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Case Report

Ureteral Obstruction Due to Radiolucent Atazanavir Ureteral Stones

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Abstract

Background: Protease inhibitors (PIs) are a well-documented cause of nephrolithiasis. Although medications such as indinavir are known to increase risk of stone formation, the association of newer HIV medications is not as well studied. In this study, we report a case of a patient who developed atazanavir stones.
Case Presentation: A 74-year-old man with HIV on antiretroviral therapy—including atazanavir, a PI—presented with right flank pain. He previously had passed two ureteral stones that were not analyzed. A CT scan showed mild right hydronephrosis without evidence of nephrolithiasis or ureteral obstruction. The patient was presumed to have passed a stone and was discharged home. He returned one day later with persistent flank pain and acute kidney injury that did not improve with intravenous fluid hydration. A right ureteral stent was placed that relieved his symptoms. Subsequent ureteroscopy demonstrated bilateral ureteral stones that were basket extracted. Stone composition was 100% atazanavir. Since being switched off of this medication, the patient has not had any further episodes of renal colic and his renal function has improved to below his baseline level on presentation.
Conclusion: Patients treated with the PI atazanavir are at risk for developing nephrolithiasis and obstructive uropathy. Because these stones can be radiolucent on CT scan, a high level of suspicion is required to accurately diagnose ureteral obstruction in these patients. Alternative effective HIV treatment regimens can to be utilized when clinically indicated.

Keywords: atazanavir, nephrolithiasis, radiolucent, uropathy, HIV, highly active antiretroviral therapy

Introduction

Protease inhibitors (PIs) are associated with increased risk of nephrolithiasis. Traditionally, indinavir has been highlighted as one of the most common stone inducers. PIs are primarily processed by the liver while the remaining unmetabolized portion is excreted in the urine. Elevated PI concentrations in the blood lead to increased urinary excretion, which when coupled with the drug's insolubility at the physiologic pH of urine lead to urinary calculus formation. Although indinavir has been replaced by newer agents over the past 20 years, many of these PIs carry a similar risk of nephrolithiasis and obstructive uropathy.[1]

Case Presentation

A 74-year-old male presented with acute onset right flank pain in May 2015. He had been taking highly active antiretroviral therapy consisting of a reverse transcriptase inhibitor (Truvada or Epzicom) combined with ritonavir-boosted atazanavir (ATV/r) since 2006. He spontaneously passed two stones previous to this presentation, but neither was analyzed. Records showed he had a steadily rising baseline serum creatinine over the preceding 8 years, which had increased from an approximate level of 1.0 to 1.5 mg/dL.

Associated symptoms included nausea and decreased appetite. Physical examination demonstrated that he was afebrile with stable vital signs, and right costovertebral angle tenderness was present. Creatinine was 1.48 mg/dL, white blood cell count was $11.38 \times 10^3/\mu$L, and a urinalysis showed microscopic hematuria (50–100 red blood cells per high power field) but no evidence of infection (nitrite and leukocyte esterase negative). A CT scan showed mild right hydronephrosis with perinephric stranding but no evidence of a stone (Fig. 1A, B). His pain completely resolved with a single

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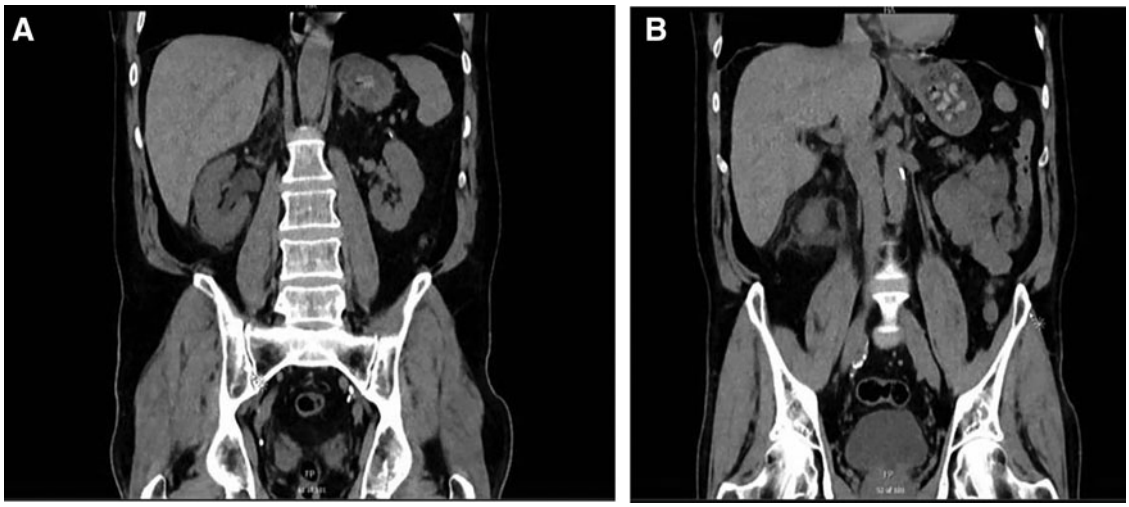

FIG. 1. **(A)** Right hydronephrosis with no visible source of obstruction on CT. **(B)** Significant right perinephric stranding.

15 mg dose of Toradol. It was felt that his pain was likely because of passed stone, so the patient was discharged home.

The patient returned the next day with recurrent right flank pain. Repeat evaluation revealed rising creatinine (2.08 mg/dL), slightly increased white blood cell count ($12.85 \times 10^3/\mu$L), similar urinalysis findings, and a renal ultrasonography showing unchanged right hydronephrosis and no evidence of a stone. His urine culture from the prior visit showed no growth. He was initially treated with IV hydration but when his creatinine did not improve, the decision was made to proceed to the operating room for cystoscopy and right ureteral stent placement.

The patient returned to the operating room after his renal function had stabilized. Bilateral ureteroscopy was performed to clear the urinary tract of any possible stone as we were concerned about medication-induced urolithiasis. Bilateral proximal ureteral stones were encountered and were basket extracted. The stones were soft, mucoid appearing, and tended to disintegrate during basketing attempts. After several passes with the ureteroscope and tipless basket, the stones and debris were cleared from the ureters and collecting system. Stone composition analysis revealed 100% atazanavir stones.

The patient was subsequently switched off of ATV/r to raltegravir, etravirine, and lamivudine. Since that time, more than 18 months ago, he has had no repeat episodes of renal colic. Renal ultrasonography at 6 months postoperatively showed no hydronephrosis, and his creatinine has returned to a baseline of 1.28 mg/dL.

Discussion

ATV/r and ritonavir-boosted darunavir (DRV/r) are the two PIs recommended as first-line choices in the U.S. Department of Health and Human Services and European AIDS Clinical Society guidelines for the initial treatment of patients infected with human immunodeficiency virus-1. Both DRV and ATV are noted in the European guidelines as carrying an increased risk of nephrolithiasis, and ATV and ritonavir are further identified as having a negative long-term impact on estimated glomerular filtration rate.

ATV/r is associated with a nearly 7% incidence of stone formation, which is one of the highest among PIs.[1] This is thought to be the result of a higher urinary excretion rate in unmetabolized form (7%) when compared with other PIs such as nelfinavir and amprenavir (3%).[1]

PIs are processed by the liver as a substrate of CYP3A that makes them vulnerable to inherited deficits in clearance and to drug–drug interactions, thus adding significant complexity to proper dosing to achieve a level within the desired therapeutic window. One study found that a significant proportion of patients treated with the traditional dosage of ATV/r (300/100 mg) had a plasma concentration exceeding the upper therapeutic threshold, thus putting them at risk for atazanavir-related complications such as nephrolithiasis.[2]

Reports of ATV-associated nephrolithiasis have been described in various case studies and small case series, sometimes leading to obstructive uropathy and worsening renal failure. In a few of these cases, as in our case, the patients had baseline chronic renal insufficiency that acutely worsened during their episode of renal colic, presumably because of obstruction by the stones. These cases did not detail when the renal function began to worsen or whether other comorbidities existed; but in our case, the chronic renal impairment happened gradually over an 8-year period after the patient was started on ATV/r.

Because PI-induced nephrolithiasis is often not associated with significant hydronephrosis and can be radiolucent on X-ray and CT imaging, as demonstrated in our case, it presents a significant diagnostic challenge. Renal ultrasonography has been useful in observing stones with 85% sensitivity in one study,[3] but in our case both CT and ultrasonography identified hydronephrosis but did not show a stone. In these scenarios, the diagnosis can be missed initially, placing patients at risk of worsening renal insufficiency and recurrent episodes of renal colic, leading to emergency room visits.

A high index of suspicion for nephrolithiasis is required when patients on PI therapy present with renal colic or acute renal insufficiency. To avoid these complications, alternative antiretroviral regimens should be considered. Smaller retrospective studies have shown a decreased incidence of nephrolithiasis PI regimens that avoid atazanavir[1]; however, these findings have not been shown in large population studies. PI-free regimens, in contrast, have been shown to

possibly reduce the risk of nephrolithiasis in a large 2014 U.S. population study.[4]

Conclusion

PIs can induce nephrolithiasis and acute kidney injury because of obstructive uropathy. This case report is an example of atazanavir-associated stones and how these stones can present a diagnostic challenge in patients presenting with renal colic. Specifically, atazanavir is known to increase the risk of nephrolithiasis more than other PI regimens. Owing to the diagnostic challenges associated with PI stones, patients on atazanavir could be better served to have levels checked to determine whether dose adjustment is necessary to avoid the known complications. Finally, patients who develop chronic renal insufficiency or who are at risk for nephrolithiasis on atazanavir should be considered for alternative antiretroviral regimens.

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Disclosure Statement

No competing financial interests exist.

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Abbreviations Used
PIs = protease inhibitors
ATV/r = ritonavir-boosted atazanavir
DRV/r = ritonavir-boosted darunavir

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