1st Edition of the Clinical Cases Contest related to the non-surgical clinical management of

Title: Is potassium citrate for everyone?

Keywords: potassium citrate, acidification, urinary tract infection, nephrolithiasis, L-methionine

1. Summary

Introduction: Calcium oxalate lithiasis are the most frequent. It is usual to find hypercalciuria associated with varying degrees of idiopathic hypocitraturia as the most prevalent disorder. Treatment with potassium citrate prevents this lithiasis formation. Nevertheless, we cannot generalize this treatment since not all stones respond adequately to alkalization.

Objective: Case presentation of a patient treated erroneously with potassium citrate and its subsequent resolution by optimizing the medical-surgical treatment.

Result: The crystallographic study showed mixed lithiasis composed of calcium oxalate monohydrate (85%) and struvite (10%). The metabolic study showed hypocitraturia related to a recent infection along with a urinary pH of 8. In this context, lithiasis load increase was caused by urinary alkalinization. The condition was resolved by surgical treatment and urinary acidification.

Conclusions: Patients subject to alkalizing treatment using potassium citrate must be correctly selected. It is essential to identify the type of lithiasis to treat it properly.

2. Introduction

Both diet and the environment play a key role in the formation of urinary stones by modulating the composition of urine and changing its solubility. Nowadays there is a wide variety of treatments available for the fragmentation and dissolution of kidney stones, that also reduce recurrences.

Calcium oxalate lithiasis are the most frequent. They represent over 80%. In patients with calcium oxalate monohydrate stones, metabolic causes should be ruled out, especially hyperoxaluria, it is also usual to diagnose hypercalciuria associated with varying degrees of idiopathic hypocitraturia. As a prophylactic treatment, thiazides or potassium citrate can be used, especially indicated in patients with increased risk of developing stones [1]. The recommendation of water intake to achieve daily diuresis close to 2.5-3 liters is basic.

However, urinary stones are not exclusively composed of calcium. They can also be mixed. There are other types of lithiasis, such as those of uric acid, waste product of the nitrogenous compound of urine, infective lithiasis formed by urease-producing bacteria, protein stones such as cystine, etc. The medical treatment must be adapted depending on the composition, since not all lithiasis respond adequately to the alkalization produced by potassium citrate.

Struvite stones represent between 5-15% of all urinary stones and are formed because of the hydrolysis of urea produced by urease-positive bacteria such as: Proteus, Klebsiella, Staphylococcus, Providencia, ... producing ammonia and carbon dioxide and increasing urinary pH. This pH favors the crystallization of magnesium and ammonium phosphate forming struvite crystals [2]. These stones cause significant morbidity and mortality if left untreated. These stones develop in alkaline pH, therefore, it is clearly contraindicated to administer potassium citrate in these cases since it contributes to the precipitation of these crystals by creating a perfect environment. To prevent its progression urine acidification should be achieved using agents such as ascorbic acid, ammonium chloride, ammonium sulfate or L-methionine. The latter has been used to dissolve residual fragments and to prevent the formation of infective stones [3]. However, it can be difficult to maintain urine acidification using these agents, particularly in the presence of infection, for this reason acidifying treatment often must be prescribed with antibiotic and surgical treatment to achieve complete resolution of lithiasis [4].

3. Description of the clinical case

Case presentation of a 70-year-old male HIV patient with an undetectable viral load, on antiretroviral therapy and chronic renal failure of multifactorial etiology (glomerular filtration rate 42 ml/min/1.73 m2). The patient was being treated for bilateral renal lithiasis in a different center since 2017. After three unsuccessful ureterorenoscopies, the last one being in January 2019, he was referred to our center. The patient was being treated with Lit-Control pH Up to avoid recurrences. The patient provides an abdominal CT scan without contrast, performed in September 2019 that shows occupation of both lower calyceal groups by a 13 mm lithiasis in the right kidney (RK) and a 14.5 mm stone (Image 1) in the left kidney (LK).

It was decided to complete the assessment with a dual-energy CT scan (Image 2) that shows progression of the bilateral global lithiasis load when compared to the previous CT, with growth of the left lithiasis reaching the middle ureter. The patient provides two spontaneously passed stones that are submitted for crystallographic study (Image 3), the overall quantitative composition reports: calcium oxalate monohydrate (85%), magnesium ammonium phosphate (10%) and protein (5%). Lab results show creatinine 1.75 mg/dl, calcium 8.1 mg/dl, PTH 92 mg/dl, 25-OH-VitD 12.6 mg/dl. 24-hour urine (2100 ml collected). pH 8, urinary citrate excretion 235 mg/24h and urinary calcium excretion

50 mg c/24h. Leukocyturia. Urine culture: negative. The renal gamma scintigraphy marked with 99m Tc-DMSA showed relative renal function corresponding to RK 61% and LK 39%.

After these findings, the alkalizing treatment was replaced by L-methionine as an attempt to acidify urine and slow down the lithiasis progression, achieving a pH of 7.2, prior to the surgery. The patient underwent an endoscopic combined intrarenal surgery (ECIRS) to treat the left staghorn lithiasis, with no incidents. He was discharged after 72 hours receiving prophylactic antibiotic therapy for one week (second generation cephalosporin). Subsequently, close clinical follow-up under treatment with L-methionine. Control CT scan with significant decrease of the bilateral lithiasis load (Image 4). Stable renal function (GFR 40 ml/min/1.73 m2).

4. Discussion

Renal lithiasis is a chronic, recurrent, very demanding disease that affects the quality of life of our patients, so we must use all our diagnostic and therapeutic tools to solve it. Urine supersaturation, urinary pH, ionic charge, solute concentration in urine and infection are the main factors contributing to lithiasis formation.

Having the kidney stone properly studied and classified simplifies the diagnosis and allows a more effective therapeutic approach since the etiological factors responsible for lithiasis can be targeted. In this case we were treating a lithiasis that was initially composed of calcium oxalate monohydrate but due to a superinfection, the stone was coated with a layer of magnesium ammonium phosphate. The formation mechanism of struvite stones involves the decomposition of urea by urease into ammonia and carbon dioxide, creating alkaline urine (pH 7.2-8.0), this pH level favors the crystallization of magnesium ammonium phosphate [2]. Urine alkalinization using potassium citrate had favored its development by creating a much more favorable environment for its precipitation, since this higher pH was maintained promoting its rapid growth occupying the renal calyces, the pelvis and even the proximal ureter significantly damaging the epithelium of the internal walls (the rapid progression can be clearly observed between the CT scans from September to December). The rate at which crystal growth occurs may differ from the urea splitting process. Struvite crystal formation initiated by urease-negative bacteria can serve as a "nest" and attract other minerals, forming mixed stone complexes [5].

Not having the stone itself does not exempt us from proceeding properly. Because with the information obtained through a good medical history, lifestyle habits, imaging techniques, basic urinary biochemical analysis, etc., etiological factors related to the identified renal lithiasis

can be identified and corrected. The metabolic assessment of our patient already revealed hypocitraturia and normocalciuria which added to leukocyturia could make us suspect about the type of lithiasis that the patient had [6].

The fact that calcium oxalate stones are the most frequent, does not always translate into systematic initiation of treatment with potassium citrate. In this case, the essential matter was to eradicate the urinary tract infection through antibiotic treatment. Once the infection is resolved, it is indicated to avoid elevated urinary pH levels (over 6), avoid excessively vegetarian diets, citrus fruits and carbonated drinks and prescribing urinary acidifiers such as L-methionine [3,7]. A study made in struvite lithiasis-forming patients treated with L-methionine revealed recurrences in only 10% of patients after a long follow-up [3]. L-Methionine effectively reduces urinary pH and the risk of struvite and calcium phosphate stone formation in healthy individuals.

5. Conclusions and recommendations

Alkalizing treatment is the gold standard to treat uric acid stones, it also reduces the activity of calcium oxalate and calcium phosphate stones contributing to their dissolution. Although, we can notice that, on certain occasions, it can be counterproductive and even contraindicated. It is essential to know the type of lithiasis we are targeting before prescribing and initiating any specific treatment.

6. Bibliographic references

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7. Images

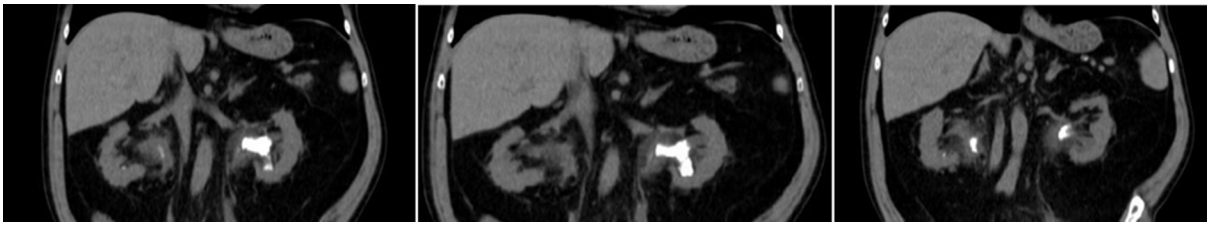

Image 1. ***CT September 2019****. Occupation of both inner calyceal groups by lithiasis measuring 13mm RK and 14.5mm LK. UH <1000.*

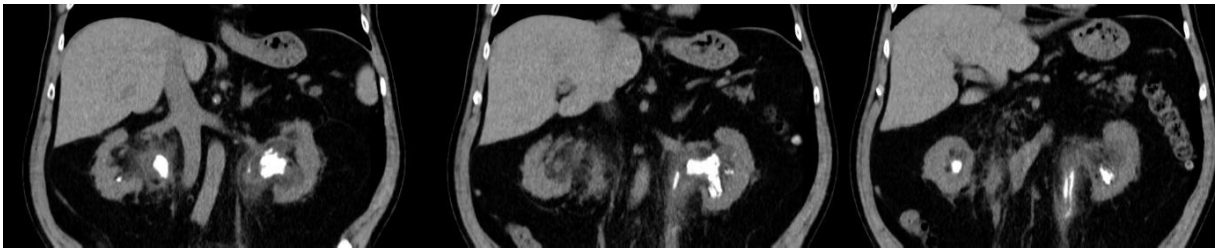

Image 2. ***CT scan December 2019****. Increase in the overall bilateral lithiasis load. The growth of the left lithiasis mold that reaches the middle ureter is highlighted. Significant dilation of the upper left calyceal group that was not previously observed can be identified.*

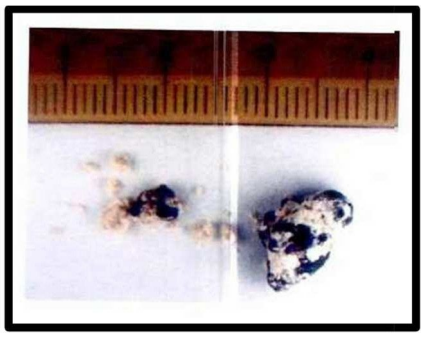

Image 3. Crystallographic study *Whewellite (calcium oxalate monohydrate) 85%. Struvite (magnesium ammonium phosphate) 10%. Protein 5%. It is an initial lithiasis of OXALO-dependent structure along with a recent urinary infection.*

*Image 4**CT scan June 2020**. After the ECIRS together with the acidifying treatment with L-methionine an evident decrease of the lithiasis load in left kidney can be observed, small lithiasis fragments persist. Decrease of lithiasis load in right kidney*