Case of drug-induced kidney stone from overuse of phenazopyridine

Suraj Pursnani, MD, Necole M. Streeper, MD
Department of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

PURSNANI S, STREEPER NM. Case of drug-induced kidney stone from overuse of phenazopyridine. *Can J Urol* 2024;31(3):11911-11913.

Drug-induced nephrolithiasis represents only 1%-2% of stone cases. Here we focus on drugs capable of crystallizing and forming stone, specifically phenazopyridine (Pyridium/Azo). This is a case of a patient who presented with a stone conglomerate in the right proximal ureter and underwent definitive treatment. Interestingly, the stone had a purple hue with FTIR spectroscopy showing stone composition of calcium oxalate (monohydrate and dihydrate) and a material resembling phenazopyridine. We retrospectively learned that she used multiple extended courses of phenazopyridine over 3 months.

Key Words: Pyridium, nephrolithiasis, drug-induced nephrolithiasis, phenazopyridine

Introduction

Stones composed of phenazopyridine (Pyridium/Azo) are uncommon, with only two case reports in the literature.[1,2] While drug-induced nephrolithiasis is uncommon, several medications can promote stone formation. Drugs may change urine pH that increases the solubility of certain substances, alter nephron reabsorption and secretion, or precipitate to compose part or all a stone.[3] This report will focus on stone formation due to supersaturation of a drug or its metabolite. Examples include guaifenesin/ephedrine, indinavir, triamterene, sulfa medications, and ciprofloxacin.[4] In 1972, Mulvaney et al described the only case report currently in the literature describing bladder calculi composed of pure phenazopyridine.[1] Crawford et al then described in 1978 a ureteral stone that was extracted with stone composition revealing 60% uric acid and the remaining was pure form phenazopyridine hydrochloride that was deposited on the surface.[2] Here we describe the first reported case of a kidney stone composed of phenazopyridine and calcium oxalate. Phenazopyridine is a commonly used medication for urinary tract symptoms and infections; however, limitations exist in its use due to side effects. Phenazopyridine-induced stone formation or enhancement of stone size is rare in the urologic community and the mechanism of action is unknown. It is possible to have pure phenazopyridine composition or, as seen in this case, phenazopyridine can be deposited on existing stone of varying compositions that serves as a nidus.

Accepted for publication May 2024

Address correspondence to Dr. Suraj Pursnani, Department of Urology, Penn State Milton S. Hershey Medical Center, Mail Code H055, 500 University Drive, PO Box 850, Hershey, PA 17033-0850 USA

Case report

This patient is a 42-year-old female with a past medical history of obesity with a body mass index (BMI) of 49, endometriosis, chronic pelvic pain, Usher syndrome (deafness and nonverbal), chronic interstitial cystitis, loin pain hematuria syndrome, recurrent urinary tract infections, and nephrolithiasis. She was doing well until January 2013 when she had worsening pelvic pain. CT imaging was notable for non-obstructing nephrolithiasis, which was unlikely the source of her pain. The etiology of her pain was difficult to diagnose, resulting in evaluation from multiple urologists and gynecologists. She was diagnosed with loin pain hematuria syndrome in July 2013. In September 2013, she underwent cystoscopy and hydrodistension with cystoscopy revealing small irregular areas at the bladder trigone, potentially representing endometriosis. After hydrodistension, she was found to have a tremendous amount of glomerulations, consistent with a diagnosis of interstitial cystitis. In October 2013, she underwent cystoscopy, bilateral retrograde pyelograms, and transurethral resection of the irregular area at the bladder trigone as a part of her hematuria work up. Bilateral upper tracts were clear of fillings defects and the pathology for the resected specimen returned as squamous metaplasia. Over the next few months to years, she was seen multiple times by providers for uncontrolled pelvic pain requiring increased levels of narcotics. This ultimately required referral to chronic pain, whom she has been following with to this day. In 2020, the patient had four episodes of recurrent UTI over the course of 3 months with significant pelvic pain for which she used phenazopyridine for 2 weeks each time she had an infection.

In October 2022, she presented with right flank pain, acute kidney injury (Cr 1.37 with baseline 0.85), and leukocytosis (WBC 13.4) with CT imaging showing multiple obstructing stones in the right proximal ureter. The patient had a history of intolerability to stents and preferred nephrostomy tube placement. A right sided nephrostomy tube was placed, and the patient was discharged with a plan to return for definitive stone treatment in the next few weeks. The patient underwent right ureteroscopy with laser lithotripsy to treat her renal stone burden. During the case, we found 1.2 cm worth of stone burden in the right proximal ureter and interestingly, we noted that the stones had an unusual purple hue that was in layers with the more common color consistent with calcium oxalate, see Figure 1. Fourier-transform infrared (FTIR) spectroscopy by ARUP laboratories was used for stone fragment analysis which showed calcium oxalate (monohydrate and dihydrate), and a material resembling phenazopyridine. Quantitation of components is not possible and no percentage was assigned to the amount of each composition. Due to her stent intolerance, we maintained her nephrostomy tube in place for an additional week.

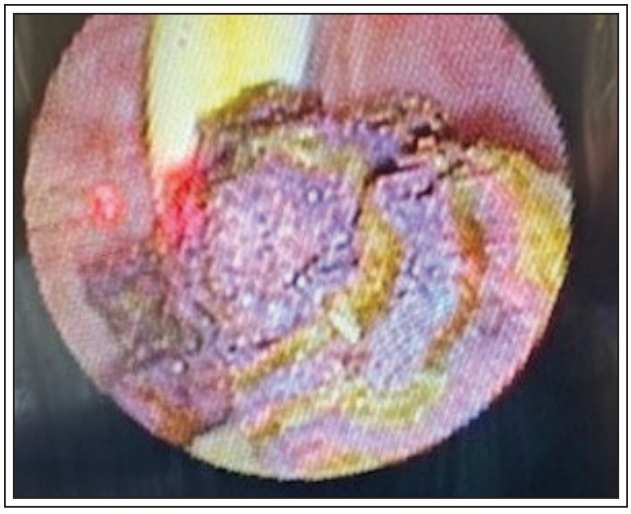

Figure 1. Pyridium stone.

Her postoperative course was overall uncomplicated, and she was discharged home the same day. However, she did have uncontrolled pain requiring a course of ketorolac. The patient was seen with interventional radiology the following week and underwent an antegrade nephrostogram which showed a non-dilated right renal collecting system and prompt drainage to the bladder. Her nephrostomy tube was removed uneventfully. The patient was seen in follow up in 2 months with a renal bladder ultrasound, which showed no hydronephrosis or nephrolithiasis.

After further investigation, we learned that the patient had remotely used phenazopyridine 2 years prior for recurrent UTIs. She had four episodes of urinary tract infections over the course of 3 months and used 2 weeks of phenazopyridine each time. She has not routinely used phenazopyridine since then.

Discussion

Drug-induced nephrolithiasis represents only 1%-2% of stone cases. This can be further classified as drug-induced metabolic calculi and calculi due to supersaturation of a drug or its metabolite.[4] In 1970, Dorfman et al described sulfonamide crystalluria.[5] Sundaram et al discussed the radiographic characteristics and management

of stones induced by a protease inhibitor, indinavir sulfate, used for HIV-positive patients. They found that pure indinavir stones are only seen on CT when intravenous contrast medium is used.[6] In 1999, Assimos et al published the first report on drug-induced stones caused by the overconsumption of guaifenesin and ephedrine.[7] Ciprofloxacin was also reported to be a culprit of drug-induced stones by Chopra et al in 2000.[8]

Stone composition consisting of phenazopyridine-like material is rare and has only been previously reported once in 1972 as bladder calculi and in 1978 as a kidney stone in combination with uric acid.[1,2] Phenazopyridine is a common medication used by urologists and primary care providers for bothersome urinary tract symptoms, especially dysuria secondary to infections or post-procedural. In our case, we present a patient who used multiple courses of phenazopyridine in a short period of time for recurrent urinary tract infections and developed stones consisting of a phenazopyridine-like material mixed with calcium oxalate. Gross inspection showed layering of the phenazopyridine stone, which indicates that the calcium oxalate stone acted as a nidus and the phenazopyridine deposited on the surface.

Different mechanisms of action exist for drug-induced stones. The first class includes drugs that crystallize in urine due to poor solubility. The second class of drugs promote calculi formation due to their metabolic effects on urine pH and excretion of calcium, phosphate, oxalate, citrate and uric acid.[9] Triamterene was identified as one of the leading causes of drug-induced nephrolithiasis due to poor solubility in the 1970s. More recently, antiretroviral medications used for HIV have become the most frequent etiology of drug-induced stones that are caused from poor solubility. Indinavir is the most recognized, however any of the antiretroviral HIV medications can form stones.[6]

Drug-induced metabolic calculi include loop diuretics, carbonic anhydrase inhibitors, and laxatives. Bumetanide and Furosemide produce a hypercalciuric state. Acetazolamide blocks resorption of sodium bicarbonate and can lead to increased urinary pH and decreased urinary citrate. Topiramate also increases the risk of stone formation, but the exact mechanism is unknown. It is hypothesized that it induces a renal tubular acidosis (RTA)-like effect, resulting in an increased urinary pH and decreased urinary citrate. Laxatives most commonly result in ammonium acid urate calculi due to low urine volumes and acidic pH.[4]

Phenazopyridine is commonly used for urgency, frequency, dysuria related to urinary tract infections. While phenazopyridine is mostly safe to use, the side effects include headache, rash, anaphylaxis, hypersensitivity hepatitis, gastrointestinal symptoms, methemoglobinemia, and hemolytic anemia. As a result, use is limited to 2 to 3 days for one course.[10] Our patient used phenazopyridine for more than the recommended course and her stone composition showed a material resembling phenazopyridine. Literature on phenazopyridine-induced stones is rare with only one previous case report of a bladder calculi and the mechanism of action is unknown. Currently, patients are not routinely counseled on stone risk as a potential side effect of overuse of phenazopyridine.

In conclusion, we describe the first reported case of a kidney stone composed of phenazopyridine and calcium oxalate. Phenazopyridine can form renal stones either in pure form or mixed with another stone composition. This is likely secondary to overuse of the medication and counseling should include this as a potential side effect. Our case further supports the notion that patients should not use phenazopyridine more than the recommended course and that stones should always be sent for analysis, even when the stone type is suspected since there may be unique findings, such as in our case. □

References

1. Mulvaney WP, Beck CW, Brown RR. et al. Urinary phenazopyridine stones. A complication of therapy. *JAMA* 1972;221(13):1511-1512.
2. Crawford ED, Mulvaney WP. Rapid increase in calculous size: a possible hazard of phenazopyridine in hydrochloride therapy in the presence of already formed stones. *J Urol* 1978;119(2(:280-281.
3. Osborne CA, Lulich JP, Bartges JW et al. Drug-induced urolithiasis. *Vet Clin North Am Small Anim Pract* 1999;29(1):251-266.
4. Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. *Rev Urol* 2003;5(4):227-231.
5. Dorfman LE, Smith JP. Sulfonamide crystalluria: a forgotten disease. *J Urol* 1970;104(3):482-483.
6. Sundaram CP, Saltzman B. Urolithiasis associated with protease inhibitors. *J Endourol* 1999;13(4):309-312.
7. Assimos DG Langenstroer P, Leinbach RF, Mandel NS, Stern JM, Holmes RP. Guaifenesin- and ephedrine-induced stones. *J Endourol* 1999;13(9):665-667.
8. Chopra N, Fine PL, Price B, Atlas I. Bilateral hydronephrosis from ciprofloxacin induced crystalluria and stone formation. *J Urol* 2000;164(2):438.
9. Daudon M, Frochot V, Bazin D, Jungers P. Drug-induced kidney stones and crystalline nephropathy: pathophysiology, prevention and treatment. *Drugs* 2018;78(2):163-201.
10. Eastham JH, Patel P. Phenazopyridine. 2024 Jun 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;2024.