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Mesalazine-induced renal calculi

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 32
Final Diagnosis: Renal colic
Symptoms: Acute colic pain • macrohematuria
Medication: Mesalazine
Clinical Procedure: CT scan of urinary tract • cystoscopy • gynecological consultation • stone analysis
Specialty: Gastroenterology and Hepatology • Clinical Pharmacology

Objective: Unexpected drug reaction

Background: Mesalazine, a 5-aminosalicylic acid compound, is one of the cornerstones in modern treatment regimens of ulcerative colitis. It is generally well tolerated, although adverse reactions such as nephrotoxicity, perimyocarditis, and pancreatitis have been reported.

Case Report: We report the case of a 32-year-old woman with colitis who developed recurrent episodes of renal colic after introduction of mesalazine to her treatment. Biochemical analysis of the stones showed that they were composed of crystalized drug material.

Conclusions: To our knowledge this is the first report of mesalazine precipitation in the urinary tract. We believe that it is vital for physicians to recognize this potentially severe adverse effect in the use of this treatment.

Key words: mesalazine • adverse reaction • IBD • renal calculi

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Background

Mesalazine is generally recognized to be effective and safe to use in the treatment of ulcerative colitis. Introduced in 1985, this 5-aminosalicylic acid (5-ASA) compound is today commonly used as first-line treatment for mild to moderate cases. Mesalazine is effective both for induction and maintenance of remission of the disease. Its relatively low frequency of systemic adverse effects is most likely because of its bowel-specific metabolism. Severe reactions have been reported in small numbers, such as perimyocarditis, nephrotoxicity, hepatitis, pancreatitis, alveolitis, and blood dyscrasias [1]. We present a case of recurrent renal stone formation in a patient with ulcerative colitis treated with 5-ASA. Analysis of the calculi showed congregates of mesalazine. This condition has not previously been reported in the literature. The patient's informed consent was obtained prior to the writing of this article.

Case Report

A 32-year-old female patient recently diagnosed with ulcerative colitis was prescribed oral mesalazine for a flare-up of her disease. She did not have a past medical history significant for renal stones. Six weeks after initiation of the therapy, she presented at the emergency department with acute colicky pain in the right flank and periumbilical area. She also complained of urinary urgency. Physical investigation showed tenderness of the right costovertebral angle. A urine analysis was positive for blood, protein, and leucocytes. The patient was afebrile and a complete blood count was within normal limits. The attending clinician suspected upper urinary tract infection and prescribed oral ciprofloxacin. The patient, however, returned to the hospital after just 1 day in obvious distress. The pain resolved spontaneously while waiting for new blood sample results. The patient was sent home and a computer tomography of the urinary tract was ordered, which showed no concrements or dilatation of the ureters. Cystoscopy was performed, with normal findings. Gynecological consultation was also ordered due to suspicion of endometriosis, but with negative results. During the course of 3–4 months, the patient experienced a total of 11 episodes of severe pain over the flanks and lower abdomen, all with concomitant macroscopic hematuria. On several occasions she passed concrements in the urine, the biggest being 6–7 mm. The stones varied from round to pellet-shaped, were yellowish-brown in color, and crumbled easily. They were sent for chemical analysis. Initial results from a laboratory in Jönköping, Sweden were inconclusive regarding the composition of the stones. Further testing at a center in Orlando, Florida demonstrated composites of mesalazine. After discontinuing mesalazine, the patient's symptoms of obstructive renal disease disappeared. Her renal function remained normal throughout the course of the disease.

Discussion

Patients with inflammatory bowel disease have a higher risk of renal calculi than the general population, the incidence being about twice as high as for normal subjects [2]. These calculi are generally composed of calcium oxalate, but uric acid concrements have also been reported. The increased risk of stone formation is believed to be due to a combination of different factors, including lower urine output due to volume depletion and diarrhea, decreased uptake of stone-inhibiting substances such as citrate and magnesium, and bicarbonate loss leading to more acidic urine [2,3].

Renal stone formation by the precipitation of a drug or one of its metabolites has been described for certain medicines. It has been estimated that 0.44% of all renal stones are formed in this manner [4]. A small number of patients with ulcerative colitis presenting with sulfasalazine-induced urolithiasis has been reported. The calculi were composed of sulfapyridine in all cases, a metabolite specific to this drug [5]. Other sulfa-containing drugs have also been reported to precipitate in the urinary tract, as well as magnesium trisilicate, ciprofloxacin, triamterene, indinavir, and ephedrine alone or in combination with guaifenesin [4].

Our patient had calculi that were not visible on computer tomography. The only stones previously known to have this quality are indinavir stones [6]. The lack of radiological findings caused uncertainty regarding the correct diagnosis, leading to further investigations and significant delay.

Stone analysis showed that they were composites of the patient's 5-ASA medication. We searched the literature for similar cases but no reports on the subject were found. The website eHealthMe, which allows patients to self-report diseases and use of medication, has 32 reports of kidney stones among patients who were under treatment with mesalazine. There is no information on the website about the association between the kidney stones and mesalazine, and no information about the type of kidney stones the patients had. Many of the patients also had comorbidity and concurrent treatment with other drugs, which makes it very difficult to draw any conclusions from the material [7].

Drug-induced urinary crystallization can present as interstitial nephritis [4]. Interestingly, rare cases of mesalazine-induced interstitial nephritis have been reported [8,9] but it is not known if precipitation of the drug could be part of the pathogenesis of this condition.

Conclusions

We describe a patient presenting with recurrent renal stone formation 6 weeks after initiation of mesalazine treatment

for ulcerative colitis. To our knowledge this is the first case report of stones formed by mesalazine products. The calculi were not visible on computer tomography, which prolonged the time to final diagnosis and caused considerable harm to the patient. We believe that awareness of the possible association between this medication and stone formation is important for clinicians in raising suspicion of obstructive renal disease in this patient group.

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