

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

Title: Clinical case presentation: pharmacological management of uric acid urolithiasis.

Keywords: Kidney Stone, Lithiasis, Uric Acid and Medical Management

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1. Summary

Objective: The prevalence of uric acid stones represents 10% of all urolithiasis and its pharmacological management has an established role in both treatment and prevention. The objective of this case presentation is to show the pharmacological management of uric acid stones.

Method: Clinical case presentation of a 67-year-old male patient with a personal history of uric stones who attended outpatient consultation presenting kidney function deterioration and a grade III ureterohydronephrosis affecting the left kidney caused by a 15mm obstructive stone in the proximal ureter and a 22mm non-obstructive stone in the lower calyx. It was decided to place a double-J stent and to prescribe pharmacological treatment with Lit-Control pH Up and allopurinol.

Results: The complete dissolution of the intraureteral stone and a reduction of the intracalyceal stone were achieved.

Conclusions: Pharmacological treatment can facilitate and even avoid surgical interventions in patients with uric stones.

2. Introduction

Urinary stones are one of the main reasons for urological care with a prevalence that varies according to the population studied, standing at around 5% in Spain. This figure resembles that found in other Western countries, contrasting with countries such as Italy or the United States, whose prevalence is over 10%¹.

Regarding the stones composed of uric acid, related to the case, it should be highlighted that its prevalence corresponds to 10% of all stones² and has a recurrence rate slightly higher than 50%³. On the other hand, among the pathogenic mechanisms underlying its formation, the most important one is urine acidification⁴.

Finally, since its management can be exclusively medical along with hygienic-dietary measures, thus avoiding unnecessary surgical procedures to the patient and, since stones can lead to kidney damage that eventually leads to end-stage kidney failure⁴, we consider convenient to present the following clinical case of a 67-year-old male patient with recurrent urinary uric acid stones.

3. Description of the clinical case

a) Relevant medical history

The patient in the studied clinical case is a 67-year-old Caucasian male. Regarding his personal history, it should be noted that he suffered from high blood pressure, dyslipidemia and had been a former smoker for 25 years. In addition, he had a previous history of hyperuricemia and recurrent left renal colic due to uric acid stones, for which he attended follow-up in Urology outpatient consultations. Previous stones episodes had been managed using potassium citrate-citric acid and sodium bicarbonate along with the corresponding hygienic-dietary measures. The treatment the patient was receiving for his underlying pathology consisted of bisoprolol 2.5 mg/12h, telmisartan 80 mg/day and atorvastatin 40 mg/day.

b) Diagnostic support studies and results

After the resolution of the last episode two years ago and subsequent follow-up, the patient attends an appointment presenting laboratory results showing worsening of kidney function with a glomerular filtration rate, according to the CKD-EPI formula, of 38.31 ml/min /1.73m² and elevated plasma creatinine, 1.78 mg/dl, in addition to hyperuricemia (8.35 mg/dl, normal values from 3.40 to 7.00 mg/dl). Urine analysis showed no red blood cells in the sediment, but an acidic urinary pH of 5. The patient had stopped the indicated medication after improvement and absence of further stone related events.

The abdominal X-ray showed no signs of stones, later an abdominal ultrasound study was performed evidencing a 15mm obstructive stone in the left proximal ureter that caused a grade III ureterohydronephrosis and another non-obstructive 22mm stone in the left lower calyx. No alteration of the morphology of the right kidney was observed, either stones or hydronephrosis. No bladder lesion was observed, and the prostate volume was 35cc. In addition, moderate-severe hepatic steatosis and atheromatosis in abdominal aorta artery were reported, having a normal caliber.

The blood test was repeated showing the previously mentioned kidney function alteration, with urea 50 mg/dl, hyperuricemia, hyperglycemia (169 mg/dl), hypertriglyceridemia (374 mg/dl), and HDL cholesterol levels of 36 mg/dl, as well as normal liver enzymes, ions and PSA values.

c) Diagnosis

The patient was diagnosed with grade III left ureterohydronephrosis due to an obstructive stone in the proximal ureter, in addition to presenting a non-obstructive left intra-calyceal stone.

d) Treatment

Urinary tract clearing was indicated through the placement of a 26 cm 6ch double-J stent, with no complications, and medical treatment was prescribed with allopurinol 300 mg/day and Lit-Control pH Up 1tab/12h.

e) Outcome

The control abdominal computerized axial tomography (CAT) scan performed at 8 weeks showed the complete resolution of both hydronephrosis and intraureteral stone, as well as a significant reduction of the intracalyceal stone, with a current size of 15mm and 491 UH. The double-J stent was normally positioned, and no other significant alterations were found.

It was decided to perform a new control CT scan in 8 weeks, maintaining the prescribed treatment. In this control, the removal of the double-J stent would be assessed.

During this time interval the patient was evaluated in the emergency room after presenting a urinary tract infection, which was empirically treated with ciprofloxacin 500mg/12h for 7 days. In the subsequent urine culture *Escherichia coli*, which was sensitive to the prescribed antibiotic was identified, treatment modification was not necessary.

During the following visit to the urology outpatient appointment, after the resolution of the previous infection, it was decided to remove the double-J stent and include the patient in the surgical list for retrograde intrarenal surgery (RIRS) since the abdominal CT scan showed the persistence of the intracalyceal stone, with no signs of size reduction (15mm) and with 540 UH.

f) Clinical results

The patient is currently asymptomatic after the removal of the double-J stent and is currently waiting for the RIRS. The blood test indicates that the patient has developed chronic kidney disease with a glomerular filtration rate that has slightly improved compared to the previous tests, 44.90 ml/min/1.73m² and serum creatinine values of 1.55 mg/dl. In addition, the patient has recently been diagnosed with type II diabetes mellitus for which Empagliflozin 10 mg/day has been prescribed.

The patient is following the indicated dietary measures, treatment with Lit-Control pH Up and allopurinol at the prescribed doses, achieving normal uricemia, 5.35 mg/dl.

4. Discussion

Uric acid stones represent 10% of all urolithiasis² and they tend to appear in more advanced periods of life compared to other types of stones, around the age of 60 on average in both genders, as in the case addressed, being more frequent in males. Additionally, the recurrence is high, slightly over 50%³ therefore, if the necessary therapeutic measures are not implemented or if they are suspended, new events will occur, as it happened to the studied patient.

Etiologically, it seems that there is both a genetic and an acquired factor, noting that the presence of uric acid stones is more frequent in certain populations such as diabetic, obese or metabolic syndrome patients⁵, or in patients with gout⁶. It must be noted that the patient was taking treatment for high blood pressure and dyslipidemia, additionally his HDL cholesterol values were below 40 mg/dl and during his evolution he was diagnosed with type II diabetes mellitus so he meets the criteria established by the ATP-III for the diagnosis of metabolic syndrome, according to the aforementioned. However, even though the patient presented high uric acid levels, he has not developed any acute episode of joint inflammation to this time.

Regarding the mechanisms involved in the formation of this type of stones, it should be noted that there are mainly three mechanisms: urinary volume reduction, hyperuricosuria (meaning values over 800 mg of uric acid in 24-hour urine in men and 750 mg in women) and acidic urinary pH (below 5.5). It is necessary to clarify that, although all three mechanisms play their own role in the formation of uric acid stones, urine acidification is the most important out of these, since it decreases the solubility of uric acid, precipitating even when urinary uric acid levels are within the normal ranges. The mechanism involved in urinary acidification is both an increase in the net acid excretion and a decrease in the renal ammonium excretion^{4,7}.

Getting back to the case, the acidic urinary pH of 5, together with personal history of uric acid stones, hyperuricemia, the radio transparency of the stone showed in the abdominal X-ray, and the Hounsfield units shown by the abdominal CT scan, were highly suggestive of a new episode of uric acid stones, therefore treatment was prescribed.

Classically, the management of uric acid stones has been based on alkalizing urine to increase solubility, causing the formed stones to dissolve, thus avoiding surgical interventions. For this purpose, substances such as citrate or sodium bicarbonate, used in this patient, are still used. The more alkaline the urine becomes, the greater the stone dissolving potential, this is why the targeted pH with oral chemolysis is between 6.5 and 7.2, while to avoid future events the recommended urinary pH is between 6.2 and 6.8. Another therapeutic target in patients with hyperuricosuria and elevated uricemia can be the xanthine oxidase enzyme, whose inhibitors, allopurinol and febuxostat, decrease hyperuricemia and, therefore, hyperuricosuria⁸.

As mentioned above, the more alkaline urine becomes, the greater the dissolving potential. However, it must be considered that alkaline urinary pH predisposes to the formation of calcium phosphate stones, but the Lit-Control pH Up food supplement not only provides urine alkalinizers, but also the only uric acid crystallization inhibitor used in clinical practice, theobromine. Theobromine is a chemical compound belonging to the methylxanthine family, which can be found in cocoa and its derivatives, and has been shown to be, both in vitro study² and in vivo study⁹, an inhibitor of uric acid crystallization, as it increases the induction time and reduces the size of the crystals formed, it also decreases the risk of crystallization respectively. Recently Hernandez et al⁷. have conducted a clinical trial that aimed to compare the efficacy of administering citrate versus citrate together with theobromine to treat this type of lithiasis. The risk of uric acid crystallization was lower in the group to which theobromine was added, however, the results did not become statistically significant probably due to the small sample size, to the fact that the citrate dose alone was sufficiently effective and in addition, to the urinary concentrations of theobromine found were below the limit of efficacy. It would be interesting to conduct future clinical trials given its potential usefulness, as excessive urine alkalization could be avoided.

In this case, there were multiple targets addressed for the resolution of the lithiasic disorder. The patient was administered both Lit-Control pH Up 1 tab/12h and allopurinol 300 mg/day, decreasing uricemia to normal levels, 5.35 mg/dl, the complete resolution of the obstructive 15 mm stone in the proximal ureter, as well as the reduction of the intracalyceal stone from 22 mm to 15 mm, RIRS is still pending. Furthermore, during the acute episode, it was necessary to perform a maneuver to clear the urinary tract by placing a double-J stent, given the degree of the hydronephrosis and the kidney function deterioration.

Finally, it is also important to highlight the importance of the correct implementation of hygienic-dietary measures, since it is possible to achieve a modification of urine composition through diet. In these patients, it should be encouraged to achieve an adequate fluid intake, thereby increasing urinary volume, and to follow a low-purine diet, limiting protein intake, since uric acid is the final result of purine metabolism¹⁰.

5. Conclusions and recommendations

In conclusion, to emphasize the potential benefit of pharmacological treatment in uric acid stones by addressing multiple pathophysiological targets, capable of facilitating and even avoiding surgical interventions in patients with high rates of recurrences, in addition to recommending an adequate prevention of these episodes by modifying predisposing factors. Finally, to communicate the relevance of achieving, on the part of the professional, a good patient adherence to long-term treatment.

6. Bibliographic references

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