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

Title: Encrusting pyelitis: importance of urinary acidification for its management.

Keywords:

Authors: Elsa Martínez Montava, Jorge Panach Navarrete, Jose María Martínez Jabaloyas

1. Summary

Introduction and objectives: Encrusting pyelitis is an infectious disease caused by *Corynebacterium urealyticum,* it is characterized by incrustations in the upper urinary tract and in the bladder walls. In the following clinical case, we present the importance of having a high clinical suspicion for its diagnosis and medical management, based on antibiotic therapy and urinary acidification.

Method: Description of the clinical case, therapeutic management, and progress of the patient.

Results: Clinical case presentation of a patient suffering from alkaline encrusting pyelitis. Both the diagnostic process and the treatment are described, based on urinary acidification and antibiotic treatment. The evolution and the obtained results are exposed.

Conclusions: High clinical suspicion is needed to reach the diagnosis of encrusting pyelitis. Urinary pH analysis, selective cultures for the bacteria and Computed Tomography play a key role in the diagnosis. Antibiotic treatment and urinary acidification are the treatment's fundamental pillars.

2. Introduction

Alkaline encrusting pyelitis is an infectious disorder caused by urea-producing bacteria, the most common causative agent being *Corynebacterium urealyticum*. It is characterized by incrustations in the upper urinary tract and in the bladder walls (1). It mainly affects transplanted kidneys, being exceedingly rare in native kidneys, with very few cases described in the literature (2).

Clinical manifestations are not very specific, this usually causes a diagnostic delay that can lead to important complications. When urine is studied, a persistently alkaline pH is observed (usually above 7.5), accompanied by hematuria or pyuria, and sometimes together with abundant detritus, crystalluria or stones (1). The delay in diagnosis can lead to acute kidney failure (AKF), chronic kidney disease (CKD) that requires hemodialysis, or urinary sepsis (2)(3).

The presence of insidious clinical signs, along with the difficulty of growth of Corynebacterium in conventional culture media, makes this disorder a hard to diagnose disease. Sometimes, as in the clinical case that will be discussed below, imaging methods can be the basis for suspecting the diagnosis. The most sensitive test for diagnosis is Computed Tomography (CT) scan, where deposits of calcium density are observed within the walls of the urinary tract. Other imaging tests, with lower diagnose value, are ultrasound, which allows to observe hyperechogenic deposits with posterior shadow in the urothelium, and abdominal X-ray where calcifications are visualized through the urinary tract (4). The treatment is based on antibiotic therapy directed at Corynebacterium together with urine acidification, in addition to lithofragmentation if necessary (4).

The objective of this work is, through a clinical case, to expose the key factors that lead to the diagnostic suspicion of encrusting pyelitis, in addition to emphasizing the importance of pH-modifying medical treatment for the resolution of the infective disorder.

3. Description of the clinical case

a) Relevant medical history

Clinical case presentation of a 64-year-old male patient with a personal history of high blood pressure, type 2 diabetes, and dyslipidemia.

The patient had a personal history of high-risk superficial bladder tumor, which after failure of BCG treatment and progression to muscle-invasive bladder tumor it was decided to perform radical cystectomy and ileal conduit. Two months after the surgery he was admitted for urinary sepsis, with right renal dilation, which required placement of right percutaneous nephrostomy. During the intervention, antegrade pyelography was performed and a filiform contrast passage to the Bricker conduit was observed at the level of the distal ureter, and stenosis of the right ureteroileal junction was diagnosed. Five months after the cystectomy, endoscopic dilation was performed, and a double J stent (6CHx26cm) was placed. Shortly after the stent removal and while receiving adjuvant chemotherapeutic treatment, he presented with new sepsis caused by a urinary infection that required admission to the Intensive Care Unit, with the growth of a beta-lactamase-producing Enterobacter cloacae in urinary and blood cultures. During the subsequent follow-up, a diuretic renogram was performed that showed obstruction of the right kidney, so it was decided to perform endoscopic dilation once again placing a 30CH ureteral stent (Allium Medical®). Seventeen months after the cystectomy, eight months after the placement of the stent, it became obstructed, therefore its extraction was required and a 7CH 28cm right mono-J stent was placed to ensure the permeability of the ureter. After five months, the patient underwent a retrograde holmium laser endoureterotomy. He presented a complicated postoperative period with intense hematuria and impaired renal function (showing creatinine levels up to 2.27 mg/dL) that required hospital admission.

b) Diagnostic support studies and results

c) Diagnosis

During admission, an abdominal-pelvic CT scan was performed that showed for the first time calcium deposits in the urothelium that suggested the presence of alkaline encrusting pyelitis along with right ureterohydronephrosis that again suggested stenosis of the anastomosis (see Image 1). Given this finding, urinary pH was analyzed showing an 8.5 pH and specific urinary cultures were collected, searching for *Corynebacterium urealyticum*, confirming its presence in urine.

d) Treatment

Empirical antibiotic treatment was initiated with Vancomycin 1g/12h for 7 days along with urinary acidification using Acetohydroxamic acid (AHA) 125mg/8h. As it was mentioned in the introduction, this bacterium is difficult to grow in conventional media and even in specific media. The empirical antibiotic treatment was maintained until the seven-day regimen was completed.

The patient presented a kidney function impairment with creatinine levels up to 5.2 mg/dL that required placement of right nephrostomy. During admission, urinary pH was monitored through urine tests every 48 hours, until a pH below 7 was achieved. The patient recovered his basal kidney function (creatinine below 1.5 mg/dL) and the AHA prescription was maintained for 2 months.

e) Outcome

f) Clinical results

Two years after the cystectomy, he underwent a laparoscopic right ureter reimplantation. During his follow-up through outpatient consultations, urinary pH continued to be monitored every 2-3 months and control CT scans every 4 months to monitor the pyelitis evolution. Gradually the calcifications were decreasing, until they disappeared completely after 2 years. The patient maintained urinary pH below 6.5 from the end of the treatment, without showing new calcifications in the imaging tests that were suggesting a recurrence of pyelitis.

Two years and eight months after the cystectomy, and eight months after the ureteral reimplantation, the right kidney presented ureterohydronephrosis again and the diuretic renogram showed an obstructive pattern, so it was decided to perform a retrograde endoureterotomy with holmium laser again, this time the resolution of the obstruction was achieved. During the follow-up, the right kidney showed no signs of hydronephrosis, and the patient did not present new infections.

4. Discussion

Encrusting pyelitis is a difficult to identify disorder, however it can destroy the renal parenchyma and cause kidney failure in a brief period of time. It is not easy to find literature regarding this disorder in patients with non-transplanted kidneys as in our case, because apart from being rare, it is difficult to diagnose and requires a high clinical suspicion. Clinical manifestations are subtle until complications appear. As described in Hertig et al. (2), patients with a personal history of cystectomy, such as the case we presented, may show even more subtle manifestations, making diagnosis even more challenging. Therefore, the search for laboratory findings such as the presence of alkaline pH are important. In this case, the disease was diagnosed by CT imaging, and from there the rest of the clinical signs were searched.

Corynebacterium urealyticum must be cultured in selective media for 48-72h, at 37ºC and in an atmosphere with carbon dioxide. A selective medium containing Tween 80 and antibiotics to prevent the growth of other contaminating bacteria would help the diagnosis. Coexistence with other more easily identifiable microorganisms is frequent, which often leads to the mistake of treating these other bacteria and forgetting the search and specific treatment of Corynebacterium (4)

The treatment of encrusting pyelitis is based on three fundamental pillars: targeted antibiotic treatment, urinary acidification and lithofragmentation if necessary.

C. urealyticum is a multidrug-resistant bacterium usually present in the hospital environment, but it remains sensitive to glycopeptides, responding to Teicoplanin or Vancomycin. The advantage of the first antibiotic is that it can be administered intramuscularly. Vancomycin, however, must be administered intravenously. Sensitivity to fluoroquinolones is irregular, with resistance rates of up to 50% in some series. Cephalosporins and ampicillin are not a better option, showing high rates of resistance. Other antibiotics such as Rifampicin or Tetracycline have an in vitro sensitivity of 60-100% and 30-83% respectively. For all this, the first line of antibiotic treatment is usually glycopeptides, if the treatment is not successful, direct it according to the antibiogram. Antibiotic therapy should be the first step before any other treatment (5). In this case, the chosen treatment was Vancomycin 1g/12h for 7 days, which was administered during hospital admission.

Acidifying treatment is another key point of its management. *Corynebacterium urealyticum* breaks down urea molecules and creates an alkaline environment in urine that facilitates the precipitation of struvite and carbapatite crystals (see Image 1), therefore it is essential to reverse the urinary acidic environment to resolve the disorder. When it comes to dissolving calcifications, the effect of urinary acidification and antibiotic therapy is synergistic, since calcifications contain microorganisms (4). In this case the prescription was Acetohydroxamic acid (AHA) 125mg/8h for 2 months.

However, several studies highlight the modest benefit of urease inhibitors, as is the case, for the treatment of alkaline lithiasis. In addition, it is not exempt from dermatological, hematological, and neurological adverse effects, which occur between 22% and 62% of patients, according to studies. Therefore, the use of AHA is limited by adverse reactions, which include tremors or venous thrombosis (6). Its use also requires normal kidney function.

There are other oral urinary acidifying drugs. Ammonium chloride has been proven to acidify urine and be useful in the treatment of infective stones. It is generally well tolerated, causing few adverse effects if used for a brief period of time, although at high doses and in prolonged treatments, it can cause hyperchloremic metabolic acidosis and cause headache or dizziness. This type of acidification is contraindicated in the presence of kidney or liver insufficiency. It also causes irritation of the gastrointestinal tract frequently (7). This drug can lower urinary pH even in the presence of residual infective stones, acting synergistically with antibiotics (8). The recommended dosage is 1g two or three times a day, depending on the urinary pH achieved.

Another useful drug in urinary acidification is oral L-methionine (L-M) (Lit-Control pH Down, Devicare ®). It is metabolized in the liver forming sulfate ions and protons. This increases the urinary excretion of sulfate, which favors lower urinary pH. In the study by Hesse et al, after a single dose of 1500mg L-M a significant decrease in pH values was observed at 6.0±6.2, and this acidification was maintained for 24h. In the study by Knebel et al. no changes were found in the serum parathyroid hormone, glucagon, insulin, or growth hormone levels during treatments with high doses of L-M (6 g per day), with particularly good tolerance and adherence. L-M has also been shown to decrease the recurrence of stones in patients with struvite stones (7). The recommended guideline is 200-300mg, two or three times a day, depending on the urinary pH.

Urinary pH monitoring during treatment is recommended, performing urinalysis during follow-ups. However, patients with a tendency to develop urinary stones and in chronic treatment with urinary pH modifiers would benefit from stricter controls than the ones performed during follow-ups. In the study by Angerri et al (9) the accuracy of urine test strips for monitoring was compared to a new pH-meter (Lit-Control pH Meter, Devicare®), with the aim of involving patients in the measurement and more strict monitoring of urinary composition. It was concluded that the new device was superior in terms of less dispersion in the measurements and greater accuracy. This is considered as a good diagnostic-therapeutic tool to facilitate and improve urinary pH control in these patients (9).

Another interesting option for chemolysis is the administration of drugs through a percutaneous catheter.

Sometimes, especially at the beginning of treatment, urinary acidification with oral drugs is not sufficient and local administrations of acidic preparations such as Thomas C 24 (sodium gluconate 27g, citric acid 27g, malic acid 27g and distilled water 1000ml) or Suby G (citric acid 32,3g, sodium carbonate 4,4g, magnesium oxide 3,8g and distilled water 1000ml) are necessary. The instillation is performed to the renal pelvis through a nephrostomy tube, and the output is collected using a ureteral catheter, a second nephrostomy, or simply waiting for spontaneous urination of the product. The requirement of intrapelvic pressure monitoring during the procedure has been described, and possible adverse effects such as lower back pain, metabolic acidosis, or the occurrence of fungal or bacterial infections should be considered during follow-up (4).

In case medical treatment fails, lithotripsy should be considered. In this case, several surgical interventions were necessary to treat the right uretero-ileal stenosis. The treatment was started using the least invasive techniques, it began with the placement of a stent, which also failed, so a holmium laser endoureterotomy was performed. This last intervention did not show satisfactory results either, therefore a laparoscopic reimplantation of said ureter was performed, which eight months later again suffered a stenosis and a second endoureterotomy was performed, which was successful.

Imaging techniques are useful for both diagnosis and follow-ups. As mentioned, CT scans are the most sensitive and specific technique for diagnosis, therefore it is also the most recommended to monitor response to treatment. Initially, a decrease in urothelial enhancement related to the infection will be observed and progressively the disappearance of urothelial calcifications. A precaution regarding the diagnosis by imaging is that it is necessary to make the differential diagnosis with other disorders that behave similarly, such as Schistosomiasis, tuberculosis, calcified necrotic urothelial carcinoma or malakoplakia (10). The combination of CT scan and the pH meter is probably a good combination for monitoring this disorder.

5. Conclusions and recommendations

Encrusting pyelitis is a disease that requires high clinical suspicion for it to be diagnosed. It is important to keep in mind that the medical treatment consists of both urinary acidification and targeted antibiotic therapy, and that both act synergistically. If treated properly, the disease resolves in months and the sequelae are minimized, as in the presented case.

6. Bibliographic references

1. Lieten S, Schelfaut D, Wissing K, Geers C, Tielemans C. Alkaline-encrusted pyelitis and cystitis: an easily missed and life-threatening urinary infection. Case Reports. 2011;2011(mar28 1):bcr1220103613-bcr1220103613.

*2. Hertig A, Duvic C, Chretien Y, Jungers P, Grünfeld J, Rieu P. Encrusted Pyelitis of Native Kidneys. Journal of American Society of Nephrology. 2000;11(6):1138-1140.

3. Audard V, Garrouste-Orgeas M, Misset B, Ali A, Gattolliat O, Meria P et al. Fatal septic shock caused by Corynebacterium D2. Intensive Care Medicine. 2003;29(8):1376-1379.

**4. Meria P, Jungers P. Encrusted pyelitis: an underdiagnosed condition?. Nephrology Dialysis Transplantation. 2000;15(7):943-945.

*5. Meria P, Desgrippes A, Arfi C, Le Duc A. Encrusted cystitis and pyelitis. The Journal of Urology. 1998;:3-9.

*6. Flannigan R, Choy W, Chew B, Lange D. Renal struvite stones—pathogenesis, microbiology, and management strategies. Nature Reviews Urology. 2014;11(6):333-341.

**7. Hesse A, Heimbach D. Causes of phosphate stone formation and the importance of metaphylaxis by urinary acidification: a review. World Journal of Urology. 1999;17(5):308-315.

8. Wall I, Tiselius H. Long-Term Acidification of Urine in Patients Treated for Infected Renal Stones. Urologia Internationalis. 1990;45(6):336-341.

**9. Angerri O, Pascual D, Haro J, Fernández X, Chigança V, Garganta R et al. Comparative study between a medical device and reagent dipsticks in measuring pH. Archivos Españoles de Urología. 2020;73(6):546-553.

10. Pollack H, Banner M, Martinez L, Hodson C. Diagnostic considerations in urinary bladder wall calcification. American Journal of Roentgenology. 1981;136(4):791-797.