencji stanowi stosunkowo rzadkie, sporadycznie opisywane w literaturze znalezisko.

Wszelkie próby jakiegokolwiek postępowania farmakologicznego nieuchronnie prowadziły do rozwoju ostrego uszkodzenia nerek (AKIN I-II). Sądzimy, iż podobne epizody AKI mogły mieć miejsce w przeszłości, co w konsekwencji doprowadziło do śródmiąższowego włóknienia nerek.

Nieproporcjonalnie wysokie stężenia kwasu moczowego mogło pośrednio wskazywać na zaburzenie syntezy/sekrecji uromoduliny typowe dla innych ciliopatii.

Obraz histopatologiczny w powiązaniu z przebiegiem klinicznym GCKD u opisywanej pacjentki może sugerować bezpośredni związek pomiędzy ciliopatiami a zwiększoną podatnością na występowanie AKI, które w konsekwencji może prowadzić do włóknienia śródmiąższowego i najprawdopodobniej przyspiesza rozwój niewydolności nerek.

Słowa kluczowe: torbielowatość kłębuszków nerkowych, ciliopatie, nawracające ostre uszkodzenie nerek (AKI)

INTRODUCTION

Glomerulocystic Kidney disease (GCKD) is a relatively uncommon type of renal cystic disease. GCKD is more frequently diagnosed in children, however, it can be dignosed at any age. It is believed that the prevalence of GCKD is underestimated among adult patients presenting with end – stage renal failure.

We report a case of GCKD first diagnosed in the age of 23-year-in a female with chronic kidney disease (stage III).

CASE REPORT

A 23-year-old female with a 16-year history of normocytic anemia was adimtted for evaluation of an accidentally diagnosed renal insufficiency. The patient denied an infection, fever or drug abuse and difficulty or pain in urination preceding the hospitalization. Prior to the admission her only medication had been oral contraceptive. She reported past recurrent urinary tract infections with no history of haematuria or lithuria. She also had a bone marrow biopsy in 1994 and oral iron therapy, but the documentary evidence was no longer available.

There was no family history of renal insufficiency, however, her father suffered from nephrolithiasis.

On admission the patient was in good general condition without any complaints. She showed a marked pallor of the facial skin and mucous membranes. The remainder of the physical examination was normal. Her blood pressure was 110/80 mm and the heart rate 72 beats/min.

Laboratory tests indicated an impaired renal function with a serum creatinine of 1.53 mg/dl, serum urea 52.6 mg% and GFR 43 ml/min, serum sodium 138 mmol/l, serum potasium 5.6 mmol/l. Moreover, the hemoglobin level was moderately decreased – 10.0 g/L, MCV, MCH, MCHC, the reticulocyte count (0.7%), the total leucocyte count and platelet count were within normal limit, The TSAT was 28%, and the concentrations of Vit B12 and Folic Acid, Serum phosphorus (3.66 mg/dl) and fasting plasma glucose (99 mg/dl) were normal. Venous blood gases indicated a metabolic acidosis with pH 7.334, pCO2 31.7 mmHg, pO2 26.8 mmHg, HCO3 – 16,9 mmol/l, BE-7,5 mmol/l with normal serum anion gap. Howerer, the significant increase in uric acid – 6.78 mg /dl, and dyslipidemia: total cholesterol 245 mg/dl, LDL-cholesterol – 135 mg/dl, HDL – cholesterol 78.9 mg/dl, Triglycerides 80.72 mg/dl and ESR of 50 mm were noted.

Routine immunological screening (c-ANCA, p-ANCA, ANA, DsDNA, anty GBM, RF) was negative. Thyrothropin as well as thyroid hormones were normal.

Urinalysis was normal with pH 5.0 and specific gravity 1015 without proteinuria or erythrocyturia.

Ultrasound examination revealed a slightly diminished kidneys measuring – right kidney 9.4 cm and the left 9.2 cm, with mild cortical hyperechogenicity and the only one cortical cyst of 1.3 cm in the left kidney. No signs of obstruction and no cysts in any other organs were found.

CT scanning was not performed due to renal insufficiency.

A percutaneous renal biopsy was done to show six glomeruli with cystic dilatation of Bowman's space, compression of the capillary loops and mild tubulointerstitial fibrosis. Immunofluorescence studies were negative. The histopatologic findings were consistent with GCKD with concomitant tubulointerstitial fibrosis (fig. 1).

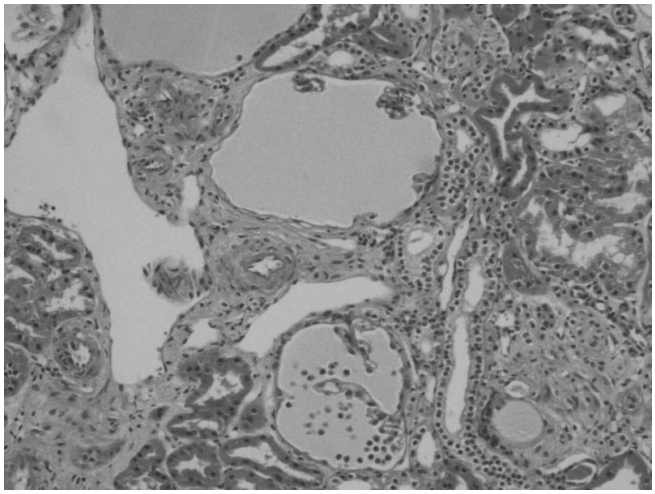

Fig. 1.

During one-year observation in our clinic there were repeated attempts to start a treatment with diuretic, statin, allopurinol or calcium carbonate but in each case acute kidney injury (AKIN I-II) resulted. Today, the patient remains on conservative therapy under medical supervision in outpatient clinic. Serum creatinine and urea levels are stable at 1.62 mg/dl and 82 mg/dl respectively. There is still present acidosis with mild hyperkaliemia as well as mild hyperuricaemia and hipercholesterolemia, however, she observes the low-purine and low-cholesterol diet.

DISCUSSION

Glomerulocystic Kidney disease (GCKD) is a relatively uncommon type of renal cystic disease. It is believed that GCKD is underestimated among adult patients presenting with end – stage renal failure. GCKD appears as a very heterogenic disease entity. Variable renal size and function is observed. Kidneys may be massively enlarged, normal -sized or hypoplastic with small diffused or clustered cysts which are principally localized throughout the cortex. In GCKD there are seen normal medullary pyramids that can help differentiate GCKD from ADPKD where cysts might be observed in both the cortex and the medulla. Loss of renal function in GCKD oscillates between mild, stable chronic kidney disease and severe renal damage including end-stage renal failure.

Renal histopathology shows cystic dilatation of Bowman's space. Glomerular capillary tufts may be reduced, rudimentary or collapsed (4). Periglomerular fibrosis and diffuse mild interstitial fibrosis appear to be rare findings in primary GCKD. GCKD has been precisely defined by Bernstein as a dilatation of Bowman's space 2-3 times in the plane of section with the presence of glomerular tufts within at least 5% cysts (1).

Ultrasonography can show the hyperechogenic cortex with a distinctive hypoechoic rim and cortical cysts (most often < 1 cm) (6).

GCKD can be currently classified into five major categories (tab. 1):

- familial nonsyndromic GCKD,
- familial/sporadic heritable malforamation syndromes GCKD,

– syndromic, non-hereditary GCKD,
– sporadic GCKD,
– aquired GCKD (3).

Table 1. Classification of glomerulocystic kidney disease.

GCKD	Example
I Familial GCKD (nonsyndromic)	Autosomal dominant GCKD
II Familial/sporadic heritable syndromes	ADPKD, ARPKD, Tuberous sclerosis complex, MCKD, juvenile nephronophthisis
III Syndromic, non hereditary (GCKD as component of other cystic diseases)	Diffuse cystic dysplasia, renal-hepatic-pancreatic dysplasia syndrome
IV Sporadic	New mutations
V Acquired	Associated with HUS, obstructive uropathy

According to the above classification, GCKD can be also associated with other specific diseases such as medullary cystic kidney disease or systemic sclerosis (tab. 2).

Table 2. Occasional association of GCKD.

Occasional associations of GCKD:
– congenital nephrotic syndrome – Marden-walker syndrome – Trisomy 9 – Trisomy 18 – Hypothyroidism – Retinitis pigmentosa – Brain and muscular atrophy – Cerebral vascular malformations – Systemic sclerosis

In our patient GCKD was accompanied with recurrent acute renal failure which probably resulted in tubule-interstitial lesions. The ethiology of this increased susceptibility to acute kidney injury in our patient remains unclear.

Recent studies shed light on the pathogenesis of GCKD (6-8), for instance, it was proved, the proteins which are defective in dominant GCKD and many other cystic kidney diseases e.g. ADPKD, ARPKD, NPHP, MCKD are connected wtoith the primary cilium. Recognition of the role of this organelle in cytogenesis led to creation of the the term “ciliopathies”. Primary cilia are micro-tubule-based organelles which extend outwardly from the surface of many eukaryotic cells including renal epithelial cells. They regulate important cellular functions like proliferation and mitotic spindle orientation to provide normal epithelial function (6).

Many cystic kidney diseases including GCKD (especially autosomal dominant type of GCKD) and MCKD are caused by mutations of uromodulin also known as Tamm-Horsfall protein. These uromodulin storage diseases may present with varying degrees of chronic renal disease, hyperuricaemia, a reduced fractional excretion of uric acid and often renal salt wasting. Recent studies revealed that uromodulin protein is also expressed in the primary renal cilia and this is why GCKD can be included into “ciliopathies” (7). Significantly, in our patient the increase in uric acid, disproportional to the stage of chronic kidney disease has been observed. This might suggest the connection with a mutation in uromodulin.

There is also a well documented association of autosomal dominant GCKD with maturity onset diabetes in the young adults second to mutations in the gene encoding hepatocyte nuclear factor (HNF 1-B) (12). Another common theory reveals that the development of GCKD may be a consequence of urinary tract obstruction in utero or due to ischaemia.

In our patient the ethiology of renal cysts formation remains uncertain. Most probably it is a sporadic type of GCKD resulting from a new mutation.

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