Mesalazine: A Novel Etiology For Drug-Induced Urinary Calculi

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We report the case of a 23-year-old woman treated by mesalazine for ulcerative colitis and who subsequently presented recurrent renal colic due to mesalazine urinary stones. This is the second case described in the literature. Mesalazine stones are soft, friable and have an orange-beige color. They are not visible on non-contrast computed tomography (CT). Their diagnosis is based on morpho-constitutional analysis and CT-urography. Patients treated by mesalazine who present renal colic should undergo CT-urography in order to make the diagnosis.

INTRODUCTION

Mesalazine or 5-aminosalicylic acid (5-ASA) is an anti-inflammatory agent used in inflammatory bowel disease management such as: ulcerative colitis, Crohn's disease, proctosigmoiditis, and ulcerative proctitis[1,2]. The marketing authorization in France has been issued in 1987 for the rectal route and in 1990 for the oral route[1]. Due to 5-ASA's short half-life (1 hour), very few side effects have been reported[1-3]. 5-ASA is metabolized into N-acetyl-5-aminosalicylic acid in the liver and the intestine[1,3]. Approximately 60% of the mesalazine is absorbed after oral ingestion, leaving the remainder available for topical action and excretion in the feces[1,3]. The absorbed N-acetyl-5-ASA is eliminated by the kidney[1,3].
Urinary side effects are rare (< 1:10000) and include renal insufficiency, acute or chronic interstitial nephritis, nephrotic syndrome and urine discoloration[1,4,5].
We report, thereafter, the case of a 23-year-old woman treated by mesalazine for ulcerative colitis who developed recurrent renal colic due to the formation of mesalazine stones in the urine. This side effect is not listed in the drug's characteristics[1,4]. Only one previous case has been described in 2013[6].

CASE REPORT

A 23-year-old woman diagnosed for an ulcerative colitis 4 years ago was treated daily by prednisone 10 mg, oral mesalazine 4 g, rectal mesalazine 500 mg, potassium chloride and calcium carbonate. She had no history of other diseases and especially no urolithiasis. After two years of mesalazine treatment, she presented with an acute col-

Figure 1. Macroscopic appearance of mesalazine stone.

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icky pain of the left flank radiating to the groin without any antalgic position. The patient was nauseous and remained afebrile. The pain regressed with non-steroidal anti-inflammatory (NSAID) and antispasmodic treatments. Non-contrast enhanced computed tomography (NCCT) was normal (no dilatation of the renal tract and no visible stone).

One year later, she presented a recurrence of the left renal colic. Another NCCT was performed and did not show any dilatation of the renal tract and no visible stone. The blood exams were normal except a mild thrombocytosis and a mild CRP increase (47 mg/L), relating to her inflammatory bowel disease. The creatinine level was 84µmol/L (CKD-EPI clearance = 84 mL/min/1.73 m^2). Eventually, she spontaneously expulsed a stone in her urine. The stone was soft, crumbly and orange-beige color (**Figure 1**). Morphological analysis and infrared spectrophotometry were performed by Biomnis Laboratory (Lyon, France). The infrared spectrum revealed a 100% mesalazine composition. Hyperhydration was recommended to the patient. Mesalazine treatment was continued. Eleven month later, there was no recurrence.

DISCUSSION

The incidence of urolithiasis is increasing in industrialized countries. Its prevalence in France is estimated at 10% [7]. Drug-induced stones represent more than 1% of renal stones in France[8] but their frequency is probably underestimated in other papers[9]. Two mechanisms can explain their constitution[8,9]. The first is the metabolic disorders induced by the drug, which can lead to a urinary environment more favorable for lithiasis formation. The second is the crystallization of the metabolites of the drug in the urine. The inducers of urolithiasis by crystallization are sulfasalazine[10], triamterene, sulphonamides, ciprofloxacin, but the most often involved drug is indinavir, an anti-protease used in anti-HIV triple therapy[11].

The first case of mesalazine urinary stone was reported in 2013[6]. The patient was a 32-year-old woman diagnosed with ulcerative colitis. Several weeks after the initiation of the mesalazine treatment, she presented with recurrent renal colic. No stone and no dilatation of the renal cavities were visible on the NCCT. The analysis of the stone revealed mesalazine lithiasis. Urinary symptoms disappeared after mesalazine discontinuation.

Mesalazine stones are radiotransparent on both radiography and CT. Their soft consistency may explain the absence of complete obstruction of the urinary tract and therefore the absence of dilation of the renal cavities on the CT. A CT-urography might be the most appropriate imaging to confront the lack of opacification. Indeed, other examinations are possible like intravenous pyelography, retrograde ureteropyelography, or even the ureteroscopy, however, they are likely to delay the diagnosis and, for the last two, have surgical and anesthetic risks.

Rare cases of acute and chronic interstitial nephritis caused by mesalazine have been reported[4]. It could be an extra-intestinal manifestation of the inflammatory bowel disease[12]. A drug may cause kidney failure by different mechanisms but their responsibility is difficult to prove[13]. The pathophysiology of these interstitial nephritides is unknown. This observation suggests that precipitation of mesalazine in renal tubules may play a role in their occurrence.

CONCLUSIONS

Mesalazine can precipitate in urine and induce repeated renal colic. Mesalazine stones are not visible on NCCT and may not cause any renal dilatation. Patients treated by mesalazine should undergo CT-urography in case of renal colic. Subsequently, infrared spectrophotometry will confirm the nature of stone.

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