Urology Case Reports 39 (2021) 101812

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Sulfamethoxazole stone in a patient with extensive history of urolithiasis and recurrent urinary tract infections

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ARTICLE INFO

Keywords:
Sulfamethoxazole-trimethoprim
Stones
Drug-induced
Nephrolithiasis
Urinary tract infection

ABSTRACT

Although rare, sulfamethoxazole-induced urolithiasis has been reported in patients taking trimethoprim-sulfamethoxazole (TMP/SMX). We present the case of a 79-year-old female who formed sulfamethoxazole stones in the setting of chronic indwelling catheterization with recurrent urinary tract infections (UTIs). The patient was a recurrent stone former with five prior stone composition analyses over a 10-year period varying from calcium phosphate to calcium oxalate, to struvite. We highlight the need for further investigation of this phenomenon given the frequent use of TMP/SMX in stone formers with recurrent infections.

1. Introduction

Sulfamethoxazole-trimethoprim (TMP/SMX), a combination of two antibiotics that inhibit purine synthesis in bacteria, is used to treat a wide array of infections. It is a common selection for the treatment of urinary tract infections due to the high renal excretion of biologically active trimethoprim. However, a metabolite of sulfamethoxazole, N-acetylsulfamethoxazole chlorhydrate, has been associated with nephrolithiasis in a handful of case reports.

The first case report describing sulfamethoxazole stones was published in 1977. A 72-year-old man on a 2-week course of TMP/SMX for chronic prostatitis presented with a stone composed of a metabolite of sulfamethoxazole.[1] In 1992, a 49-year-old quadriplegic male with a chronic indwelling urinary catheter was treated with multiple courses of TMP/SMX for recurrent urinary tract infections. The first course was accompanied by methylene blue. Months later, he was found to have stones with a blue-green nucleus composed of N-acetylsulfamethoxazole chlorhydrate surrounded by uric acid and calcium oxalate.[2] In 2020, a 43-year-old patient with HIV taking prophylactic TMP/SMX presented with obstructing, soft, orange ureteral calculi composed of 100% N-acetylsulfamethoxazole.[3] We now contribute another case of iatrogenic sulfamethoxazole stones associated with an extended course of TMP/SMX.

2. Case presentation

This is a 79-year-old female with multiple comorbidities and significant urologic history including urinary retention requiring a chronic indwelling catheter, recurrent urinary tract infections with multiple organisms (*Proteus mirabilis*, *Klebsiella pneumoniae,* and extended spectrum beta lactamase (ESBL) resistant *Escherichia coli*), and multiple episodes of nephrolithiasis. Further medical history placing her at risk of stone formation included chronic metabolic alkalosis, secondary to chronic diarrhea, vitamin D deficiency, osteoporosis, recurrent urinary tract infections, and a family history of nephrolithiasis.

She presented acutely with urosepsis secondary to obstructing ureterolithiasis in 2018. She was treated with a percutaneous nephrostomy tube and ultimately completed a 14-day course of TMP/SMX prior to definitive stone management. At the time of her ureteroscopy, stone analysis revealed 70% calcium phosphate and 30% calcium oxalate dihydrate. Over the next 20 months she was treated for recurrent urinary tract infections and developed bilateral non-obstructing nephrolithiasis and bladder stones. She underwent a mini-percutaneous nephrolithotomy and cystolitholapaxy in 2020, however due to her significant stone burden a stone-free state was not achieved. Stone analysis revealed 50% magnesium ammonium phosphate (struvite) and 50% calcium phosphate from the bladder stones and 70% calcium phosphate, 20% struvite, and 10% ammonium acid urate from the kidney stones. Her primary care physician intermittently placed her on multiple additional courses of TMP/SMX for recurrent urinary tract infections.

She presented again acutely in 2021 with urosepsis secondary to an obstructing stone. She had new bladder stones which measured 600 HU and multiple large kidney and ureteral stones which measured 750 HU on computerized tomography (Fig. 1). After placing a ureteral stent and

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https://doi.org/10.1016/j.eucr.2021.101812
Received 15 August 2021; Accepted 19 August 2021
Available online 19 August 2021

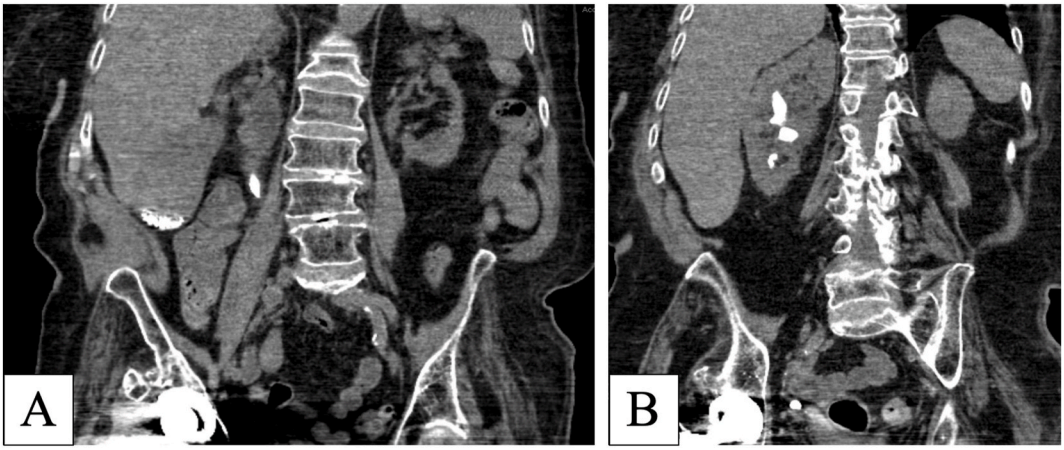

Fig. 1. Coronal imaging using computerized tomography demonstrating right ureteral stone (1a.) and partial staghorn calculous (1b.) with mean HU of 756.

administering 14 days of culture-directed TMP/SMX, she underwent cystolitholopaxy and bilateral, staged ureteroscopy due to her comorbidities. Between the two ureteroscopy procedures she received an additional 21-day course of prophylactic TMP/SMX. Only stones from the second ureteroscopy were sent for analysis with Fourier transform infrared (FTIR) spectroscopy which revealed that the brown stones were composed of sulfamethoxazole. The patient was discharged to her skilled nursing facility with seven days of nitrofurantoin prophylaxis and recovered well.

3. Discussion

These four cases document iatrogenic stone formation after extended courses of TMP/SMX. Our patient had repeated exposure to TMP/SMX over the last three years making it impossible to identify the moment of stone formation. However, certain circumstances surrounding her most recent and longest course of TMP/SMX may have affected her urinary microenvironment to promote supersaturation and lithogenesis. One factor was a urinary tract infection identified the day prior to starting TMP/SMX. While all four cases involve a patient with an infection, so do the majority of administrations of TMP/SMX, most of which do not cause stones. Another promoter may have been urinary stasis due to extant stones in our patient's urinary tract and recent instrumentation leading to urothelial inflammation that decreased flow and encouraged crystal formation in otherwise metastable urine. A history of recurrent UTIs has been noted in other patients with sulfamethoxazole stones[4] and pre-existing calculi and UTIs are risk factors for drug-induced crystalluria.[5]

The most common management strategy employed in the case reports summarized in our introduction was discontinuation of TMP/SMX after sulfamethoxazole stone identification. However, the case of TMP/SMX and methylene blue co-administration calls this logic into question. Although TMP/SMX was also subsequently administered without methylene blue, all sulfamethoxazole stones extracted months later were blue-green at the core dating them to that first administration. This implies that there was a period of stone-promoting disequilibrium that then resolved allowing subsequent doses of TMP/SMX to remain metastable in urine. Throughout her many courses of TMP/SMX our patient also had only one episode of sulfamethoxazole stones. Both cases show that the same drug in the same person will not always precipitate, implying that lithogenesis depends on the dynamic urinary microenvironment. We need to further understand the specific mechanisms and circumstances of sulfamethoxazole-induced urolithiasis so that we can focus on optimizing the urinary microenvironment rather than stopping this useful oral agent. These cases illustrate that longer courses of TMP/SMX may be associated with stone formation, so it would be prudent of providers to avoid extended use when able. Further, behavioral practices for stone prevention, such as adequate fluid hydration with a urine output goal of greater than 2.5 L daily, should be implemented if the inciting drug is unable to be discontinued for medical reasons.

4. Conclusion

Our patient's unique history of urolithiasis and recurrent UTIs contributes more information about the circumstances under which sulfamethoxazole stones form. However, the specific effects on the urinary microenvironment that lead to stone formation elude us. Further research into sulfamethoxazole-induced urolithiasis is needed and extended and repeated use of TMP/SMX for prophylaxis and treatment should be considered carefully, especially in patients with chronic and recurrent infections, in light of this rare, iatrogenic complication.

Consent

Obtained from patient's son, health care proxy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

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