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

Title: Is it possible to stop infective stones from growing only by controlling the urinary pH?

Keywords (between 3 and 6): infective lithiasis, urinary acidification, L-methionine, phytate

1. Summary (not over 150 words)

Clinical case report of a 26-year-old female patient with left staghorn renal lithiasis that occupied the entire kidney. A left percutaneous nephrolithotomy was performed. The STONE score assessment resulted in 10 points; 42% resolution probability of the case in a single surgical intervention, not being stone free after this first procedure. In the first post-surgical follow-up a control CT scan was performed, showing non-obstructive remaining fragments in the calyx. For the second surgical time an endoscopic combined intrarenal surgery (ECIRS) is proposed which the patient rejects as she is asymptomatic. The analysis of the composition reported infective lithiasis composed of magnesium ammonium phosphate. Treatment with acetohydroxamic acid is proposed (previous urine cultures reported *Proteus Mirabilis*) which the patient rejects due to its possible adverse effects. It was agreed to initiate acidifying medical treatment using Lit Control pH Down© and strict control of urinary pH. After two years of treatment, the patient remains asymptomatic and her lithiatic condition remains stable.

2. Introduction

The prevalence of lithiasis disease in the world has not stopped increasing in the last few decades, also its prevalence in females has also increased. Additionally, in the last 20 years, a change in the composition of kidney stones has been observed, with a notable increase in phosphate stones without a clear cause, but attributing it to multifactorial causes.

The formation of phosphate lithiasis is based on the supersaturation of phosphate salts, when the solubility of the product is exceeded, the supersaturation process starts along with a slowed crystal growth. However, if the critical limit of supersaturation is exceeded, crystal precipitation increases at a very rapid rate [1,2]. Because the solubility of phosphate stones increases when the urinary pH is below 6.5, chemolysis can be achieved through oral acidification, especially for infective stones, since the effectiveness of antibiotic therapy increases with urinary acidification [3]. Nevertheless, it can be difficult to maintain urine acidification with these agents, particularly when there is an infection, so usually the treatment is combined, including antibiotics, surgical treatment and urine acidifying treatment for the complete resolution of lithiasis [4].

3. Description of the clinical case:

Clinical case report of a 26-year-old female, with no relevant personal history, who was referred to the urology department for pain in the left renal fossa. Laboratory results were normal except for the urine sediment which showed leukocyturia, and a positive urine culture for *multi-sensitive Proteus mirabilis*. A CT urogram scan was performed that showed a large staghorn stone in the left kidney *(image 1 and 2)* which increased the diameter of the ureter (0.84 cm). Surgical intervention of the lithiasis was proposed, through a left percutaneous nephrolithotomy, which the patient accepted. The STONE score assessment during consultation resulted in 10 points; 42% resolution probability of the case in a single surgical intervention, not being stone free after this first procedure.

Image 1. Coronal section of the CT urogram, where a large left staghorn lithiasis is observed.

Image 2. Reconstruction of CT urogram images in which a left staghorn lithiasis occupying the entire left kidney is observed.

The left percutaneous nephrolithotomy was performed in October 2019 and was very complex given the challenging calyceal access due to the patient's anatomy and the volume of the lithiasis. After a prolonged surgical procedure and in the presence of considerable bleeding, which made the exploration difficult due to the friability of the urothelium, it was decided to end the surgery having fragmented most of the stone. A left double-J stent was placed and was later removed 2 weeks after surgery.

Postoperative control CT scan was performed where some non-obstructive stone fragments were observed in the upper, middle, and lower calyx of left kidney. The study of the stones obtained during surgery concluded that the stones had an struvite composition (ammonium phosphate and magnesium hexahydrate). Clinically, the patient was asymptomatic and had only presented with infection once after surgery, which was resolved without incident with antibiotics.

A second surgery is proposed, suggesting an endoscopic combined intrarenal surgery (ECIRS) which the patient rejects as she is asymptomatic.

Treatment with acetohydroxamic acid is proposed, which she rejects due to its possible adverse effects, so it was agreed to initiate acidifying medical treatment with Lit Control pH Down© 1 tablet every 12 hours along with a strict urinary pH control at home, for which *Lit Control pH meter©* is recommended.

At the present time, after 2 years of medical treatment with Lit Control pH Down© and urinary pH control, the patient remains asymptomatic. Periodic urine cultures are performed showing the presence of *Proteus mirabilis* which she decides not to treat, as she is asymptomatic. In addition, the radiological control of lithiasis continues to show calyceal radiopaque images in the left kidney with the same characteristics as in previous radiographs *(image 3).* Therefore, thanks to the medical treatment, the patient has not required a second surgery to manage her lithiasis.

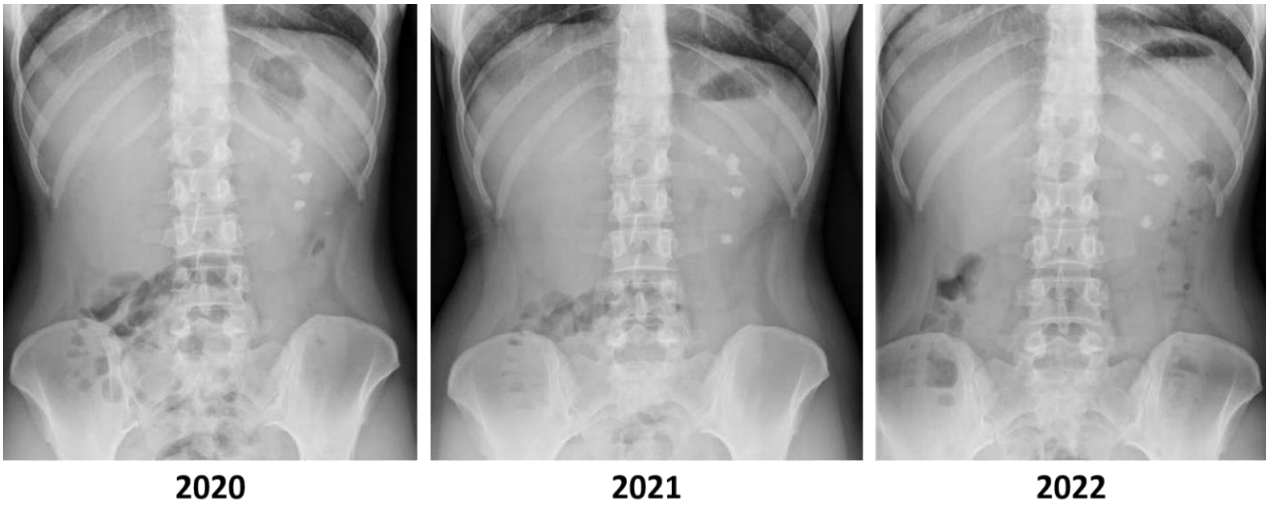

Image 3. Imaging follow-ups of the remaining stone fragments.

4. Discussion

Renal lithiasis is a chronic, recurrent disease that affects the quality of life of our patients, so we must use all available tools in our attempts to solve it. In the case of infective stones, bacteria adheres to the interstices of the stone, making it difficult for antibiotics to penetrate. In addition, they create a persistently alkaline environment that promotes the growth of such lithiasis. Therefore, most of the time we have to resort to an active treatment for these stones by preforming surgery since its complete elimination is essential to avoid recurrence. Percutaneous nephrolithotomy is the *gold standard* for the treatment of staghorn.

lithiasis [5]. Nevertheless, surgery is not always resolutive, leaving some remaining fragments, so a combined treatment that includes surgical treatment, antibiotics and urine acidifying treatment is usually required for the complete resolution of lithiasis.

Since phosphate stones are usually closely related to urine infections, antibiotic therapy is part of the fundamental medical treatment to achieve the elimination of the infection and, with it, the effects of urease. Urease is an enzyme produced by more than 45 microorganisms, the most frequent being *Proteus mirabilis.* The clinical guidelines of the European and American associations of Urology recommend giving short-term or long-term antibiotics to all patients with infective stones [5]. Choosing the most suitable antibiotic should be established based on the antibiogram. In addition, it should be considered that an acidic urinary pH is optimal to favor the activity of many antibiotics [3].

Once the infection has been eliminated, it is advisable to maintain acidic urinary pH values to ·impair the growth of urease-producing bacteria but also to avoid the crystallization of the elements that compose said infective stones. Therefore, the acidifying urine treatment is another key point in the management of this type of lithiasis. However, the acidification of urine using medications is not simple due to the limited number of molecules available for it and the recalcitrant mechanism of urine alkalization in patients with urine infection caused by urease-producing bacteria.

One of the molecules used as a urinary acidifier is acetohydroxamic acid (AAH). Its clinical utility has been demonstrated in double-blind placebo-controlled studies, but serious side effects in approximately 20% of patients prevent its use, in addition to the required prudence when using it in women of childbearing age due to its teratogenic potential.

Another medication that could be used as a urinary acidifier is methionine. A new medication has recently been commercialized, Lit Control pH Down©. This medication has as main components L-Methionine and rice bran extract (rich in calcium magnesium phytate). L-Methionine is an essential amino acid with acidifying properties recommended by clinical guidelines [5]. Through various studies, it has been found that after the administration of L-Methionine there was a significant decrease in pH values which were maintained for at least 24h. In addition, it has been shown to reduce the recurrence of struvite lithiasis after a long-term treatments[6]. On the other hand, phytate has been shown to inhibit the crystallization of calcium salts in urine and in soft tissues [7,8]. Thus, this drug has turned out to be effective and, in addition, it is well tolerated by patients and has few adverse effects.

There are other urine acidifying medications such as ammonium chloride which is used for urine acidification test in renal tubular acidosis, but its use has not been widespread. There are also other medications with urine acidifying properties such as phenazopyridine and sulfadiazine, but they have not been used to modify urinary pH in infective stones. The efficacy and safety of other medications such as propionyl hydroxamic acid and hydroxyurea have also been evaluated, but their success has been limited as well.

On the other hand, it should be noted that the satisfactory results obtained have not only been due to medical treatment but also to strict control of their urinary pH [9]. The most accurate measurement of urinary pH is made with a glass electrode and a pH-meter but these devices are used in laboratories and are not easy to use. For this reason, the most widely used method for many years have been the test strips, despite the fact that they are considered an inaccurate method [9, 10]. During the last few years, new devices for measuring urinary pH that are reliable and simple for the patient have been investigated. Recently one of these devices has been commercialized, Lit Control pH Meter©. In a comparative analysis with test strips, Lit Control pH Meter© shown superiority in the reliability of the results obtained, in addition to being an easy-to-use alternative for patients at home [10].

5. Conclusions and recommendations

The good tolerance to treatment with Lit Control pH Down©, as well as a correct monitoring of urinary pH with Lit Control pH Meter©, stands as a useful alternative in the prevention of lithiatic recurrence in patients with infective lithiasis.

Lit Control pH Down© it is a feasible and safe option to treat patients with infective lithiasis who prefer not to undergo surgery or treatment with acetohydroxamic acid due to their adverse effects.

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