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Endourological management of a rare radiopaque ritonavir-composed urinary calculus

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ABSTRACT

Protease inhibitors are a source of nephrolithiasis in HIV + patients, and these stones are described as not detected by CT. While urinary stones are commonly associated with certain protease inhibitors, stones composed of ritonavir are rare. We present the case of a 58-year-old female on ritonavir-boosted atazanavir who presented to our clinic complaining of gross hematuria and flank pain secondary to a ureteral stone. Surgical removal revealed the stone to be composed of 100% ritonavir with no usual urinary stone components. This is the first report of an HIV medicine stone being detectable by CT scan described as 100% ritonavir.

Introduction

Protease inhibitors (PIs) have become integral to HIV treatment, but a well-documented side effect of these medications is drug-induced renal stone formation.[1,2] Nephrolithiasis represents an important cause of morbidity in this patient population, leading to significant renal dysfunction, drug discontinuation, pain, and invasive interventions. These stones are primarily composed of the PI and its metabolites, with most cases linked to the PIs indinavir and atazanavir.[1] While still documented, cases with other PIs are considered rare. Notably, the PI ritonavir is not traditionally considered a cause of renal calculi formation, as the majority of ritonavir-documented cases are composed of <5% of the drug itself.[1] At the time of this writing, only one other case report could be found showing a primarily ritonavir-composed stone, indicating the rarity of this phenomenon.[3]

All of these PI-related stones are described as radio-lucent on CT scan.[4] Here, we report the unique phenomenon of a pure ritonavir ureter stone with CT imaging and spectroscopy report. This is the first reported incidence of an HIV PI medicine forming stone that is detected by CT scan imaging. Additionally, this is the first known instance of such a stone presenting with symptoms over a decade after the initiation of a ritonavir-boosted atazanavir regiment.

Case presentation

Clinical history

The patient is a 58-year-old HIV + woman (diagnosed 26 years ago) with a complex medical history including chronic kidney disease, sickle cell trait, recurrent urinary tract infections, pyelonephritis and obesity but no prior history of known urolithiasis. Family history was significant for renal stones in her paternal grandmother and paternal cousin. Her viral load was well-controlled since 2008 on ritonavir-boosted atazanavir and raltegravir. She presented to her primary care physician with left flank pain and gross hematuria for one week.

Diagnosis

A CT abdomen/pelvis without IV contrast was performed showing mild left hydroureteronephrosis secondary to a 4 mm obstructing calculus in the proximal left ureter, as well as another non-obstructing 4 mm stone in the right lower pole (Fig. 1). Symptoms of flank pain and hematuria had resolved prior to CT scan, and she elected to undergo a trial of spontaneous passage over a month-long period.

At her return visit a month later, her hematuria had not returned but she now had acute left flank pain similar in quality to her prior episode.

Abbreviations: CT, computed tomography; PI, protease inhibitor; UVJ, uterovesicular junction; ATV/r, ritonavir-boosted atazanavir.

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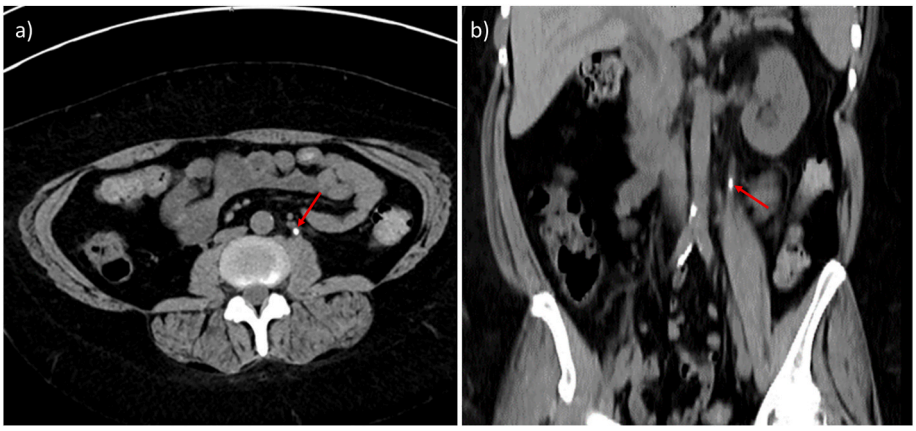

Fig. 1. CT abdomen/pelvis without IV contrast for subject presenting with gross hematuria and flank pain. a) axial scan b) coronal scan. Red arrows depict radio-opaque stone in the proximal left ureter. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

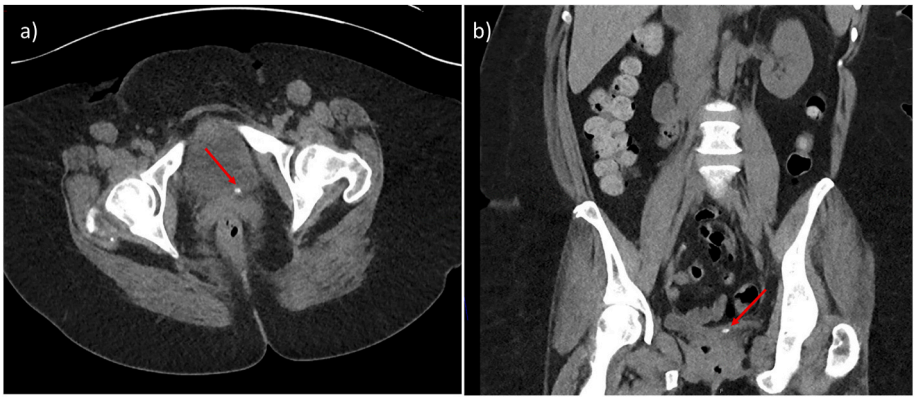

Fig. 2. Low dose CT abdomen/pelvis without IV contrast for subject presenting with gross hematuria and flank pain. a) axial scan b) coronal scan. Red arrows depict radio-opaque stone in the distal left ureter at the UVJ. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

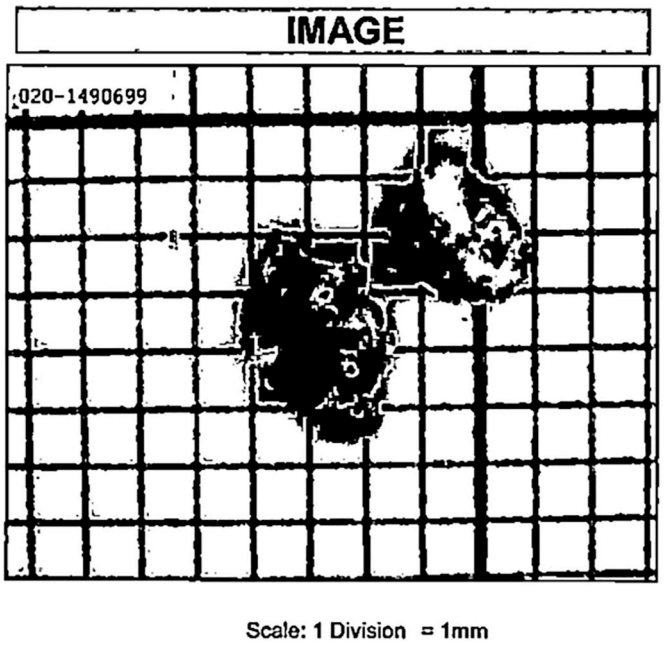

Fig. 3. Left ureteral stone fragment analysis by Quest Diagnostics using infrared spectroscopy. Report stated that the sample is composed of crystals resembling ritonavir.

A low-dose CT abdomen/pelvis without IV contrast showed the 4 mm left ureteral stone was now at the ureterovesicular junction (UVJ), with mean 400 Hounsfield units, and unchanged non-obstructing 4 mm renal stone in right lower pole, with an associated bump in creatinine from 1.20 to 1.70 (Fig. 2). Therefore, after discussion of risks and benefits, the patient opted for endoscopic intervention.

Intervention and follow-up

The patient underwent cystoscopy, left ureteroscopy, laser lithotripsy, basket extraction and stent placement. Pertinent operative findings included a left distal ureteral stone identified at the left UVJ with edema of the left ureteral orifice. Using a short semi-rigid ureteroscope, the stone was fragmented with 200-μm Holmium laser fiber and extracted with a zero-tip nitinol basket. A short-term 6 Fr x 26 cm left ureteral stent was placed without complication. Gross pathology described a 0.8 × 0.5 × 0.4 cm aggregate of brown irregular friable granular calculi. Analysis with infrared spectroscopy showed that the sample did not contain any constituents normally found in urinary stones and was instead composed of crystals resembling ritonavir (Fig. 3).

The patient's HIV drug regimen was subsequently changed to Combivir (lamivudine/zidovudine) and raltegravir, and to date, she has had no recurrence of symptoms.

Discussion

HIV anti-retroviral medications, specifically protease inhibitors, are the most common cause of drug-based kidney stone formation to date.[1,2] The anti-retroviral regimen of ritonavir-boosted atazanavir (ATV/r) has been shown to be associated with nephrolithiasis, even relative to other PI drugs.[2] However, when stone composition has been measured, these stones were composed primarily of atazanavir, ranging from 40 to 100% of this drug. Other mixed components of these stones have been described, often calcium phosphate, but not ritonavir, demonstrating the rarity of this phenomenon.[5] To date, there has been only one other case of a primarily ritonavir-based stone in the literature, also in a patient on a ATV/r regimen.[3]

This case challenges the dogma that CT scan imaging is "blind" to PI composed stones.[4] This stone was readily detectable on CT even when the composition was 100% ritonavir. This fact informs the clinician to include such types of stones in the differential diagnosis when assessing HIV patients on the medicine ritonavir presenting with nephrolithiasis.

Atazanavir is often given with ritonavir because ritonavir is a potent inhibitor of the cytochrome P450 system, allowing increased levels of atazanavir in an ATV/r regiment. While the mechanism of stone formation is poorly understood, it is thought that PIs that are partially renally-excreted, such as atazanavir and indinavir, can then precipitate in the urinary system.[1] On the other hand, PIs like ritonavir which have minimal renal excretion may be rarer causes due to lack of renal clearance.[1] Our patient had been on the ATV/r regiment for over a decade before presenting with a symptomatic stone, with the possibility that, over an extended period, ritonavir may have accumulated and led to stone formation. ATV/r urolithiasis with atazanavir-based stones has been shown to present around two years after regimen initiation, and most patients are switched to a different medication regimen,[1,2] potentially explaining this rarity of ritonavir-based stones in the literature. Forming a ritonavir stone a decade into treatment has never been described prior to this case.

Conclusion

We present the unique phenomenon of a 100% ritonavir-based urinary stone (2nd case ever reported) that most importantly was detectable by CT scan imaging (1st case ever reported). Furthermore, we have demonstrated that such a stone can occur even a decade into treatment with ritonavir which to our knowledge has also never been previously reported. This knowledge may contribute to our synthesis of the HIV patient on ritonavir presenting with nephrolithiasis.

Author disclosure statement

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Declaration of competing interest

None.

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