Sulfasalazine is an anti-inflammatory agent commonly used in the treatment of autoimmune conditions such as inflammatory bowel disease and rheumatoid arthritis. Sulfasalazine is converted by gut bacteria into sulfapyridine and the clinically active metabolite 5-aminosalicylic acid (5-ASA), and its efficacy is proportional to the 5-ASA concentration within the intestinal lumen. Renal complications are commonly reported for the chemically similar 5-ASA derivative mesalamine, but are not well-known side effects of sulfasalazine therapy. We report a 72-year-old patient with Crohn's disease managed with sulfasalazine for more than 10 years who presented with severe acute kidney injury (serum creatinine, 9.7 mg/dL). Renal ultrasound revealed calculi and he subsequently spontaneously voided innumerable stones, which were composed of sulfasalazine metabolites. His renal calculi cleared and serum creatinine concentration improved to 3.1 mg/dL after discontinuing sulfasalazine therapy and intravenous fluid hydration. His kidney function eventually returned to baseline. This case demonstrates that renal complications, in particular nephrolithiasis, may be an under-reported but potentially serious phenomenon in patients with inflammatory bowel disease treated with sulfasalazine and that their hydration status may play an important role in this process.

INDEX WORDS: Sulfasalazine; inflammatory bowel disease (IBD); Crohn's disease; kidney stones; crystalluria; acute kidney injury (AKI); nephrolithiasis; renal calculi; adverse effect; case report.

Sulfasalazine is generally well tolerated and, unlike mesalamine, is not commonly associated with renal
complications. We present a case of severe kidney failure due to massive crystalluria in a patient with Crohn’s disease who had been treated with sulfasalazine stably for more than 10 years.

CASE PRESENTATION
Clinical History and Initial Laboratory Data
A 72-year-old man with a history of Crohn’s and Parkinson diseases was admitted to the general medicine service after he was noted to be confused at his nursing home and routine laboratory test results revealed an elevated serum creatinine concentration. He denied constitutional symptoms, but nursing home staff reported that the patient had felt unwell for 4 to 5 days before presentation, with decreased oral food and liquid intake and reduced urinary output. He had no history of chronic kidney disease (CKD); prior imaging of the abdomen had revealed multiple renal cysts up to 5 cm in diameter that had been unchanged during the past 4 years. Home medications included carbidopa-levodopa, 25-100 mg, 4 times daily; donepezil, 10 mg/d; and sulfasalazine, 2,000 mg, 3 times daily, which he had been taking for approximately 10 years (full medication list in Item S1, available as online supplementary material).

Physical examination findings were notable for mild confusion and vital signs were unremarkable; notably, the patient did not have costovertebral angle tenderness. The patient’s admission laboratory test results were notable for creatinine concentration of 9.7 (reference range, 0.5-1.2 mg/dL, corresponding to estimated glomerular filtration rate (calculated with the CKD-EPI [CKD Epidemiology Collaboration] equation) of 4.8 mL/min/1.73 m²). His most recent previous creatinine value, recorded 3 months prior, was 1.0 mg/dL and had never been >1.1 mg/dL for the previous 8 years in his chart. Additional admission laboratory values included the following: potassium, 5.6 mEq/L; serum urea nitrogen, 67 mg/dL; sodium, 136 mg/dL; and bicarbonate, 21 mmol/L. Urinalysis, which was collected after he received ~1 L of intravenous normal saline solution, showed the following values: specific gravity, 1.008; protein, 30 mg/dL; pH 5.5; moderate white blood cells; moderate leukocyte esterase; and moderate blood; no eosinophils or casts were identified. Automated urine microscopy identified amorphous crystals (1+) and uric acid crystals (4+). Serum sodium concentration at this time was 136 mg/dL, and urine creatinine and sodium concentrations and osmolality were 68 mg/dL, 57 mmol/L, and 260 mOsm/kg, respectively, corresponding to fractional excretion of sodium of 5.5%. He was admitted to the internal medicine service and kept his oral and intravenous fluid intake). Within 12 hours, he was noted to void small stones painlessly through the urethra. Im- munerable small cream-colored stones measuring 0.5 to 2 mm were collected in the urinal (Fig 2B). Serum creatinine concentration at this time was 6.5 mg/dL. He continued to pass approximately 100 of these stones during the next 24 hours. The stones were collected, washed in normal saline solution, crushed, and examined via light microscopy (Fig 2C). Macroscopically, the stones resembled N-acetylsulfadiazine (see Fig 19-2(a) of Nagaraja et al), and microscopically, the crystals had poor resemblance to uric acid or oxalate crystals, but a close resemblance to indinavir crystals. The stones were sent off-site for Fourier Transform Infrared (FTIR) calculi analysis, which revealed that the stones were composed of acetylated sulfapyridine compounds (metabolites of the sulfasalazine derivative sulfapyridine), primarily acetylated 2-sulfanilamidopyrimidine (Fig S1). The patient’s kidney failure was attributed to precipitation and crystallization of sulfasalazine metabolites within his urinary collecting system.

Clinical Follow-up
The patient was discharged 1 week after admission when his serum creatinine concentration was 3.1 mg/dL (estimated glomerular filtration rate, 19.1 mL/min/1.73 m²) and serum urea nitrogen concentration was 28 mg/dL; sulfasalazine therapy was discontinued. Follow-up laboratory tests were ordered to evaluate for further improvement in kidney function, but the patient did not keep this appointment. However, he was readmitted to the hospital 6 months later after a fall at his nursing home. Sulfasalazine therapy had never been restarted, and his creatinine concentration was 0.95 mg/dL (estimated glomerular filtration rate, 79.6 mL/min/1.73 m²) at presentation (Fig 1).

DISCUSSION
Acute kidney injury is an infrequently reported complication in patients treated with sulfasalazine. This case demonstrates the dramatic extent to which sulfasalazine may induce nephrolithiasis and the severity of kidney injury that may ensue. Due to the vast quantity of stones collected (estimated at ~20 g), we concluded that stone formation had taken place over a long period and that this patient’s acute kidney injury at presentation was due to an obstructive uropathy. The quantity of stones recovered, visualization of hydropnephrosis, and lack
of urine eosinophils or casts, which would have suggested acute interstitial nephritis or acute tubular necrosis, respectively, altogether supported an obstructive cause. Of note, hydronephrosis was visualized via ultrasonography only on the right kidney, but numerous echogenic foci were identified within both kidneys. We therefore surmised that calculi within the renal calyces and/or pelves contributed to obstruction, together with the innumerable stones that were almost certainly present in the ureters and bladder.

Dehydration and low urinary pH are both risk factors for sulfonamide stone formation, and this patient’s history of poor oral fluid intake before presentation likely contributed to his acute decompensation. His rapid improvement, as well as the subsequent voiding of renal calculi after intravenous hydration, further suggests that adequate hydration is crucial to both prevent and treat sulfasalazine-derived calculi. This is of particular importance in patients with IBD who may experience significant gastrointestinal fluid losses.

Sulfasalazine is a commonly used anti-inflammatory agent in IBD and is generally well tolerated, with the most common side effects involving gastrointestinal upset/nausea and vomiting, rash/skin discoloration, fever, and macrocytosis. Renal complications are not generally associated with sulfasalazine, in contrast to other sulfonamide-based compounds, such as the antimicrobial sulfadiazine or the 5-ASA–containing mesalazine, both of which are known to predispose to nephrolithiasis.

Published side-effect profiles of mesalazine and sulfasalazine highlight the lack of association between sulfasalazine with acute kidney injury. Mesalazine is a newer alternative to sulfasalazine that releases 5-ASA in a pH-dependent manner and has an overall more favorable side-effect profile. However, it is strongly associated with renal complications, most commonly interstitial nephritis, but also renal calculi. A review comparing serious adverse reactions to mesalazine and sulfasalazine identified 393 and 514 adverse reactions per million prescriptions for mesalazine and sulfasalazine, respectively, over a 7-year period. Whereas 23% of adverse reactions to mesalazine involved the kidneys, there were no serious renal complications reported for sulfasalazine. Most adverse reactions to sulfasalazine involved the hematopoietic system (75%), followed by hepatic (15%) and dermatologic...
(11%) issues.15 Although interstitial nephritis,18-20 nephrolithiasis,21,22 and renal tubular acidosis,23 have been reported for sulfasalazine, the lack of association of sulfasalazine with renal complications in large-scale studies suggests that sulfasalazine-induced kidney injury is potentially under-reported or under-recognized.

The under-recognition of sulfasalazine-induced nephrolithiasis may be explained in part by the very common association of IBD and calcium oxalate stones. Calcium oxalate stones in patients with IBD are thought to result from intestinal inflammation causing malabsorption of bile salts and fatty acids that leads to increased oxalate absorption and subsequent hyperoxaluria.24 Oxalate stones were initially suspected in this patient, and it was not until calculi analysis was completed that sulfasalazine was unexpectedly identified as the cause of the stones. Based on the lack of literature association of sulfasalazine with nephrolithiasis and the common association of IBD and calcium oxalate stones, it is likely that nephrolithiasis in patients with IBD treated with sulfasalazine may be incorrectly attributed to oxaluria, especially if calculi analysis is not performed.

Of note, renal calculi composed of sulfadiazine metabolites have been reported to exhibit particularly low attenuation on computed tomography and be poorly visualized on ultrasonography.25 Our visualization of few echogenic foci on renal ultrasonography compared with the vast quantity of stones collected is consistent with these reports. This suggests that failure to observe renal calculi radiographically in a sulfasalazine-treated patient should not exclude sulfasalazine-induced crystalluria from the differential diagnosis.

In summary, sulfasalazine-induced nephrolithiasis is an uncommon but potentially under-recognized complication of sulfasalazine therapy that should be considered in any patient treated with sulfasalazine who presents with acute kidney injury. Calculi analysis should be obtained before oxalate stones are diagnosed in such sulfasalazine-treated patients with IBD, after which the decision to continue or stop sulfasalazine therapy should be made. This patient’s return to normal kidney function indicates that kidney prognosis can be good after discontinuation of sulfasalazine therapy and prompt treatment with intravenous hydration. Early awareness of this process may facilitate proper therapy, as well as urologic management when necessary.

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SUPPLEMENTARY MATERIAL

Figure S1: FTIR spectrum of renal calculus and calculi analysis. Item S1: Outpatient medications and radiology report.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2017.05.013) is available at www.ajkd.org

REFERENCES


