



Endourology

100% N⁴-acetyl-sulfamethoxazole stone induced by Trimethoprim-Sulfamethoxazole in an HIV patient being treated for toxoplasmosis

Matthew S. DeMasi^{a,*}, Ari P. Bernstein^b, Michael Schulster^b, Mark V. Silva^b

^a Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, United States

^b Department of Urology, NYU Langone Medical Center, 222 East 41st Street New York, NY 10017, United States

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ABSTRACT

Trimethoprim-Sulfamethoxazole is a common antibiotic used to treat urinary tract infections, as well as a prophylactic agent in HIV patients with low CD4 counts. Exceedingly rare are stones consisting purely of its metabolite, N⁴-acetyl-sulfamethoxazole, and management strategies are not well documented in the literature. We present a case of a patient with HIV who was found to have obstructing ureteral calculi composed of 100% N⁴-acetyl-sulfamethoxazole. Our report contributes a unique case of a Bactrim-induced stone in an immunocompromised patient. Similar patients can be prophylactically treated with diuresis and urinary alkalinization, as well as consideration for alternative medication use.

1. Introduction

Bactrim, or Trimethoprim-Sulfamethoxazole, is a common antibiotic used to treat urinary tract infections. The drug is also an effective prophylactic agent against *Toxoplasma gondii* Encephalitis and *Pneumocystis* Pneumonia (PCP) in HIV/AIDS patients. Exceedingly rare are “Bactrim” stones consisting purely of its metabolite, N⁴-acetyl-sulfamethoxazole.¹ We present a case of a patient with HIV on Bactrim prophylaxis who was found to have obstructing ureteral calculi composed of 100% N⁴-acetyl-sulfamethoxazole.

2. Case presentation

The patient was a 43-year-old man with a past medical history of poorly controlled HIV (on Bactrim prophylaxis and Biktarvy HAART therapy: bictegravir, emtricitabine, tenofovir) and Type 2 Diabetes Mellitus who was found to have biopsy-confirmed toxoplasmosis after presenting to the ED with seizures. This was treated with pyrimethamine and sulfadiazine; however, he was concurrently found to be febrile with an obstructing stone after an acute onset of right-sided flank pain during the same admission. The patient was immediately started on broad spectrum antibiotics.

Non-contrast computerized tomography (CT) scan showed a 5 mm

calculus in the proximal right ureter and a 1.1 cm calculus in the right ureterovesical junction with moderate right-sided hydro-ureteronephrosis (Fig. 1). There were no left sided stones or hydro-nephrosis. Patient was febrile to 102F though other vitals were within normal limits. Physical exam was significant for mild right costovertebral angle tenderness, and labs were significant for a Creatinine of 2 (baseline 0.7), a urinalysis with squamous cells and likely contaminated, and a CD4 count of 37.

The patient underwent emergent cystoscopy with bilateral ureteral stent placement. During the operation, stones were visibly orange and soft. Stone fragments were collected and sent for analysis, which revealed a 100% N⁴-acetyl-sulfamethoxazole stone.

The patient was switched from Bactrim to Atovaquone for continued PCP prophylaxis in the setting of Bactrim-related stone formation. At follow up bilateral ureteroscopy several months later, no stones were visualized and the patient underwent uncomplicated bilateral ureteral stent exchange.

4. Discussion

Although rare, sulfonamides are known to provoke urolithiasis by causing intratubular crystallization of the drug.^{1,2} According to a study by Albala et al., most develop symptoms 1–4 weeks after drug initiation

* Corresponding author. Department of Urology, Albert Einstein College of Medicine 1912 Lurting Avenue Bronx, NY 10461, United States.

E-mail addresses: matthew.demasi@einsteinmed.org (M.S. DeMasi), ari.bernstein@nyulangone.org (A.P. Bernstein), michael.schulster@nyulangone.org (M. Schulster), mark.silva@nyulangone.org (M.V. Silva).

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Fig. 1. Moderate right-sided hydronephrosis with a 1.1cm distal ureteral stone.

with the bladder being the most common location for stone formation.²

Following absorption, sulfonamides are acetylated in the liver and then eliminated via the kidney.² Precipitation depends on the urine drug concentration, the degree of acetylation, and urinary stasis, as well as the urine pH and temperature. Pre-existing processes like urinary tract infections or obstruction can predispose to precipitation at lower dosages or durations.^{1,2} The incidence of sulfonamide-induced stone formation has notably decreased as sulfonamides have been developed with greater solubility, which has reduced crystallization and thus renal complications.¹ Sulfamethoxazole, in particular, can be associated with crystalluria but is rarely responsible for obstructive uropathy, with only a select few case reports of Bactrim-induced urolithiasis.^{1,3} The losangic shape of the crystals does not favor crystal retention within the kidney, and therefore it is extremely rare to see stone formation secondary to precipitation of this compound, especially in a pure state such as discovered in our patient's stone analysis.¹

Sulfamethoxazole is a component of Bactrim, or Trimethoprim/Sulfamethoxazole, with its primary metabolite N⁴-acetyl-sulfamethoxazole. Our patient was being treated with Bactrim for PCP prophylaxis in the setting of poorly controlled HIV with low CD4 counts. His disease process was evidently poorly controlled, reflecting a chronic inflammatory state that perhaps lowered his threshold for drug-induced stone formation. We were unable to obtain information on the duration of the patient's Bactrim prophylactic therapy as the patient himself was unaware and it was not well-documented in his clinical notes. Perhaps a recent and acute change in the characteristics of the patient's urine, either volume or acidity, could have promoted precipitation of this Bactrim metabolite during his hospital stay for seizure management.

This case is notable for the purity and rarity of the stone analyzed, as well as the young age of the patient. Prior reports describe men who were older or tetraplegic, which are common predispositions toward infection or urinary stasis which could influence stone development.^{3,4} Siegel et al. described an elderly patient with oliguria who had a 5 mm N⁴-acetyl-sulfamethoxazole stone after being treated with Bactrim for chronic prostatitis 2 weeks prior; however, he also presented with a concomitant obstructing calcium oxalate stone in the contralateral ureter.⁴ Rince et al. also described a case of an N⁴-acetyl-sulfamethoxazole stone; the patient was a middle-aged man with flaccid tetraplegia

secondary to trauma, who presented with persistent urinary tract infections. He was administered Bactrim numerous times over a few months, and later presented with calculi. However, unlike our patient, these stones were also composed of uric acid and calcium oxalate.³

There is currently no standard regimen for treating sulfonamide-related renal complications, likely given the rarity of these events in clinical practice and the absence of quality literature on their management. Urinary alkalization and diuresis are considered the therapy of choice due to the increased solubility of sulfonamides at an alkaline pH. Early ureteral stenting or nephrostomy tubes may often be necessary if there is obstruction, inflammation, or risk of renal impairment.² Additional preventative measures include terminating drug usage or changing therapy at any sign of symptomatic stone burden or renal dysfunction. Patients on Bactrim should be encouraged to increase fluid intake, and urinary alkalization may be used to increase the solubility of the drug in the urine.^{1,2} Bactrim should be avoided in those with chronic urinary stasis or foreign bodies within the bladder; if necessary, such patients should be encouraged to maximize hydration and should be considered for urinary alkalization.³

5. Conclusion

Bactrim stones are extremely rare to crystallize and cause obstruction; this case is notable for the rarity and purity of the stone analyzed, as well as the young age of the patient as prior reports have discussed older and tetraplegic patients. Our report thus contributes a unique case of a Bactrim-induced stone in an immunocompromised patient. Similar patients can be prophylactically treated with diuresis and urinary alkalization, as well as consideration for alternative medication use.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying image. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Disclosure statement

No competing financial interests exist.

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Declarations of interest

None.

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