Title: RECIDIVANT INFECTIVE LITIASIS: IS IT POSSIBLE TO DEFEAT THEM?

Keywords: Lithiasis, infective, struvite, recurrence, acidification, urine pH

SUMMARY

Acidifying treatment and control of urinary pH may be an effective strategy to address recurrent lithiasic disease secondary to infective calculi. We present the case of a 39-year-old man with bilateral urolithiasis that led to episodes of complicated Reno ureteral colic. After undergoing multiple treatments by retrograde endourological surgery, he presented recurrence and progression of lithiasis disease, finally requiring percutaneous approach for treatment of a coralliform stone, after which he was free of lithiasis. It was then decided to start treatment with an acidifying oral supplement and home pH control by means of an electronic medical device as a complement to the surgeries he underwent, thus achieving stability of the disease, with absence of urinary tract infection or lithiasis recurrence.

The patient, with poor adherence to previous treatments, presented in this case a correct follow-up of the treatment, as well as a high level of satisfaction with it.

KEYWORDS

Lithiasis, infectious, struvite, recurrence, acidification, urinary pH.

INTRODUCTION

Seventy-five percent of all calculi have calcium in their composition, the most common being those associated with oxalate or phosphate. Within calcium phosphate stones we find those formed by apatite (7% of stones) and brushite (1%). Struvite stones (ammonium-magnesium phosphate) account for 5-10% of cases, while uric acid stones constitute 10% and cystine stones 1-4%[1].

Struvite calculi can be large, are weakly radiopaque in radiographic tests (300-900UH) and the etiological factor responsible for their formation is the presence of urealitic germs in the urine, so their identification by urine culture is recommended. Certain microorganisms can induce crystallization by their action on urine pH. Proteus and other bacteria such as Ureaplasma urealyticum or certain strains of Klebsiella or Serratia have the capacity to hydrolyze urea releasing ammonia and carbon dioxide, thus increasing the urine pH and favoring crystallization, often mixed, of magnesium ammonium phosphate, calcium phosphate and ammonium urate[1].

If we analyze by sex, women are more likely to form pure struvite stones than men (3:1) since they present more risk factors for developing an upper urinary tract infection. Other patients susceptible to infection, such as those with neurogenic bladder or urinary diversion, may also form pure struvite stones[2].

As for the clinical picture, patients present with symptoms of urinary tract infection, mild flank pain or hematuria. Lithiasis of this composition can grow rapidly over a period of weeks to

months and, if not adequately treated, can develop into a coralliform stone occupying the entire pelvis and renal calyces.[2]

Exclusively medical treatment of struvite stones is not sufficient in most cases. Bacteria live within the interstices of the lithiasis, where it is more difficult for antimicrobial agents to penetrate, and create a persistently alkaline local environment that promotes stone growth. Therefore, most of the time we have to resort to an active treatment of these lithiasis by means of different surgical techniques, since its complete elimination is essential to avoid recurrence of the lithiasis[3].

Since struvite lithiasis are infective, eradicating the infection by antibiotic treatment is essential. Once eliminated, it is advisable to maintain low urinary pH values (below 6) in order to hinder the growth of urease bacteria and the crystallization of the elements that make up these infective lithiasis. For this purpose, some general hygienic-dietary measures can be taken, such as avoiding excessively vegetarian diets, citrus fruits and carbonated beverages; it is recommended to consume urinary acidifiers, such as cranberries or commercially available food supplements[4] such as Lit-Control pH Down®. The main components of this product are L-Methionine and rice bran extract (rich in magnesium calcium phytate). L-Methionine is an essential amino acid with acidifying properties (reduces urinary pH) recommended by the EAU guidelines on urolithiasis for the treatment of infectious stones. On the other hand, phytate inhibits the crystallization of calcium salts in urine and soft tissues.[5,6].

Other conservative treatment strategies to prevent stone growth are the reduction of phosphorus in the diet or the administration of urease inhibitors such as acetohydroxamic acid (AHA), which can cause a complete and non-competitive inhibition of urease production hindering stone growth. However, AHA treatment is not without side effects (20-60% of patients) such as palpitations, edema, headache, abdominal discomfort, skin rash and some serious side effects such as hallucinations, anemia, loss of taste and reticulocytosis[7].

DESCRIPTION OF THE CLINICAL CASE

He acknowledges poor compliance with previous treatments and irregular follow-up in consultation for not attending multiple appointments. We present a 39-year-old male with a history of urinary lithiasis of years of evolution with pictures of obstructive uropathy that required urinary diversion and subsequent endourological surgery for resolution of the same.

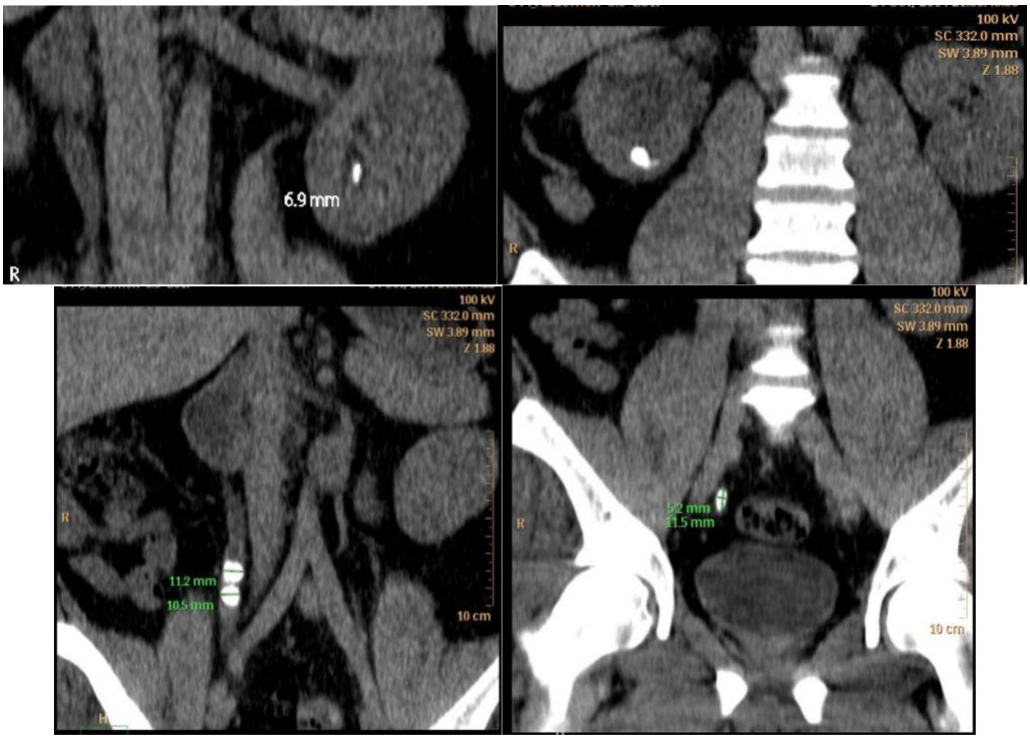
As baseline pathology he presents grade II obesity and sleep apnea-hypopnea syndrome (SHAS) in treatment with nocturnal noninvasive mechanical ventilation (CPAP). He reports a family history of lithiasis in his father and brother.

He acknowledges poor compliance with previous treatments and irregular follow-up in consultation for not attending multiple appointments.

Our patient came to the first urology consultation referred from the emergency department after having presented episodes of uncomplicated colic and radiographic images compatible with urinary lithiasis.

A CT scan was requested which showed bilateral renal lithiasis in the lower calcific groups, the largest being about 13 mm in the right lower calcific group (ICG).

He presents moderate right hydronephrosis with marked renal atrophy, secondary to two stones in the middle third of the ureter, 10 and 11 mm respectively and another stone in the ipsilateral distal ureter of approximately 5 mm in width and 11 mm in length (see images 1 and 2).



Images 1 and 2. Abdominal-pelvic CT scan without contrast in coronal view showing right ureteral and bilateral renal lithiasis described in the case.

The urine systemic study showed a pH of 6.5, positive nitrites, leukocyturia and microhematuria. The urine culture prior to surgery showed growth of multi sensitive Proteus Mirabilis.

In view of these findings, it was decided to perform a right semi-rigid ureterorenoscopy with antibiotic prophylaxis adjusted to the antibiogram for resolution of the ureteral lithiasis. Postoperatively, the patient had a good evolution with no relevant incidents.

The control CT scan at the revision visit showed resolution of the ureteral lithiasis, with the presence of bilateral nephrolithiasis and residual right renal hydronephrosis.

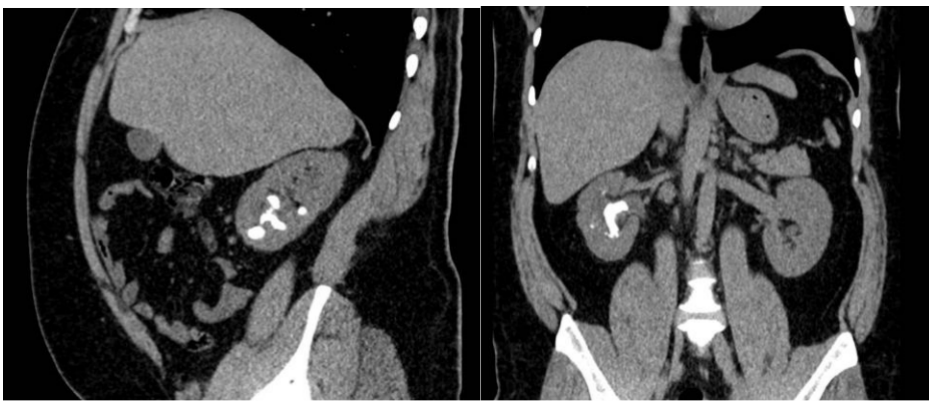
After analyzing the calculi, it was found that their composition was magnesium ammonium phosphate hexahydrate (struvite) 60% apatitic calcium phosphate (apatite) 40%, so it was decided to start treatment with acetohydroxamic acid 125 mg with a regimen of 1 tablet every 8 hours.

The patient did not comply with the treatment because he initially presented problems with the pharmaceutical visa and subsequently a marked digestive intolerance from the beginning. In the subsequent quarterly check-ups, control imaging tests showed stability of bilateral renal lithiasis that did not cause symptoms, so a watchful waiting attitude was decided with control urine cultures, which were negative.

A year and a half after the first intervention, the patient consulted with an abdominal X-ray showing progression of his lithiasis disease, with the presence of a 1 cm stone at the level of right L3 and growth of the lithiasis of the LM GCI of the RD. He required new surgery by means of URS on that side. In addition, the urinary pH at that time was 7, so it was decided to start acidifying treatment, which the patient did not comply with for fear of presenting side effects again.

In subsequent revisions, he continued to present an increased lithiasis load in the right kidney with the formation of a coralliform stone in the GCI and middle calcific group (GCM) with a larger diameter up to 4 cm (see image 3), so it was decided at this time to perform a combined

surgical approach by percutaneous nephrolithotomy (PCNL) and retrograde approach with the intention of resolving the lithiasis on that side, requiring 2 surgical times.



Abdominal-pelvic CT scan without contrast in sagittal and coronal view showing right choreiform calculus.

The metabolic study showed hyperuricosuria, hyperphosphaturia and hypercalciuria and he was diagnosed with hyperparathyroidism secondary to vitamin D deficiency, for which he was prescribed treatment with vitamin D supplements and hygienic dietary measures to lose weight and reduce the high uric acid levels in urine.

After the interventions, the lithiasis load on the right side was eliminated and the patient only presented lithiasis in the left GCS of about 8 mm, which was treated with ESWL without subsequent complications.

Likewise, after insisting to the patient on the importance of following an adequate acidifying treatment, we decided by consensus to start treatment with Lit-Control pH Down® and we instructed him to strictly control his urinary pH at home by means of an electronic device that facilitates this task (Lit-Control pH Meter®).

The patient continued treatment with Lit-Control pH Down® with a high level of satisfaction on his part, good tolerance (no adverse reactions) and good follow-up, managing to acidify urine to a pH of 5 after one month of starting to take it.

At the present time, the patient is free of lithiasis and has had no recurrence 12 months after the last surgical intervention and the initiation of therapy with the acidifying oral supplement. In addition, all control urine cultures were negative.

DISCUSSION

Infective lithiasis is a type of lithiasis that cannot be eliminated by conservative treatment alone and usually requires surgery to reduce or eliminate the load of lithiasis in the urinary tract.

To eliminate recurrent lithiasis we have had to perform endourological surgery, once the lithiasis-free state was achieved, our patient has achieved stability and absence of progression after treatment with an acidifying oral supplement (Lit-Control pH Down®). We consider that it is important to avoid recurrence in this type of patient with poor adherence to chronic conservative treatment and a urinary tract that has been operated several times, and therefore probably more fragile to iatrogenesis, as well as to improve their quality of life and reduce the health care costs derived from the treatment of this type of patient.

On the other hand, avoiding admissions and surgeries is of great relevance in the current times of COVID-19 pandemic, minimizing the patient's exposure to the hospital environment and reducing the risk of contagion.

In addition, we must emphasize that the conservative treatment of our patient has not only consisted of taking an acidifying oral supplement, but also in strict management of his urinary pH. Urinary pH analysis is a very useful tool in routine clinical practice and it is in lithiasic pathology of the urinary tract where its management has been best documented to be key.

For this purpose, we can use medical devices to measure urine pH in order to monitor it adequately. In our case, the device used was the Lit-Control pH Meter® that accompanies the oral supplements taken by our patient.

Traditionally, the most commonly used tool for measuring pH has been the test strips. Despite their widespread use, they are not always a simple and precise element to obtain a reliable value of the patient's pH since they are exposed to multiple factors that can alter the results (misuse of the strip by not immersing it properly and for the right time, subjectivity when interpreting the color of the strip, color perception deficit by the observer in pathologies such as macular degeneration, Alzheimer's, diabetic retinopathy, etc.).[8]

In recent years, new pH measurement devices have been developed as an alternative to the well-known test strips. These devices have been shown in different studies to be superior to the test strip in terms of resolution, precision and accuracy. Angerri O et al[8]. performed an analysis comparing the Lit-Control pH Meter® digital electronic device with the test strips, obtaining superior results with this portable pH meter, with a reduction of data dispersion and more accurate values. In addition, the correlation analysis showed that the pH values obtained with this device were the closest to the actual pH values.

In addition to the infectious nature of our patient's lithiasis, based on the metabolic study he was diagnosed with hyperparathyroidism secondary to vitamin D deficiency, accompanied by hyperphosphaturia and hypercalciuria.

Vitamin D deficiency has a high prevalence in patients with renal lithiasis, although its true role in the pathophysiology of lithiasis remains controversial.

In the study of Arrabal-Polo et al.[9] which analyzed the presence of secondary hyperparathyroidism in patients with lithiasis and the influence of 25-OH vitamin D deficiency, did not observe statistically significant differences in urinary calcium excretion between cases with vitamin D deficiency and patients with normal vitamin D levels. Nor did they observe significant differences in serum levels of calcium, phosphorus or urinary excretion of other metabolic factors such as uricosuria, citraturia, oxaluria or magnesuria.

It was seen that hyperparathyroidism produced by a vitamin D deficit or a deficit in calcium intake can be corrected by dietary changes, with the aim of slowing the action of iPTH and preventing the appearance of further lithiasic events in the future. However, the real role of vitamin D in renal lithiasis remains controversial and unclear[9].

This theory is also supported by a similar study of Tang et al[10] where it was concluded that the effect of nutritional use of vitamin D on stone formers is still unclear.

CONCLUSIONS AND RECOMMENDATIONS

The better adherence to treatment obtained with the Lit-Control pH Down® supplement compared to other alternatives, as well as correct pH monitoring with the electronic device, are key in the prevention of lithiasis recurrence in patients with infective calculi.

The correction of vitamin D levels together with the rest of the hygienic-dietary measures have also been relevant, both in the adequate control and in the reduction of the recurrence rate of lithiasic disease.

Therefore, it can be concluded that in those patients with multiple risk factors (metabolic, infective lithiasis, etc.), an integral management of the pathology together with an adequate combination of surgical and medical treatment is the most beneficial strategy for the patient.

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