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

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A B S T R A C T

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 chloridehydrate, 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-acetyl sulfamethoxazole chloridehydrate 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-acetyl sulfamethoxazole.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...
administering 14 days of culture-directed TMP/SMX, she underwent
cystolitholapaxy and bilateral, staged ureteroscopy due to her comor-
bidity. 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 skil-
led 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 stones4
and pre-existing calculi and UTIs are risk factors for drug-induced
crystalluria.5

The most common management strategy employed in the case re-
ports 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 meta-
stable 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 microenvi-
ronment. 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 prac-
tices 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 con-
tributes more information about the circumstances under which sulfa-
methoxazole 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

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Declaration of competing interest

None.

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