2nd Edition of the Contest of Clinical Cases related to the non-surgical clinical management of kidney stones

Title: Acidification of urine as a measure to prevent recurrent encrustation of long-term urinary stents.

Keywords: Lithiasis, instrumentalization, acidification, calcification, encrustation.

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1. Summary

The role of metabolic treatment of kidney stones is widely reported in the scientific literature. However, there is little evidence associated with the prevention of complications related to calculi events or calcification of urinary diversion devices. We present the case of a 75-year-old woman with a long history of kidney stones who finally required permanent percutaneous nephrostomy placement. Subsequent follow-up showed a persistent tendency to calcification of the device, leading to repeated episodes of obstruction and very difficult replacement, which significantly affected her quality of life. Finally, urine acidifying treatment with Lit-Control pH Down© was chosen, with highly satisfactory results. A remarkable decrease in the degree of calcification of the nephrostomy was observed in successive replacements, as well as the absence of new obstruction events.

2. Introduction

In the current literature there are few references and a lack of global consensus on the specific management of kidney stones complications, calcification, or encrustation, of urinary diversion elements. If we perform a detailed keyword search, we can easily verify that most of what has been published refers to a much greater extent to instrumentation by double J stent than by percutaneous nephrostomy (PCN). The main cause of these phenomena in this group of patients is the colonisation of the diversion devices by urease-producing bacteria. The presence of these bacteria favours an alkaline urinary microenvironment, which leads to the precipitation of soluble salts in the urine and the formation of urinary calculi. In the case of patients with urinary diversion devices, there is a possibility that they may adhere to their surface, leading to episodes of obstruction and other associated complications. [(1)].

At present and based on the available evidence, there is no global consensus regarding the specific management of urinary stent encrustation. In general, the specific treatment of the embedded device is differentiated, which usually requires combined management through various surgical, endourological and extracorporeal lithotripsy techniques.

On the other hand, there is its prevention where medical treatment plays its role, based mainly on antibiotic therapy and increased water intake associating different compounds (potassium citrate, citrus juices ...) [(2)]. Most of the existing recommendations on the management of urinary diversion element encrustation focus on different strategies for prevention, generally based on low-quality and sometimes relatively contradictory evidence.

3. Description of the clinical case

a) Important background information

We present the case of a 75-year-old woman with a history of bilateral kidney stones, leading to recurrent episodes of renal colic, pyelonephritis and even associated sepsis. As medical history of interest, the patient suffers from advanced Parkinson's disease with motor fluctuations and severe postural alteration, as well as chronic pancreatitis. Throughout her evolution she has on occasion required urgent urinary diversion, as well as endoscopic surgery for the treatment of the calculi.

b) Diagnostic support studies and results

- Metabolic study carried out in 2008, prior to any intervention on the urinary tract:
    - General blood analysis: Unchanged ions, Creatinine 0.8 mg/dl with eFG 75 ml/min, PTH intact in range. Vit D within normality.
    - 24h urinalysis: Total balance diuresis 1650ml. pH 7. Only relevant finding slight hypocitraturia (273 mg/24h), rest of elimination values in range.
- 2015 imaging tests, after first referral for complicated renal colic:

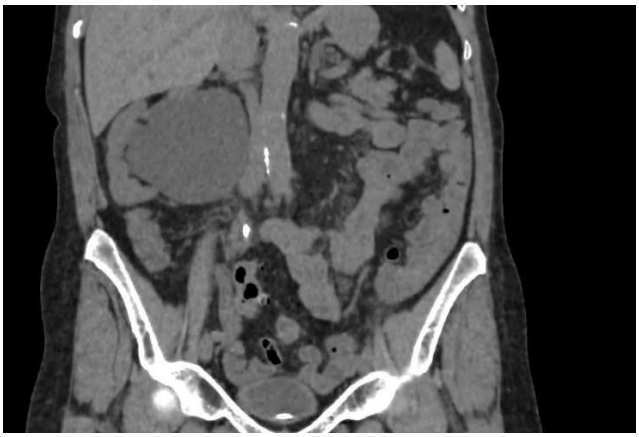


Image 1 and 2: Abdominopelvic CT without contrast in which right hydronephrosis secondary to stenosis of the pyeloureteral junction (PUJ) is observed despite the right DJS that required complicated renal crisis. Multiple millimeter lithiasis in left kidney without obstructive repercussion on the urinary tract, 450 UH compatible with uric acid stones.

c) Diagnosis

The patient went for the first time in 2005 to our center consulting the symptoms described above, as well as intermittent hematuria. In complementary tests, a stenosis of the pyeloureteral junction (PUJS) was observed, conditioning an important right pielocalicial dilation as a possible predisposing factor of its clinical profile.

d) Treatment

During his illness, he required urgent intervention by urinary diversion on several occasions, as well as surgery with the intention of resolving the stone by means of ureterorenoscopy (URS) with fragmentation and posterior extraction. Given the persistent tendency to suffer from urinary tract infections complicated by significant associated right-sided hydronephrosis, it was finally decided to place a permanent right percutaneous nephrostomy (PCN).

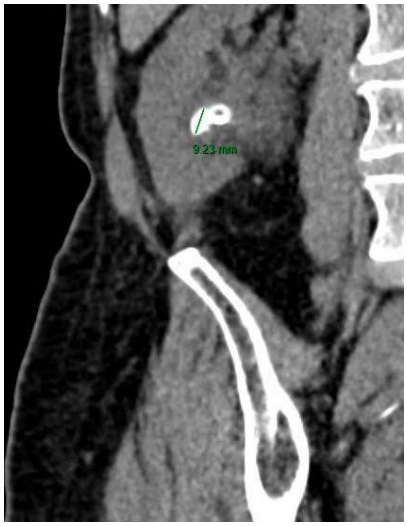
The patient always rejected by express wish, considering her baseline situation and after evaluating the available options, any type of surgical intervention to correct the stenosis of the right pyeloureteral junction. The reason why NPC was chosen instead of DJ stent was primarily due to apparent ineffectiveness of the catheter when presenting a tendency to calcification and obstruction, as well as to avoid going periodically to the operating room for successive replacements.

e) Evolution

In the first postoperative control after placement of the right PCN, persistent significant pyelocaliceal dilatation was observed despite its normal position and good functioning. The first PCN replacement was very difficult due to significant calcification of the tube. Subsequently, he presented with a new case of urological sepsis associated with several calculi in the left ureteral tract, requiring admission for intravenous antibiotherapy and urgent urinary diversion via left double J stent (DJS) and replacement of the right PCN. Based on the available evidence on the use of larger bore devices to prevent obstruction associated with lithiasic encrustation, the patient opted for placement of a 14 Ch straight tip bladder catheter (IDC) as a nephrostomy. After stabilisation of the infectious condition, the patient underwent deferred left retrograde intrarenal surgery (RIRS) to remove stone debris, as well as replacement of the right PCN. The PCN replaced was found to be highly calcified in a relatively short period of time since its insertion, and it was decided to increase the calibre of the new replacement to 18Ch.

The morpho-compositional analysis of the calculus obtained in this last intervention reveals a composition of 90% calcium phosphate with the remaining 10% corresponding to calcium oxalate.

In her subsequent evolution, the patient showed a clear tendency to present symptoms of obstruction of the right PCN due to significant calcification of the same, which led to both malfunctioning and difficult replacement, despite the large calibre of the PCN. The patient initially presented with *Klebsiella pneumoniae* isolated in urine and in the cultured tips of the first PCN exchanges.



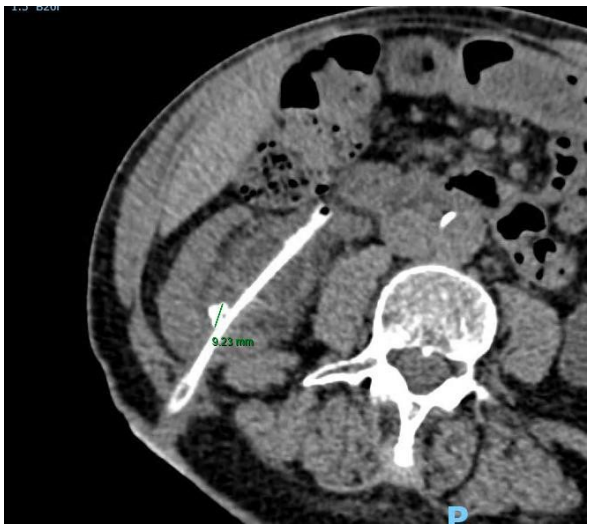


Image 3 and 4: non-contrast abdominopelvic CT scan obtained at subsequent follow-up, showing a tendency towards calcification of the right PCN. In the image, calcification adhering to the tube with a maximum diameter of 9.2 mm x 9.2 mm. It can also be seen in coronal section, occupation of the lumen of the device by calcium dense material.

Image 5 and 6: Right nephrostomy (18Ch bladder catheter) with intense calcification of intraluminal predominance after replacement

In view of this clinical evolution, it was decided to start Lit-Control pH Down© as a preventive adjuvant medical treatment, as well as a prolonged 14-day course of antibiotic therapy with oral Cotrimoxazole adjusted to previous urine culture.

Successive replacements are scheduled at shorter intervals, every four weeks, always ensuring an aseptic environment by means of prophylaxis in each manipulation using Cefuroxime for cultures. At the end of the prescribed antibiotic cycle, the patient is maintained with frequent scheduled replacements under conditions of asepsis and antibiotic prophylaxis, always associating acidifying treatment.

f) Clinical results

Successive replacements after the start of acidifying treatment (Lit-Control pH Down©) and antibiotic therapy are less complicated than the previous ones, with minimal associated calcification and no complications.

The patient has been clinically stable since then, with no further episodes of renal colic or associated UTI. She has no further episodes of PCN obstruction and reports a great improvement in terms of quality of life, with no need for urgent care for problems related to PCN function.

Subsequent replacements, in which urine obtained through PCNs was cultured, as well as the tips of the PCNs removed, showed microbiological negativisation, thus eliminating the *K. pneumoniae* isolated in the first instance. Urine analyses obtained during follow-up revealed a pH of around 5 with progressive acidification after starting treatment with Lit-Control pH Down©. In previous urine pH controls, figures of up to pH 9 had been observed prior to the start of the acidifying treatment.

Image 7: PCN not calcified in successive spare parts

4. Discussion

Calcification or encrustation of urinary diversion devices is a known and somewhat expected complication of their use. The fundamental pathophysiological mechanism that favours its occurrence is the colonisation of its surface by urease-producing bacteria. The urease produced favours the degradation of the urea present in the urinary tract into ammonium and bicarbonate, which causes the progressive alkalinisation of the urine, enabling the precipitation of soluble mineral salts in the urine. These urine-soluble salts are normally already in supersaturated concentrations, which also favours their crystallisation and the formation of stones.

In patients with external urinary tract devices, these stones may adhere either on the intraluminal surface of the device (causing obstruction) or extraluminal (causing traumatic or difficult replacements) [(1)].

The main risk factor demonstrated in most of the series published to date in the development of encrustation in external devices is the maintenance time [3]. Other factors to be considered with a transcendental role in the physiopathogenesis of the encrustation phenomenon are bacterial biofilms. In general, it is estimated that approximately 90% of the devices removed and analysed show bacterial colonisation and about 55% show adherent films (bacterial biofilms) on their surface [4]. These structures, although there is no clear evidence of the exact mechanism by which they favour the described phenomenon, may represent a microenvironment that perpetuates bacterial colonisation, favouring the lithogenic mechanisms previously mentioned.

The most important pathogen associated with encrustation of urinary diversion devices is *Proteus mirabilis*, although other urease-producing microorganisms may also be associated, such as other enteric bacteria (*Klebsiella* or *Morganella* among others). The composition of kidney stones associated with encrustation is generally attributed to a greater extent to magnesium ammonium phosphate (struvite) or calcium phosphate (apatite) [4].

The structural characteristics of the urinary diversion device also appear to play a major role in the pathophysiology of the encrustation phenomenon. The calibre of the device has been shown to play a determinant role in development of the described mechanism. Several retrospective series have shown significantly lower encrustation rates associated with devices with a larger calibre (>7 Fr) compared to smaller calibre devices (<6 Fr) [3]. In turn, the device material used also seems to be closely related to the risk of subsequent encrustation. A wide variety of materials and even devices with pharmacoactive substances on their surface are available on the market today. Most devices used in current clinical practice are composed of blends of different synthetic polymers based on polyurethane. Recently, new materials have been used, such as silicone, which seem to favour lower encrustation rates in experimental in vitro studies [5]. At present, new models are being studied based on the association with pharmacoactive substances (glycosaminoglycans, different types of antibiotics, etc.) that allow lower rates of colonisation, as well as calcification and encrustation. The possibility of developing biodegradable devices has also been explored [6], which would represent a major advance in the management of all these types of complications. However, at present, the available evidence is limited and is purely experimental.

For the prevention of encrustation in patients with temporary or permanent urinary diversion devices, a wide variety of alternatives have been studied. It has been shown that there is no evidence to conclude that different treatments such as cranberry or vitamin C supplementation reduce encrustation rates in these patients.[7]. Nowadays, there is also no solid evidence to conclude that urine acidifying treatment is beneficial in preventing the complications associated with encrustation in these patients [8].

These treatments, based on the combination of an acidifying agent such as L-Methionine and crystallisation inhibitors such as phytate (composition of Lit-Control pH Down©), have proven useful in the prevention of recurrence and even definitive treatment of urinary stones in general. Its mechanism of action is mainly based on the reduction of pH in patients predisposed to an alkaline urinary environment, as well as on the inhibition of the crystallisation of calcium salts present in the urine through the action of phytate. Although we could consider extrapolating this mechanism of action and therefore its efficacy in reducing encrustation rates in this subgroup of patients, the reality is that there is no solid evidence at present to allow us to make such an inference.

As noted above, most recommendations for the management of encrustation focus on prevention. A simple, obvious and highly effective recommendation is based on regular device replacement on a more regular basis, preventing the formation of large calcifications.[(2).]. On the other hand, there are clinical trials showing that something as simple as increasing water intake, based on liquids with a high citrate content (citrus juices; orange, lemon...) significantly reduces encrustation rates compared to control groups or water intake based only on water.[(9)] . The use of prolonged antibiotic therapy is discouraged by most scientific societies on the grounds of the possible development of bacterial resistance due to its use.[(10)]. However, it is a widespread practice, and several studies show that as a last alternative in patients in whom other therapeutic options have failed and with repeated microbiological isolations, it can be a valid option as a concomitant treatment to other measures.[(1)] Finally, definitive treatment of the encrustation of the device that cannot be replaced on an outpatient basis is generally based on a combination of different techniques. Again, there are no fixed recommendations; a recent systematic review of the subject proposes a therapeutic algorithm based on the degree of encrustation as well as the location of the device [(1)(2)]. In actual practice, it is usually based on a combination of endourological techniques, extracorporeal lithotripsy or even open surgery, although based on the available evidence and the absence of strict recommendations, each case must be assessed on an individual basis.

In our specific case, the management of the condition was based on the combination of different therapeutic alternatives. Special emphasis is placed on the importance of medical treatment in this particular case, based mainly on acidifying treatment using Lit-Control pH Down© and targeted antibiotherapy, as this was what really improved the patient's baseline condition. The patient had an already deteriorated baseline functional status due to her previous neurological condition. The main perpetuating mechanism of her lithiasic disease, the UPJ stenosis described above, could not be treated primarily, so a permanent urinary diversion had to be chosen. The improvement in the patient's quality of life was then largely relegated to the proper functioning of her percutaneous nephrostomy, which, as we have explained, was far from working well. There were therefore not many other non-invasive therapeutic alternatives to offer her, something that was completely ruled out by consensus from the outset.

Urine acidification, as well as targeted antibiotic treatment, allowed for a remarkable, simple and minimally invasive way to efficiently treat the patient's condition, as well as allowing for a huge improvement in her quality of life. Of course, concomitant treatment with interventions aimed at kidney stone disease resolution should not be forgotten, as well as the scheduling of periodic, more closely spaced replacements and the use of devices with a larger calibre. The combination of all these techniques in a specific case, in which the evidence offers little support when it comes to consulting it to draw up a therapeutic plan, is what has allowed an adapted and effective treatment to solve the problem.

5. Conclusions and recommendations

Permanent urinary diversion is the last therapeutic option in the treatment of obstructive uropathy when definitive surgical treatment cannot be offered. Unfortunately, it entails a series of complications, mainly encrustation of the device used, with severe consequences on the patient's quality of life or vital prognosis. Given the lack of consensus on the therapeutic approach to the encrustation of urinary diversion devices, each case must be studied and planned on an individual basis and after a thorough review of all available alternatives. The role of metabolic medical treatment for kidney stones applied to external device encrustation, has little evidence in the current scientific literature. Although it may offer a possible theoretical applicability based on its mechanism of action in the treatment of urinary stones in general, a greater number of prospective, comparative studies of higher scientific quality are needed to be able to offer solid recommendations.

6. References

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