

Case Report

Cystinuria in a patient with polycystic kidney disease

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Abstract

Cystinuria is a rare autosomal recessive metabolic disorder of renal and intestinal cystine transport. Cystine stones are found in only 1–2% of all stone formers. Patients with cystinuria are at high risk for nephrolithiasis and subsequent morbidity. Our patient is a 37-year-old male who presented for routine follow-up for polycystic kidney disease (PKD). He denied any history of passing nephroliths. He had no family history of PKD or personal history of kidney stones. Serum creatinine was 1.2 mg%. On routine urine microscopy, he was found to have multiple hexagonal cystine crystals. Urine pH was 7.5. Renal CT scan revealed enlarged polycystic kidneys and scattered bilateral intra-renal calculi. Urinary quantification of cystine was 1645 mg/day (normal excretion rate 30 mg/day). Patients with PKD are at increased risk for nephrolithiasis for a number of reasons including urinary acidification, concentrating defects and hypocitraturia. The molecular, cellular and genetic basis for cystinuria is distinctly different and presumably unrelated to the genetic defects in PKD. We suspect that the occurrence of these two unrelated genetic diseases in the same patient is a coincidental finding. Even after a thorough review of the published literature, we were unable to find a genetic relationship between cystinuria and cystic renal diseases. To our knowledge, this is the first report of a finding of cystinuria in an adult with PKD.

Keywords: cystinuria; nephrolithiasis; polycystic kidney disease

Introduction

Polycystic kidney disease (PKD) is one of the most common inherited diseases in adults affecting 1 in 400–1000 live births [1]. It is the third most common cause of end-stage renal disease (ESRD) in the United States and accounts for ~10% of all cases of ESRD [2]. PKD is a member of a family of inherited renal cystic disorders and is characterized

by simple cysts distributed throughout the kidney, although the disease is not limited to the kidneys. It is better thought of as a systemic disease with cystic abnormalities found in the kidneys, liver, cerebral vasculature, colon and a higher propensity for inguinal hernias and nephrolithiasis.

Stone formation occurs in ~20% of patients with PKD [3]. Uric acid stones occur at a much greater frequency than the general population, while struvite and calcium phosphate stones occur at similar frequencies [3]. Calcium-oxalate-containing stones seem to occur with decreased frequency in patients with PKD. Interestingly, cystinuria or cystine stones have not been described in patients with PKD, despite the high risk of stone disease in this patient population.

Cystinuria is a complex genetic metabolic disorder that results in high urinary excretion of cystine and other dibasic amino acids [4]. Affected patients may have recurrent renal colic, urinary tract obstruction, cystine crystalluria or precipitate cystine calculi.

We report a case of a patient with PKD who was incidentally found to have cystine crystalluria, an interesting clinical observation not previously reported in the medical literature.

Case report

A 37-year-old male presented to renal clinic for routine follow-up for PKD. His initial diagnosis of PKD was made after an evaluation of an episode of painless gross haematuria at age 27. Physical examination at that time was normal except for the blood pressure that was 148/86 mmHg. His past medical history is unremarkable, specifically for no history of flank pain, renal colic or symptomatic kidney stones. He takes no medications. He has no family history of renal disease, kidney stones or PKD. Computed tomography scanning at initial presentation revealed marked renal volume enlargement, greater than 50 cystic lesions in each kidney bilaterally all consistent with simple cysts (Figure 1). Additionally, hepatic cysts and colonic diverticuli were noted. Finally, several renal parenchymal calcifications were noted, thought to be consistent with retained bilateral nephrolithiasis. Serum creatinine at that time was 1.3 mg/dL. Urinalysis at initial presentation was notable for

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Fig. 1. Computed tomography image indicating multiple bilateral simple renal cysts.

specific gravity of 1.005, pH 7.5, trace blood and no proteinuria. He was diagnosed with PKD in accordance with Ravine's criteria [5].

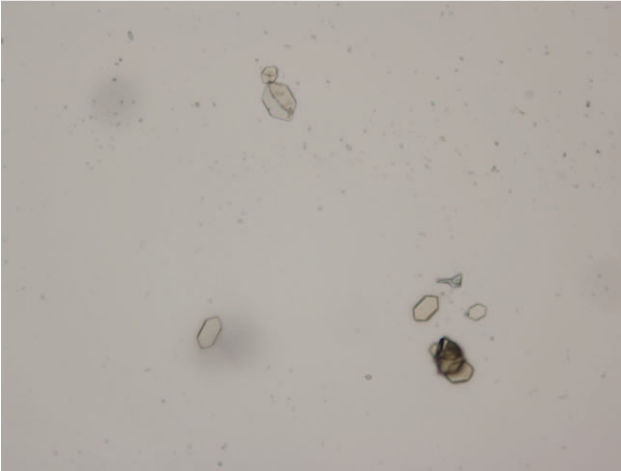
He has done well over time with only an occasional episode of painless gross haematuria, always associated with physical sports activity. His hypertension has worsened prompting treatment with an angiotensin receptor blocker, irbesartan 75 mg orally per day.

On recent routine follow-up evaluation, the patient was asymptomatic with normal physical examination. Blood pressure was 132/76 mmHg. Urinalysis revealed a specific gravity of 1.005, pH 7.5, no protein, trace blood and numerous hexagonal-shaped crystals (Figure 2). The patient was further evaluated with a 24-h urine collection that revealed 1645 mg/day cystine, creatinine 2100 mg and volume 3010 mL. Since the patient was asymptomatic, no specific pharmacologic treatment was given. He was counseled about the increased risks of nephrolithiasis, and hydration strategies were discussed. The patient remains in good health and has yet to develop a symptomatic kidney stone over a 3-year follow-up period.

Discussion

Kidney stones occur at an increased frequency in patients with PKD [6]. In a study by Torres *et al.*, 20% of patients with PKD had an episode of nephrolithiasis [6]. Interestingly, uric acid stones occurred with a much greater frequency than that in a cohort of patients without PKD. The aetiology of stone disease in PKD has not been completely elucidated, but recent reports suggest that it is multifactorial in nature, including both anatomic and metabolic factors [7]. Anatomic abnormalities include parenchymal distortion from cystic displacement leading to urinary stasis, which is thought to contribute to the pathogenesis of kidney stones formation in patients with PKD [8]. Urinary concentrating defects that occur early in the development of PKD seem to correlate with degree of renal anatomy distortion and the subsequent development of kidney stones [9]. Metabolic factors suggested to contribute to nephrolithiasis include hypocitraturia, and perhaps disordered uric acid tubular physiology. It would appear that disruption of normal tubular transport mechanisms by cystic dilation is

10x



40x

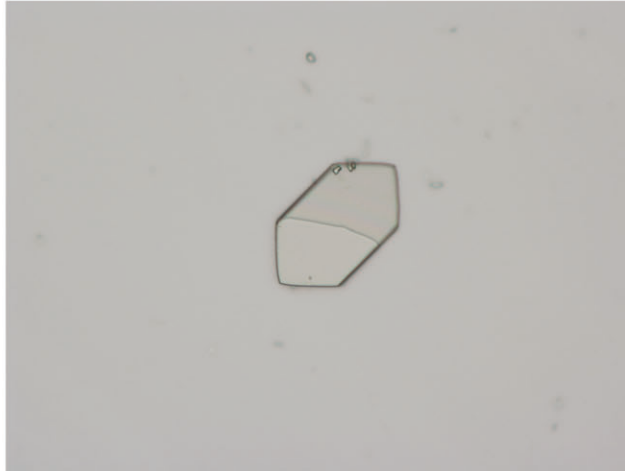


Fig. 2. Urine sediment revealing hexagonal-shaped crystals consistent with cystinuria (10×). Urine sediment with hexagonal-shaped crystal consistent with cystinuria (40×).

central to these metabolic issues. Hypocitraturia was found to be significantly decreased in 10 of 15 patients described in a study by Torres *et al.* [3]. While hypocitraturia is associated with increased stone formation risk in the general population, it is unclear if this defect is specific to PKD. Defective renal ammoniogenesis likely leads to a reduction in renal buffering capacity and is proposed to contribute to the increased frequency of uric acid nephrolithiasis in patients with PKD [10].

Cystinuria is a rare autosomal recessive metabolic disorder associated with urinary supersaturation of di-basic amino acids [11]. In the general population, cystine stones represent 1–2% of all urinary calculi; cystine stones or cystine crystalluria have not been described in patients with PKD despite the multiple risk factors these patients have for development of nephrolithiasis [12]. Cystinuria is transmitted via an autosomal recessive trait that results in decreased proximal tubular cystine reabsorption and increased urinary cystine excretion. The defect is located on chromosome 2 on gene *SCL3A1* or on chromosome 19 on gene *SCL7A9*. This gene product normally produces a protein involved with cystine transport in both the kidney and small intestine. The severity of the defect depends on the chromosome involved and the amount of cystine excreted.

Diagnosis of cystinuria is relatively straightforward. Identification of the pathognomonic hexagonal-shaped crystals on urine sediment analysis and measurement of daily urinary cystine excretion are accepted diagnostic methods. The definitive diagnosis is stone analysis. The normal excretion rate for cystine is ~20–30 mg/day. Patients with cystinuria generally excrete >500–1000 mg/day. However, not all patients with cystinuria will excrete observable cystine crystals; thus, there appears to be a certain level of excreted cystine required to precipitate crystals in addition to other stone formation factors [13]. Other urolithiasis risk factors observed in patients with cystinuria include hypercalciuria, hyperuricosuria and hypocitraturia. In patients with homozygous cystinuria, mixed calcium–cystine stones can account for up to half of these stones [14].

While patients with PKD are at increased risk for kidney stones in general, there does not seem to be increased risk for cystine crystalluria or cystine stones. This may simply be due to the fact that cystinuria and PKD are completely unrelated genetic diseases.

Clearly, both diseases produce stones by altered tubular transport mechanisms. In both diseases, factors that favor stone formation include similar risk factors that are observed in the general population, including hypercalciuria, relative urinary stasis and perhaps hyperuricosuria. Interestingly, a promoter of stone formation in PKD is low urinary pH, a finding consistently not present in our patient. We postulate that our patient likely has either a genetic or acquired renal acidification defect. The nature of this defect is unknown in our case, as in the work by Torres *et al.* [15]; renal ammonia trapping and transport seems to be impaired in patients with advanced PKD. Alkaline urine may be protecting our patient from overt symptomatic stone cystine formation.

Another possible mechanism for reduced cystine stone formation in patients with PKD and cystinuria may be due to the relative frequency that these patients are prescribed ace-inhibitors. Ace-inhibitors, specifically captopril, due to their thiol group bind to cystine and increase their solubility almost 200-fold [16]. However, the efficacy of captopril in cystinuria crystalluria has been challenged recently [17]. Of note, our patient was not taking captopril, nor was he genetically tested for either PKD or cystinuria.

In conclusion, PKD is a relatively common genetic disease characterized by cysts in the kidney and other organs in the body. In addition to cysts, patients with PKD are at high risk for nephrolithiasis, nearly twice that of the general population. Patients with PKD tend to form calcium and uric acid and based stones at a higher rate than patients without PKD. Cystine crystalluria and stones are rare in the general population, and there is no description of their formation to date in a patient with PKD. We have presented an interesting unique circumstance of cystine crystalluria in a patient with PKD. We suspect that this astute clinical

observation has occurred by chance, though it is compelling that these two genetic diseases have occurred together in the same patient, and perhaps could represent digenic inheritance outside the scope of Mendelian inheritance. While it is commonly accepted that other genetic associations may occur in patients with cystic renal diseases, no instances of these two genetic defects have been described together, nor have been systematically studied. This observation should serve as a notice that further study may reveal a potential relationship between these two genetic renal diseases. Finally, this patient has yet to experience a single symptomatic nephrolithiasis, which is remarkable, considering the cumulative risk for nephrolithiasis in patients with PKD in general and this patient in particular.

Conflict of interest statement. The views expressed in this report are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Received for publication: 7.9.08

Accepted in revised form: 6.10.08