CASE REPORT

Recurrent nephrolithiasis associated with atazanavir use

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SUMMARY

A 64-year-old man with HIV on antiretroviral therapy (including atazanavir, a protease inhibitor) presented with left flank pain, nausea and vomiting. A kidney stone was suspected, and a CT scan demonstrated left hydronephrosis but failed to demonstrate nephrolithiasis or extrinsic compression. The patient had a ureteral stent placed which relieved his symptoms. A few months later, he underwent left ureteroscopy and a large ureteral calculus was found. The stone was removed and analysis showed 43% atazanavir and 57% calcium oxalate. Several months later, the patient developed flank pain on the opposite side. A renal ultrasound suggested right-sided nephrolithiasis and he subsequently underwent ureteroscopy with laser lithotripsy of two stones. Stone analysis showed that they were composed of 100% atazanavir. This case highlights the fact that patients treated with protease inhibitors remain at risk for developing nephrolithiasis. Ultrasonography can be a useful diagnostic tool in the setting of these radiolucent calculi.

BACKGROUND

Indinavir and atazanavir—protease inhibitors used in the management of HIV—have been associated with an increased risk of nephrolithiasis. Indinavir has been shown to precipitate in urine and is associated with nephrolithiasis in up to 22% of patients.^{1 2} Similar to indinavir, of which 19% is excreted unchanged in urine, approximately 7% of atazanavir is excreted unchanged in urine.³ The aetiology of nephrolithiasis associated with atazanavir is not well understood but reports have demonstrated that atazanavir is associated with a higher rate of nephrolithiasis than other antiretroviral agents.^{4 5} In addition, several studies have shown that the compound itself contributes to stone composition.^{6–9} Comparable to stones primarily composed of indinavir, atazanavir stones can be radiolucent and therefore can pose a diagnostic challenge from the radiological perspective.⁶ In an effort to increase the awareness of this entity and to improve the management of atazanavir stones, we present a case report of an individual with recurrent atazanavir-associated nephrolithiasis.

CASE PRESENTATION

The patient is a 64-year-old African-American man who was diagnosed with HIV in 1990. His medical history includes hepatitis C, chronic renal insufficiency, hypertension, type 2 diabetes mellitus and asthma. He did not have a personal or family history of kidney stones. The patient was started on

Epzicom (abacavir and lamivudine), atazanavir and ritonavir therapy in 2007. He had an abdominal ultrasound in 2008 to evaluate his liver for possible cirrhosis. This study showed no evidence of nephrolithiasis. In November 2010, the patient had an episode of gross haematuria and was empirically treated with antibiotics for a presumed urinary tract infection based on urinalysis. His haematuria resolved and haematuria work-up including CT scan and cystoscopy was negative. In January 2012, the patient presented to the emergency department with left flank pain, nausea and vomiting.

INVESTIGATIONS

Initial work-up revealed a creatinine of 2.42 mg/dL, a white cell count $15.4 \times 10^3/\mu\text{L}$ and a urinalysis showing microscopic haematuria. A CT scan of the abdomen and pelvis demonstrated left hydroureteronephrosis down to the pelvic brim. However, no stone or evidence of extrinsic compression was found (figure 1).

TREATMENT

The patient underwent cystoscopy and placement of a left ureteral stent. No stone was visualised on fluoroscopy or on retrograde pyelogram. Several months later, the patient underwent left ureteroscopy with holmium laser lithotripsy of a large obstructing, radiolucent stone in the distal ureter. Stone analysis showed 43% atazanavir and 57% calcium oxalate monohydrate (figure 2A). The atazanavir was discontinued in January 2012 and was replaced with darunavir.

OUTCOME AND FOLLOW-UP

In October 2012, the patient reported new right flank pain with a renal ultrasound demonstrating two shadowing echogenic areas consistent with nephrolithiasis in the right kidney. Of note, these stones were not seen on the CT scan 10 months prior or during intraoperative fluoroscopy for his previous contralateral procedures. He subsequently underwent right ureteroscopy with holmium laser lithotripsy of the two stones in the right kidney. The stones were easily fragmented and stone analysis showed that they were composed of 100% atazanavir (figure 2B). The patient underwent 24 h urine collection showing a pH 6.8, mild hyperoxaluria and hypercitrauria. The patient has not reported any further episodes of renal colic at 1 year of follow-up.

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Figure 1 Selected CT images from January 2012 showing hydroureteronephrosis with no calculus visualised. (A) Left hydronephrosis with perinephric stranding; (B) left hydroureter (green arrow) with no evidence of calculus.

DISCUSSION

Nephrolithiasis associated with atazanavir treatment has been described in several case reports and in small retrospective series. Chan-Tack *et al* reported on 30 cases of atazanavir stones in patients who received the medication for a median of 1.7 years (range 5 weeks–6 years). The authors found that the majority of stones analysed contained atazanavir, ranging from 40% to 100% of the total stone composition.⁷ Some of these patients were diagnosed solely by clinical findings or urine/stone analysis, whereas others had stones visualised on CT or ultrasonography.⁷ Hamada *et al*⁴ compared the incidence of nephrolithiasis in patients receiving atazanavir with those receiving other protease inhibitors and found that atazanavir was associated with a substantially higher rate of stone formation and that discontinuation of atazanavir resulted in no further stone formation. It has been suggested that patients with low water intake, higher urinary pH, a history of nephrolithiasis or impaired metabolism of atazanavir

(eg, in hepatic dysfunction) have a higher rate of stone formation while on this medication.^{2–5} While stone formation appears to cease after discontinuation of atazanavir in the majority of cases, Rockwood *et al*⁵ described several cases of nephrolithiasis after discontinuation of atazanavir, including one with evidence of atazanavir in the stone analysis.

In this case, the patient was initially diagnosed with nephrolithiasis based on his overall clinical presentation despite negative radiological findings. His first episode of renal colic was 5 years after initiation of atazanavir treatment. However, he did have an episode of asymptomatic gross haematuria 2 years prior with a negative urological evaluation. His second episode of renal colic occurred 10 months after discontinuation of atazanavir but the stone composition in this case was 100% atazanavir. The elimination half-life of atazanavir is 7 h³ and therefore, formation of new stones many months after discontinuation of the medication is not likely. We suspect that the patient developed atazanavir

Figure 2 (A) Stone fragments retrieved from January 2012 presentation; (B) stone fragments retrieved from October 2012 presentation.

stones in the right kidney (second episode) prior to discontinuation of the medication and, thus, before treatment for his left-sided stone (first episode). The stones were radiolucent and therefore missed on the CT scan at the time of the first episode of renal colic. Similar to radiolucent indinavir stones, radiolucent atazanavir stones can escape detection on plain radiographs and CT scans but can be diagnosed by ultrasonography. A retrospective study of patients with indinavir stones demonstrated that while abdominal radiographs and CT scans showed no evidence of stones in 42–58% of patients, respectively, renal ultrasonography offered evidence of stones in 82% of patients,¹⁰ indicating that ultrasonography improves the diagnostic accuracy in radiolucent calculi. Similarly, patients on atazanavir or those with a history of atazanavir use who present with clinical signs or symptoms suspicious for nephrolithiasis would benefit from a diagnostic work-up including ultrasonography.

While this patient did not have a history of nephrolithiasis, he had other factors that may have predisposed him to atazanavir-associated nephrolithiasis. He had hepatitis C which may have impaired the hepatic metabolism of atazanavir and led to higher concentrations in the urine. In addition, the solubility of atazanavir is highly dependent on pH, with a maximal solubility at pH 1.9.² Therefore, his urinary pH 6.8 may have resulted in decreased solubility of this drug. Together, these factors likely contributed to formation of atazanavir stones in this individual. In conclusion, a higher index of suspicion and a proper imaging of atazanavir-associated kidney stones could have led to earlier diagnosis and treatment of this patient's condition and decreased the need for urgent intervention.

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Contributors LCW wrote and revised the manuscript. ECO provided the initial clinical analysis and contributed to drafting the manuscript. SGD developed the concept for this article and provided the interpretation and critical revision. JSR provided the interpretation and critical revision. All the authors approved the final version.

Competing interests None.

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Learning points

- ▶ Atazanavir is associated with an increased nephrolithiasis risk over other protease inhibitors in patients treated with highly active antiretroviral therapy for HIV.
- ▶ Consider other risk factors for atazanavir-associated stone formation—elevated urine pH, hepatic dysfunction, decreased fluid intake or a history of nephrolithiasis—when starting this medication.
- ▶ When patients taking atazanavir or those with a history of atazanavir use present with clinical signs or symptoms of nephrolithiasis, ultrasonography can be a useful diagnostic tool.

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