4th Edition of the Clinical Case Competition related to the non-surgical clinical management of renal lithiasis.

Official template

Title: Effective alkalinizing chemolysis in multiple uric acid nephrolithiasis and coralliform calculi.

Key words (between 3 and 6): uric acid, chemolysis, coraliform, low pH

1. Abstract

A 73-year-old diabetic woman with high cardiovascular morbidity was referred to the emergency department with clinical and laboratory findings of urinary sepsis. Urinalysis showed urinary pH 5 and abundant amorphous urates in the sediment. The CT scan showed multiple bilateral nephrolithiasis and a large pseudocoraliform stone in the right kidney, causing ipsilateral obstructive uropathy. Urgent placement of a double J catheter and admission to the intensive care unit was performed. Once the septic process was concluded, she was reviewed in consultation and alkalinizing treatment with Lit-Control® pH Up was decided. After four months, she presented a satisfactory evolution, good tolerance to treatment, and dissolution of almost all uric acid lithiasis. Subsequent control showed normal renal ultrasound, and the metabolic study showed normal uric acid and citrate excretion in urine, as well as improvement of renal function and urinary pH with a current value of 6.

2. Introduction

Uric acid lithiasis constitutes about 10% of the stones. The prevalence of these stones varies according to demographic factors, with a clear predominance in women over 60 years of age.
In industrialized countries the incidence of these stones continues to rise, reaching figures between 5% and 40%.

At the pathophysiological level, uric acid lithiasis is caused by acid supersaturation of urine due to: urinary pH <5.5, this being the main cause; hypovolemia, diuresis of less than 2 liters per day and hyperuricosuria (defined as excretion of more than 800 mg/day in men and 750 mg/day in women).
There are many predisposing factors: Patients with gout (up to 25-40% are uric acid lithiasis formers), ileostomy carriers, genetic alterations, chronic diarrhea, purine-rich diet and insulin resistance.

Diabetic patients have 6 times more risk of forming uric acid lithiasis. Some studies have shown that low urinary pH is related to body mass index and insulin resistance. This causes a clear decrease in uric acid solubility and tubular ammonium genesis, increasing tubular sodium reabsorption and leading to urinary acidification. [1]

There are therapies capable of altering the genesis of urinary lithiasis, being useful for both prevention and treatment. We find different options depending on the composition of the lithiasis and the metabolic alterations diagnosed in a 24-hour urine study.

In calcium lithiasis, potassium citrate is used in patients with hypercalciuria and hypocitraturia. In patients with hyperoxaluria, therapy with a diet low in oxalates is carried out and in cases with a basic intestinal malabsorption, it is recommended to add calcium supplements.
For uric acid stones, urinary alkalinization is sought as an objective through oral treatments, among which potassium citrate (20-60 mEq/d) or potassium bicarbonate (3-4 g/d) stand out, accompanied by hygienic-dietary measures based on a low-purine diet. In patients with primary gout, the use of allopurinol (100-

300mg/day) is useful. [2]

Since its discovery in 1993 by Violle[3], oral chemolysis has become one of the main treatments for dissolution of uric acid stones due to its good results at 3 months (50-70%) with an increase to 83% at 6 months, establishing the recommendation to prolong pharmacological therapy when the size and lithiasis load is significant.[4]

The efficacy of the different alkaline solutions has been evaluated in vitro.[5] The most commonly used was potassium citrate due to its greater solubility in urine. Most of its adverse effects are gastrointestinal and can be avoided by abundant water intake or consumption during main meals. On the other hand, hyperkalemia is the most feared effect; for this reason, in case of Renal Insufficiency, the use of sodium bicarbonate or magnesium citrate is preferred and recommended.

There are also substances that inhibit the formation of lithiasic precipitates, such as vitamin A, inorganic substances (zinc or magnesium) and alkaloids. Theobromine is an alkaloid belonging to the xanthine family, comes from the cocoa tree, and has fewer neurological side effects than theophylline and caffeine. In addition, it is capable, due to its structural characteristics, of inhibiting the formation and crystallization of uric acid. It is thus a great complement to alkalinizing therapies, as it has been shown to prevent the formation of uric acid lithiasis and to promote its dissolution with an adequate safety profile. [6]

3. Description of the clinical case:

a. Relevant background

A 73-year-old woman with a history of: Obesity, type 2 diabetes mellitus, permanent non-valvular atrial fibrillation, arterial hypertension and chronic bronchitis phenotype COPD. The patient came to the emergency department after a hypotensive and febrile episode with subsequent syncope, loss of consciousness and obnubilation at home. The patient presented severe disorientation, generalized dysthermia, pain in the right renal fossa, dysuria and pollakiuria.

b. Estudios de apoyo diagnóstico y resultados

BLOOD TEST:

Biochemistry: Creatinine 3.61 mg/dL, GGT 227 U/L, LDH 400 U/L, C-Reactive Protein 37.7 mg/dL, Procalcitonin 335 mg/dL, Estimated glomerular filtration rate (CKD-EPI) 12ml/min/1.73m2.

Arterial blood gasometry: pH 5, pCO2 25 mmHg, pO2 68 mmHg, HCO3-11 mmol/L, Lactate 6.4 mmol/L. Blood count: Hemoglobin 13.0 g/dL, Leukocytes 10.4 x10^3/µL, Neutrophils 9.8 x10^3/µL, Platelets 46 x10^3/µL.

Coagulation: Prothrombin activity 49 %, INR 1.65.

URINE SYSTEMATIC: Urine pH 5.5, Nitrites Positive, Leukocytes 25cel/µl, Erythrocytes 300 cells/µl.

URINARY SWALLOW: Abundant amorphous Urates.

UROCULTURE: Escherichia coli isolated (> 100,000 cfu/ml).

ABDOMEN RX: No apparent radiopaque images on renal silhouettes.

URINARY APPARATUS US: Right kidney increased in size, with a major axis of 133 mm. Good corticomedullary differentiation, grade 2 pyelocaliceal dilatation, with abundant pyelocaliceal lithiasis.

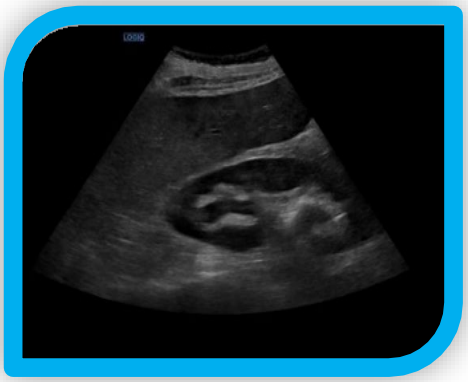

Figure 1

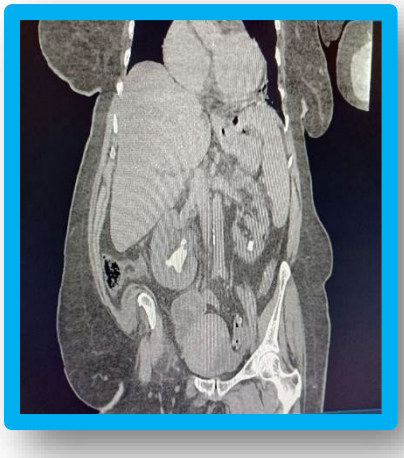

Figure 2 Pseudocoraliform stone (Coronal)

CT WITHOUT CONTRAST: Right kidney shows a marked descent, compatible with renal ptosis. Ipsilateral pyelocaliceal dilatation grade 2, probably due to obstruction caused by lithiasis of 9 mm in the pyeloureteral junction, adding numerous lithiasis in calcific groups, including a pseudocoraliform that occupies the renal pelvis and lower calcific groups. In addition, there is endoluminal gas in the different caliceal groups. Contralateral non-obstructive nephrolithiasis

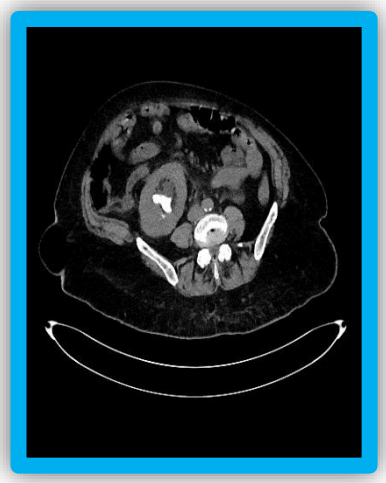

Figure 3 Pseudocoraliform stone (Axial)

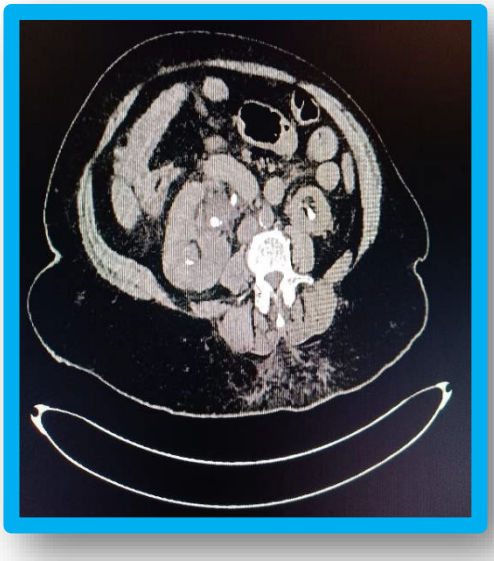

Figure 4 Multiple lithiasis (Axial)

c. Treatment

Diagnosed with urinary sepsis secondary to acute obstructive lithiasic uropathy, an urgent urinary diversion was performed with the placement of a right double J catheter, and establishing expansive fluid therapy and empirical intravenous antibiotic therapy, with which the patient overcame the acute infectious condition.

After discharge, the patient was evaluated in the outpatient department, where given the anatomical and basal conditions of the patient, which made her a high surgical risk, it was decided to opt for conservative management by means of oral chemolysis. Therapy was started with 1 capsule every 8 hours of Lit-Control pH Up, scheduling a review after 4 months. Compliance with hygienic-dietary measures is advised, avoiding constipation and abundant daily water intake. In addition, urinary pH control is carried out 2 weeks after the beginning of the alkalinizing treatment.

d. Evolution and follow-up

During the follow-up visit, the patient remained asymptomatic, without episodes of colicky pain, reporting good tolerance to chemotherapy and good adherence to therapy.

URINE TEST: pH 7.5, nitrites, erythrocytes and leukocytes negative.

CONTROL CT: Right renal lithiasis in lower calcific group, not obstructive. Punctiform lithiasis in left middle calcific group and lower calcific group, subcentimeter, non-obstructive. There are no lithiasis images in the ureters or bladder.

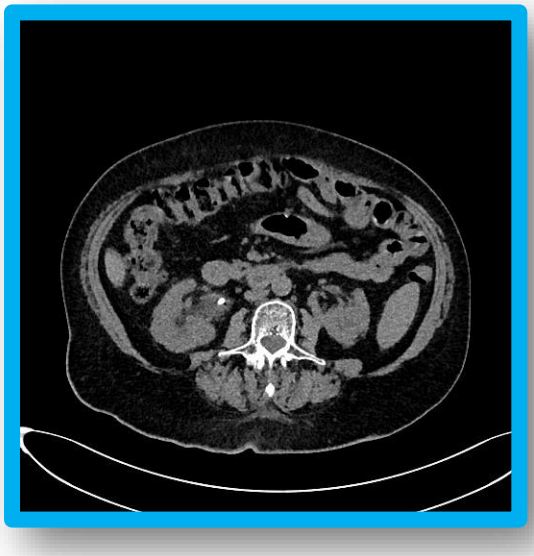

Figure 5 Axial

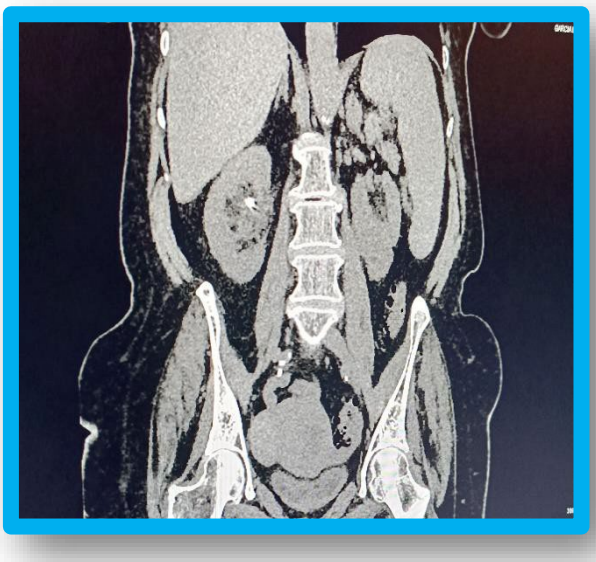

Figure 6 Coronal

In view of the excellent clinical and radiological evolution, it was decided to remove the double J catheter, scheduling a new review in 4 months with control ultrasound and metabolic study, maintaining the oral treatment.

f) Clinical results

- URINE SYSTEMATICS: pH6, nitrites and leukocytes negative.

- BIOCHEMISTRY OIRNA 24H: Creatinine 95 g/dL, Uric Acid 40 mg/dL, Citrate 530mg/24h.

- HEMOGRAM: Hb 12.3g/dL, no leukocytosis or neutrophilia, platelets in normal range.

- URINARY APPARATUS ECOGRAPHY: Kidneys with good cortico-medullary differentiation, morphologically normal. No findings of perirenal space occupation. Pyelocaliceal dilatation in right kidney resolved. No images compatible with lithiasis were visualized.

- Patient clinically asymptomaticnegativos

4. Discussion

The diagnosis of calculous disease and its complications begins with a complete clinical evaluation, including a correct anamnesis and physical examination. Patients present with abrupt onset colicky pain, which gradually increases in intensity and radiates ipsilaterally to the genital region. However, in patients with urinary sepsis criteria, the presentation may undergo certain variations, as in this case, in which the lithiasic obstruction generates a hypotensive picture with obnubilation and syncope.

The radiolucent nature of uric acid lithiasis means that abdominal radiography (the first complementary test in the emergency department) has a low yield in the identification of uric acid lithiasis. Given its high sensitivity and specificity, non-contrast CT is the imaging test of choice for the diagnosis of urinary lithiasis.

In our case, non-contrast CT allows the visualization of multiple bilateral lithiasis, the largest of them in the right lower calyx, defined as pseudocoraliform.

The diagnosis of coraliform calculi is usually clinically serious and is generally associated with infection of the lower urinary tract (struvite with or without apatite carbonate component), so they usually benefit from surgical management. [7] However, there are coraliform calculi belonging to the metabolic type, among which is uric acid, and whose incidence continues to increase.

Currently, the population presents greater cormobility and fragility, making a major surgical procedure difficult in many cases. Chemolytic management is, therefore, a safe and effective alternative for the treatment of selected lithiasis. [8]

European guidelines support the use of medical treatment for uric acid lithiasis. The situation of urinary sepsis in our patient required urgent placement of a double J catheter. Previous urinary diversion, according to some retrospective studies, has not shown any impact on the success of oral chemolysis on uric acid stones; however, both their size and urinary pH maintain an inversely proportional relationship with the effectiveness of chemolytic treatment. The urinary acidosis and the radiolucent character of the lithiasis in our patient, makes us suspect the presence of uric acid lithiasis, so it was decided to opt for oral chemolysis with a compound that combines potassium and magnesium citrate with potent crystallization inhibitors such as theobromine, which allows alkalinizing the urine and avoiding the formation of crystals in the urinary tract, as is the case of Lit-Control pH Up, demonstrating effectiveness in its dissolution, despite the risk factors for recurrence such as insulin-resistant diabetes and obesity.

Therapeutic follow-up in consultations is essential. On the one hand, through urinalysis, allowing urinary pH monitoring, maintaining target values between 5.5-6.2. This provides great information to know the risk of developing new urinary calculi.

Another relevant aspect that requires ambulatory monitoring is renal function, especially through creatinine and potassium levels in the blood. A deterioration of this can alert of the appearance of adverse effects of the prescribed drugs, as is the case of potassium citrate; contraindicated in patients with chronic renal insufficiency.

In addition, follow-up imaging tests are recommended. The cost-effectiveness of each test varies according to the characteristics and composition of the calculi, with abdominal X-ray being a diagnostic resource with little

effectiveness in the control of our patient given the radiolucent character of uric acid lithiasis. Therefore, non-contrast CT is used to evaluate the effectiveness of chemolytic treatment.

Finally, the performance of a metabolic study provides a comprehensive approach, searching for physicochemical factors involved in the lithogenesis process and enabling intervention in lifestyle and dietary habits. In the present case, its indication is justified given the composition of the stones, the high lithiasis load and the possibility of recurrence due to her medical history and baseline situation. The normalization of uric acid and citrate levels in urine constitute solid arguments in favor of alkalinizing chemolytic therapy.

5. Conclusions and recommendations

- Oral chemolysis is an effective therapy for prevention and treatment of uric acid lithiasis.

- There are many predisposing factors for uric acid lithiasis. Metabolic syndrome and insulin resistance are strongly related to their formation.

- The presence of coralliform stones is not an absolute indication for surgical treatment. It is necessary to individualize our cases.

- Therapies based on alkalinizing solutions such as Lit-Control® pH Up show excellent results in patients with large stones and high lithiasis load.

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

1) Türk C, etal EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. European Urology 69 (2016) 468-474

2) Uhlir K. The peroral dissolution of renal calculi. *J Urol.* 1970;104:239–247. doi: 10.1016/S0022-5347(17)61708-7. [PubMed] [CrossRef] [Google Scholar]

3) Elbaset MA, Hashem A, Eraky A, et al. Optimal non-invasive treatment of 1–2.5 cm radiolucent renal stones: oral dissolution therapy, shock wave lithotripsy or combined treatment—a randomized controlled trial. *World J Urol.* 2020;38:207–212. doi: 10.1007/s00345-019-02746-2. [PubMed] [CrossRef] [Google Scholar]

4) Tyler Haden, Paige Kuhlmann, Jacqueline Ross, Stephen Kalkhoff, Carrie Johans, Alex Jones, Stephen Weinstein, Mark Wakefield, Daniel Hoyt, James Cummings, and Naveen Pokala: MP01-13 IS THERE A SHIFT FROM INFECTIOUS STONES IN STAGHORN CALCULI? https://doi.org/10.1016/j.juro.2017.02.088

*5) Heimbach D, Jacobs D, Muller SC, Hesse A. Influence of alkaline solutions on chemolitholysis and lithotripsy of uric acid stones. *An in vitro study Eur Urol.* 2000;38:621–626. doi: 10.1159/000020342. [PubMed] [CrossRef] [Google Scholar]

**6) Julià, F., Costa-Bauza, A., Berga, F., & Grases, F. (2022). Effect of theobromine on dissolution of uric acid kidney stones. *World journal of urology*, *40*(8), 2105–2111. https://doi.org/10.1007/s00345-022-04059-3.

7) G.M. Preminger, D.G. Assimos, J.E. Lingeman, S.Y. Nakada, M.S. Pearle, J.S. Wolf Jr., *et al.*Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendationsJ Urol, 173 (2005), pp. 1991-2000

**8) Tsaturyan, A., Bosshard, P., Bokova, E., Bonny, O., Stritt, K., & Roth, B. (2022). The impact of stenting prior to oral chemolysis of upper urinary tract uric acid stones. *International urology and nephrology*, *54*(1), 37–45. https://doi.org/10.1007/s11255-021-03072-6