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Nephrolithiasis and Multicystic Kidneys in a Young Patient: A Quiz

Valentine Gillion, Karin Dahan, Cristina Anca Dragean, and Nathalie Demoulin

Clinical Presentation

A 23-year-old man with no relevant medical history or active medication presented with gross hematuria and hypogastric pain. Kidney ultrasound revealed medullary hyperechogenicity, suggestive of nephrocalcinosis, and bilateral cysts (Fig 1). A month later, he developed acute renal colic secondary to an obstructive 14 mm stone located in the right pyeloureteral junction, requiring placement of a double J stent. The stone was removed by ureterorenoscopy. Infrared spectroscopy showed the stone to be of mixed type: carbapatite, brushite, and calcium oxalate mono- and dihydrate. Metabolic work-up revealed mild hypercalcemia with suppressed parathyroid hormone (PTH), elevated 24-hour urinary calcium excretion, 25-hydroxyvitamin D level within the reference range, and high 1,25-dihydroxyvitamin D level (Table 1). Family history was negative for nephrolithiasis or cysts and the parents were not consanguineous. Kidney magnetic resonance imaging showed normal-sized kidneys, multiple renal cysts bilaterally, and the absence of liver cysts.

- **What is the differential diagnosis for this patient's hypercalcemia, suppressed PTH, and nephrolithiasis?**
- **What additional work-up may confirm this diagnosis?**
- **What treatment options are possible for this patient?**

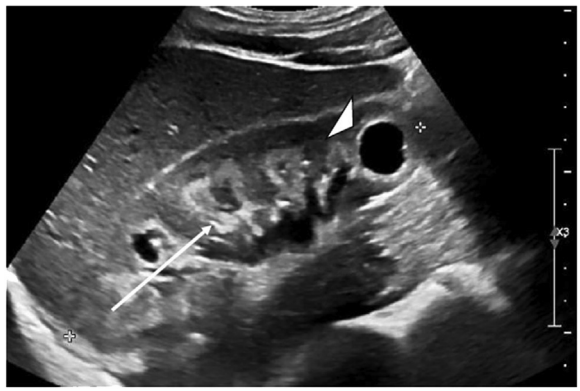

Figure 1. Ultrasound of right kidney with mild echogenicity around medullary pyramid borders (arrow) and pyramidal cyst (arrowhead).

Discussion

What is the differential diagnosis for this patient's hypercalcemia, suppressed PTH, and nephrolithiasis?

This patient has non–parathyroid-related hypercalcemia, of which the most common cause is neoplasia. Both solid tumors and hematologic malignancies may increase bone resorption by various mechanisms: induction of osteolysis by bone metastases, release of osteoclast activating factor in multiple myeloma, secretion of PTH-related protein by some solid tumors (especially squamous cell carcinomas), or production of 1,25-dihydroxyvitamin D (usually by lymphomas).[1]

Nontumor etiologies of non–parathyroid-related hypercalcemia include excessive intake of vitamin D supplements or 1,25-dihydroxyvitamin D_3 and increased endogenous production of 1,25-hydroxyvitamin D_3 in patients with granulomatous disorders (especially sarcoidosis).

Other rare causes of hypercalcemia include lithium therapy, thiazide diuretics, hypervitaminosis A, thyrotoxicosis, pheochromocytoma, adrenal insufficiency, milk-alkali syndrome, and prolonged immobilization.

A rare additional cause of high vitamin D levels is a monogenic disorder caused by biallelic (or occasionally

Table 1. Laboratory Findings

	Value	Reference Range
Blood		
Creatinine, mg/dL	1.16	0.6-1.3
Calcium, mmol/L	2.57	2.20-2.50
Ionized calcium, mg/dL	5.8	4.44-4.80
Phosphorus, mmol/L	1.18	0.81-1.45
iPTH, pg/mL	<3	15-80
Total 25-hydroxyvitamin D, ng/mL	54	>30
1,25-hydroxyvitamin D, pg/mL	106	19.9-79
Urine		
Volume, mL/d	1,500	
pH	6.4	5.0-7.5
Creatinine, g/d	1.86	0.81-2.01
Calcium, mmol/d	8.9	<7.5
Oxalate, mg/d	38	<45
Sodium, mmol/d	180	40-220

Abbreviations: iPTH, intact parathyroid hormone.

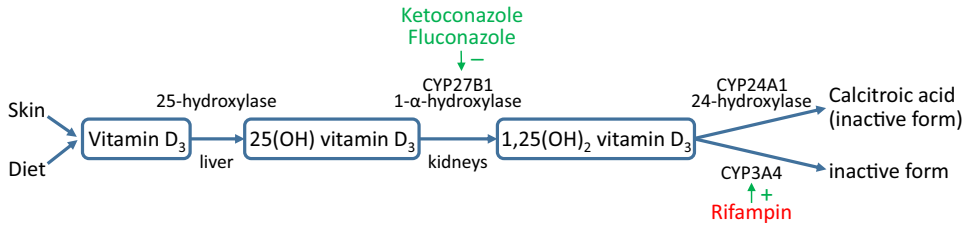

Figure 2. Vitamin D metabolism. Vitamin D is produced in the skin upon exposure to UV light. Vitamin D_3 is first converted to 25-hydroxyvitamin D_3 (calcidiol) in the liver and then to 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidneys, the active form with actions on bone, intestine, and parathyroid. CYP27B1 is the key hydroxylase for the generation of 1,25-dihydroxyvitamin D_3 and can be inhibited by ketoconazole and fluconazole. The catabolism of 1,25-dihydroxyvitamin D3 is mainly catalyzed by CYP24A1 as well as CYP3A4.

monoallelic) pathogenic variants in the gene encoding 25-hydroxyvitamin D_3 24-hydroxylase. This enzyme, also known as CYP24A1, catalyzes the conversion of 1,25-dihydroxvitamin D_3 and 25-hydroxyvitamin D_3 into inactive 24-hydroxylated products that are excreted (Fig 2). CYP24A1 deficiency leads to persistently high levels of 1,25-dihydroxvitamin D_3. Loss-of-function variants in CYP24A1 may lead to infantile hypercalcemia type 1 (OMIM 143880), also called hypersensitivity to vitamin D_3. This hypersensitivity to vitamin D_3 can be severe and potentially fatal in infants after prophylactic vitamin D_3 supplementation for the prevention of rickets.[2] Adult patients may present with recurrent calcium kidney stones, with or without nephrocalcinosis. Recently, medullary and/or corticomedullary junction cysts (a mean of 5.3 cysts per patient) were reported in 16 patients with CYP24A1 deficiency (half of whom had nephrolithiasis as the presenting symptom).[3] The mechanisms of cystogenesis remain unknown, but sustained hypercalciuria and/or exposure to increased calcitriol levels could contribute to kidney cyst development.

The diagnosis of CYP24A1 deficiency should be suspected in patients with bilateral kidney cysts, high levels of 1,25-dihydroxvitamin D_3, nephrocalcinosis, and kidney stones composed of carbapatite, brushite, and/or oxalate calcium dihydrate, which are typically associated with hypercalciuria.

What additional work-up may confirm this diagnosis?

Chest imaging, measurement of serum levels of angiotensin-converting enzyme, and eye examination were performed to rule out sarcoidosis.

Genetic testing using a next-generation sequencing targeted gene panel revealed a homozygous variant in the *CYP24A1* gene predicted to lead to a substitution of tryptophan for arginine at amino acid 396 (p.Arg396Trp); this variant has been previously reported to result in complete loss of function.[2] The patient's parents were both heterozygous for the variant.

What treatment options are possible for this patient?

The management of CYP24A1 deficiency remains challenging.

The patient received dietary counseling on the need to increase water intake; reduce intake of salt, protein, and oxalate; and maintain a diet moderately rich in calcium to enhance bone formation. The patient was also counseled to avoid vitamin D supplements and sun exposure.[4] Thiazide diuretics must be used with caution when treating hypercalciuria, as they may worsen or cause hypercalcemia. Use of imidazole derivatives such as ketoconazole or fluconazole to partially inhibit CYP27B1 (to decrease calcitriol levels) or rifampin (to increase CYP3A4 activity), has shown short-term benefits, but the long-term safety of such therapies remains uncertain.[5-7]

Final Diagnosis

CYP24A1 deficiency secondary to a homozygous pathogenic variant.

Article Information

Authors' Full Names and Academic Degrees: Valentine Gillion, MD, Karin Dahan, MD, PhD, Cristina Anca Dragean, and Nathalie Demoulin, MD.

Authors' Affiliations: Division of Nephrology (VG, KD, ND) and Department of Medical Imaging (CAD), Cliniques universitaires Saint-Luc, Brussels, Belgium; Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium (VG, CAD, ND); and Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium (KD).

Address for Correspondence: Valentine Gillion, MD, Division of Nephrology, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium. Email: valentine.gillion@uclouvain.be

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