3rd Edition of the Clinical Cases Contest related to the non-surgical clinical management of renal lithiasis.

Title: Recurrent renal lithiasis due to Dent's disease

Keywords (between 3 and 6): Dent's disease, recurrent renal lithiasis, phytate, potassium citrate

1. Summary (not over **150 words**)

Clinical case report of a 21-year-old male with severe hypercalciuria, elevated bone resorption and bilateral renal lithiasis. Due to nephrocalcinosis and hypercalciuria (476 mg/24h), treatment using potassium citrate (Lit-Control pH Up®) and hydrochlorothiazide was initiated at age 13. Despite the treatment, when the patient arrived at the adult Urology service, he maintained hypercalciuria and, in addition, he had a symptomatic, 2.2 cm lithiasis in the right kidney, and another asymptomatic lithiasis, 1 cm in size in the left kidney. For this reason, the right percutaneous nephrolithotomy (PCNL) was performed and phytate (Lit-Control pH Balance®) was added to the treatment. Despite good metabolic control, a new stone formed and another right PCNL had to be performed. After the second surgery and with good therapeutic compliance, the patient reaches radiological and clinical stability of the lithiatic disease.

2. Introduction

Hypercalciuria is one of the most frequent disorders that can be observed in patients who develop lithiasis and can be caused by three mechanisms: increased intestinal absorption, bone resorption or renal losses (1). However, the clinical significance of the mechanisms is unclear, and patients may present with a combination of these.

A rare cause of hypercalciuria is Dent's disease, which is an inherited X-linked disorder caused by a mutation of the Cl^-/H^+ channel of the endosomes of the proximal tubule cells of the glomeruli. The most frequent mutations are in the CLCN5 gene. These mutations prevent the pH of the interior of the endosomes from remaining acidic, therefore, the proteins that have been filtered cannot be degraded, causing low molecular weight proteinuria (2).

Patients with Dent's disease may also suffer from hypercalciuria of intestinal origin, although the exact mechanism of hyperabsorption is not known(3).They may also have hyperphosphaturia and an increase in 1,25-OH-vitamin D due to activation of parathyroid hormone receptors (PTHr), which is a low molecular weight protein, located in the last section of the proximal tubule(4).

Those affected by Dent's disease usually present in childhood with low molecular weight proteinuria, hypercalciuria, nephrocalcinosis and/or recurrent urinary lithiasis and impaired kidney function (2).

Clinical case report of a male patient with hypercalciuria since childhood with recurrent kidney stones despite good metabolic control with phytate (Lit-Control pH Balance®), potassium citrate (Lit-Control pH Up®) and hydrochlorothiazide.

3. Description of the clinical case:

a. Relevant medical history

Clinical case report of a 21-year-old male with severe hypercalciuria, elevated bone resorption and bilateral renal lithiasis who was diagnosed with nephrocalcinosis in childhood. Despite establishing treatment for hypercalciuria (potassium citrate + hydrochlorothiazide), it persists when the patient visits the urology department. In addition, he also has a stone of 2.2 cm in size in the symptomatic right kidney and another stone of 1 cm in the asymptomatic left kidney.

b. Diagnostic support studies and results

1) Abdominal X-ray upon arrival at the adult urology department (09/2019): stone of 2.2 cm in size in the lower right calyces and a 1 cm stone in the lower left calyces (Image 1).

2) 24-hour urinalysis upon arrival at the adult urology department, on treatment with potassium citrate + hydrochlorothiazide (09/2019): pH 6.66, hypercalciuria (412 mg/24h), hypocitraturia (109 mg/24h) and hyperphosphaturia (1170 mg/24h).

3) 1, 25-OH-vitamin D (09/2019): 118 pg/mL.

4) Furosemide stress test (10/2019): the patient can acidify urine (distal renal tubular acidosis is ruled out).

5) Beta crosslaps (10/2019): 2.95 ng/mL.

6) Proteins in urine (10/2019): 0.6 g/24h.

7) Densitometry (12/2019): within normal limits.

8) CT urogram (12/2019): no anatomical abnormalities.

c. Diagnosis

After the first right PCNL (02/2021) the patient is left without clinically significant remaining fragments. Despite this and the addition of phytate (Lit-Control pH Balance®) to the treatment, 1 year later he presents with right renal colic due to a 3 cm stone in the pyelo-ureteral junction, therefore a right double-J stent is placed. In addition, the patient has another stone of 1cm in size the right upper calyces. Later (03/2022), a new right PCNL is performed, after which there are no remaining fragments.

The furosemide stress test rules out that the patient has distal renal tubular acidosis. Despite having elevated levels of beta crosslaps, which suggests a high bone resorption, the bone densitometry results are within normal limits.

Due to the recurrence of lithiasis despite good metabolic control and the remaining tests alterations, a genetic test for Dent's disease is performed, which is positive for a mutation in the CLCN5 gene.

d. Treatment

To manage both the initial and the recurrent lithiasis, a PCNL is performed using a 24Ch sheath and an ultrasonic lithotripter. The first through the upper calyx due to mobilization of the stone and the second through the lower calyx.

As for metabolic control, treatment was initiated using potassium citrate (Lit-Control pH Up®, 1 capsule/12h), phytate (Lit-Control pH Balance®, 1 capsule/12h), hydrochlorothiazide 25 mg and dietary measures (high water intake and a diet low in protein and salt).

e. Progress and monitoring

After the first surgery, the patient had to be monitored in outpatient visits with a 24-hour urinalysis and an abdominal X-ray, but he came to the emergency room presenting a right renal colic due to a 3 cm stone in the pyelo-ureteral junction, therefore a right double-J stent is placed and he was also included in the waiting list for a new right PCNL.

Six months after the second surgery and with good therapeutic compliance, the patient remains asymptomatic and free of lithiasis.

f. Clinical results

1) Abdominal X-ray after the first PCNL (02/2021): remaining lithiatic fragments with no clinical significance (image 2).

2) Stone analysis after the first PCNL (02/2021): brushite + hydroxyapatite.

3) Abdominal X-ray one year after the first PCNL in addition to good metabolic control (02/2022): a 3 cm stone in the lower right calyces and a 1 cm stone in the upper right calyces (Image 3).

4) Abdominal X-ray after the second PCNL (03/2022): no signs of remaining fragments (image 4).

5) Urine analysis (24 hr.) after adding treatment with phytate (08/2021): pH 6.35, calciuria 275 mg/24h, citraturia 184 mg/24h and phosphaturia 875 mg/24h.

6) Genetic test for Dent's disease (04/2022): positive for mutation in the CLCN5 gene.

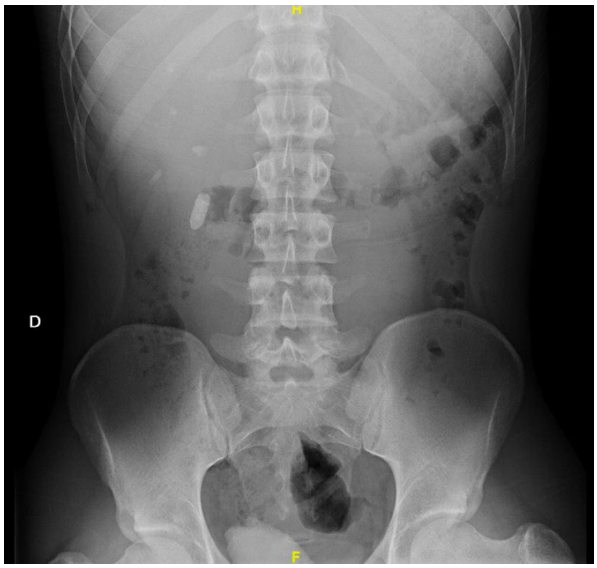

Image 1

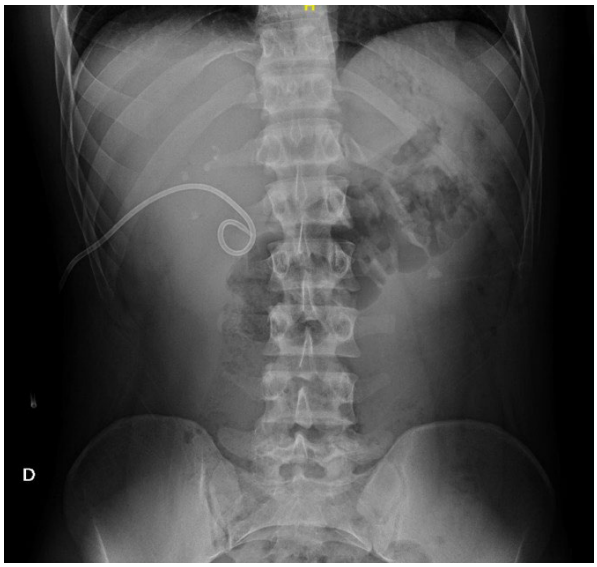

Image 2

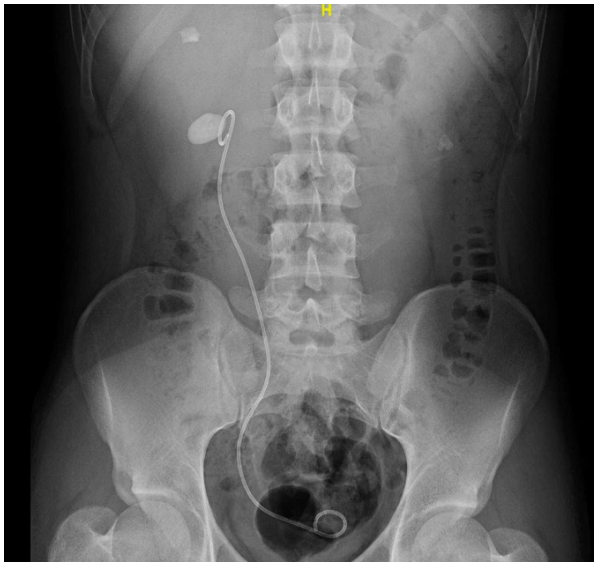

Image 3

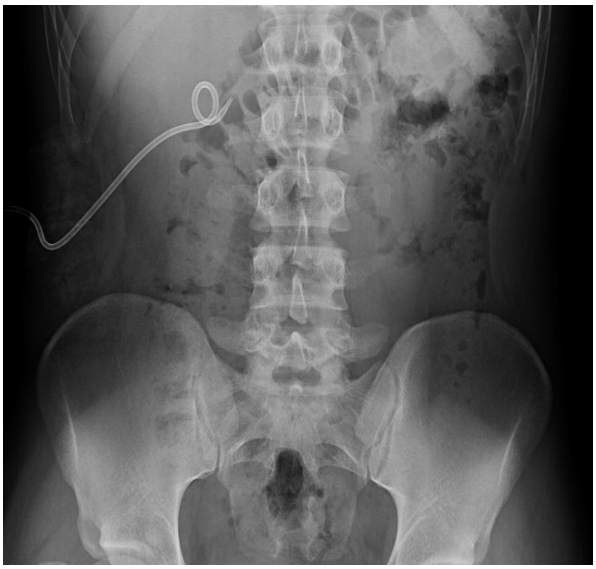

Image 4

4. Discussion

Dent's disease is a rare cause of recurrent urinary lithiasis. Despite being frequently diagnosed in childhood, we should not rule it out in adult patients. It is suspected in patients with proteinuria, hypercalciuria, hyperphosphaturia and recurrent bilateral renal lithiasis or nephrocalcinosis since an early age.

The patient whose case is reported, in addition to recurrent renal lithiasis, presents with low molecular weight proteinuria, hypercalciuria, hyperphosphaturia and an increase in 1,25-OH-vitamin D. These last two metabolic alterations are due to the excess of parathyroid hormone (PTH), a low molecular weight protein, in the urine, which stimulates the PTHr of the distal section of the proximal tubule (4). This stimulation increases bone resorption directly and indirectly (through the activation of 1,25-OH-vitamin D) (5). Despite the increase in bone resorption, the patient, due to his early age, has bone mineral density within normal limits (6).

The hypercalciuria that was found is due, in part, to intestinal hyperabsorption (3). In addition, this will be exacerbated due to the "hormonal" effect of 1,25-OH-vitamin D, which is increased in these patients, along intestinal calcium absorption (5). However, dietary calcium restriction is not recommended because it can worsen bone disease (2).

The management of these patients is based on decreasing lithiatic events and preventing kidney function worsening (2). Hypercalciuria in these patients is also secondary to high bone resorption and its treatment is based on the use of thiazide-type diuretics, which increase calcium resorption in the distal tubule (7).

In this reported case, hydrochlorothiazide 25 mg and potassium citrate (Lit-Control pH Up®) were incorporated into the treatment as the latter is a urine calcium chelator, which also inhibits the crystallization of calcium phosphate stones (8). Subsequently, in adult urology consultation, we initiated treatment with phytate (Lit-Control pH Balance®) due to its ability to inhibit calcium phosphate stones growth and decrease bone resorption (9,10)

The prognosis of patients with Dent's disease will be marked by chronic kidney disease. The exact cause of chronic kidney disease remains unknown, it is believed that it is caused due to glomerular sclerosis, proteinuria, or the presence of cytokines in the tubule. When the patient reaches the end stage of kidney disease, a kidney transplant is a good option because the disease does not recur after transplant (2).

5. Conclusions and recommendations

Dent's disease is an inherited disease linked to the X chromosome that usually affects males and is diagnosed during childhood. Although it can rarely go unnoticed in the first years of life and the patient can reach adulthood without a diagnosis, we must consider it as a differential diagnosis for patients with recurrent urinary lithiasis with hypercalciuria, hyperphosphaturia and proteinuria despite good compliance of metabolic treatment.

The importance of an early and accurate diagnosis resides in the fact that, if the right treatment is established, we can avoid the complications caused by the disease, which are the ones that most affect the patient's quality of life. In addition, through the control of the alterations inherent to the pathology, we also avoid invasive procedures and their associated comorbidities.

Ultimately, it should be noted that the treatment for this disease is not curative, but is based on preventing complications, including kidney function worsening. Once kidney disease has established, the best option is kidney transplantation as the disease does not recur after transplant.

6. Bibliographic references (*of special interest, **of extraordinary interest)

1. Levy FL, Adams-Huet B, Pak CYC. Ambulatory Evaluation of Nephrolithiasis: An Update of a 1980 Protocol. Am J Med. 1995 Jan;98(1):50–9.

*2. Scheinman SJ, Lieske JC. Dent disease (X-linked recessive nephrolithiasis). In: UpToDate, Goldfarb S (Ed), UpToDate, Waltham, MA. (Consultado el 22 de octubre de 2022).

3. Luyckx VA, Leclercq B, Dowland LK, Yu ASL. Diet-dependent hypercalciuria in transgenic mice with reduced CLC5 chloride channel expression. Proc Natl Acad Sci U S A. 1999 Dec 10;96(21):12174–9.

*4. Piwon N, Günther W, Schwake M, Bösl MR, Jentsch TJ. ClC-5 Cl- -channel disruption impairs endocytosis in a mouse model for Dent's disease. Nature. 2000;408(6810):369.

5. Khazai N, Judd SE, Tangpricha V. Calcium and Vitamin D: Skeletal and Extraskeletal Health. Current Rheumathology Reports. 2008 Apr;10(2):110–7.

6. Reinhart SC, Norden AG, Lapsley M, Thakker R v, Pang J, Moses AM, et al. Characterization of Carrier Females and Affected Males With X-Linked Recessive. Journal of the American Society of Nephrology. 1995 Jan 1;5(7):1451–61.

7. Bergsland KJ, Worcester EM, Coe FL. Role of proximal tubule in the hypocalciuric response to thiazide of patients with idiopathic hypercalciuria. Am J Physiol Renal Physiol. 2013 May 8;305(4).

8. Guimerà J, Martínez A, Tubau V, Sabate A, Bauza JL, Rios A, et al. Prevalence of distal renal tubular acidosis in patients with calcium phosphate stones. World J Urol. 2020 Mar 1;38(3):789–94.

**9. Guimerà J, Martínez A, Bauza JL, Sanchís P, Pieras E, Grases F. Effect of phytate on hypercalciuria secondary to bone resorption in patients with urinary stones: pilot study. Urolithiasis. 2022 Sep 10; 50:685–90.

**10. Grases F, Isern B, Sanchis P, Perello J, Torres JJ, Costa-Bauza A. Phytate acts as an inhibitor in formation of renal calculi. Frontiers in Bioscience. 2007; 12:2580–7.