Protease Inhibitor-Induced Nephrolithiasis

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A 37-year-old man presented with a 10-day history of right flank pain, which he described as cramping and constant but with variable intensity. He had also episodic nausea and vomiting and several episodes of blood-tinged urine. He was seen at an outside facility several days prior and underwent renal ultrasonography, noncontrast computed tomography (CT), and magnetic resonance imaging (MRI), the results of which were reportedly normal except for the presence of mild right hydronephrosis. He had a history of mild renal disease and HIV infection. His medications included ritonavir-boosted atazanavir, emtricitabine, and tenofovir.

EXAMINATION AND DIAGNOSTIC TESTS

At presentation, the patient's temperature was 36.9°C, his pulse was 63 beats/min, and his blood pressure was 119/99 mm Hg. His abdomen was flat, soft, and nontender to palpation. He had mild right costovertebral angle tenderness.

Laboratory test results included a peripheral white blood cell count of 6100/µL.

Table 1. Characteristics of Imaging Modalities for Nephrolithiasis[1,2]

Modality	Advantages	Disadvantages	Difficult-to-Visualize Stones
Plain film	Wide availability Low cost Minimal radiation Rapid	Low sensitivity (45%-58%) Lack of anatomic detail Does not assess obstruction Limited by patient body habitus, overlying bowel gas, and extra-renal calcifications	Uric acid Matrix Protease inhibitor Triamterene Xanthine Pseudoephedrine/guaifenesin
Ultrasonography	Wide availability Low cost No radiation May detect hydroureter and hydronephrosis	Variable sensitivity Poor at finding ureteral stones and small renal stones	Ureteral stones (particularly mid-ureter) Small (<5 mm) renal stones
Noncontrast CT	Highest sensitivity and specificity Good availability Can determine stone density, size, location, and obstruction Good anatomic detail Rapid	High radiation dose High cost Incidental findings	Protease inhibitor
MR Urography	No radiation Good anatomic detail Can assess obstruction	Limited experience and availability High cost Time consuming Stones are not directly detected (stones, blood clots, and tumors appear as signal void) Small stones may be difficult to visualize	Small (< 5mm) stones Cannot differentiate stones from tumor or clot

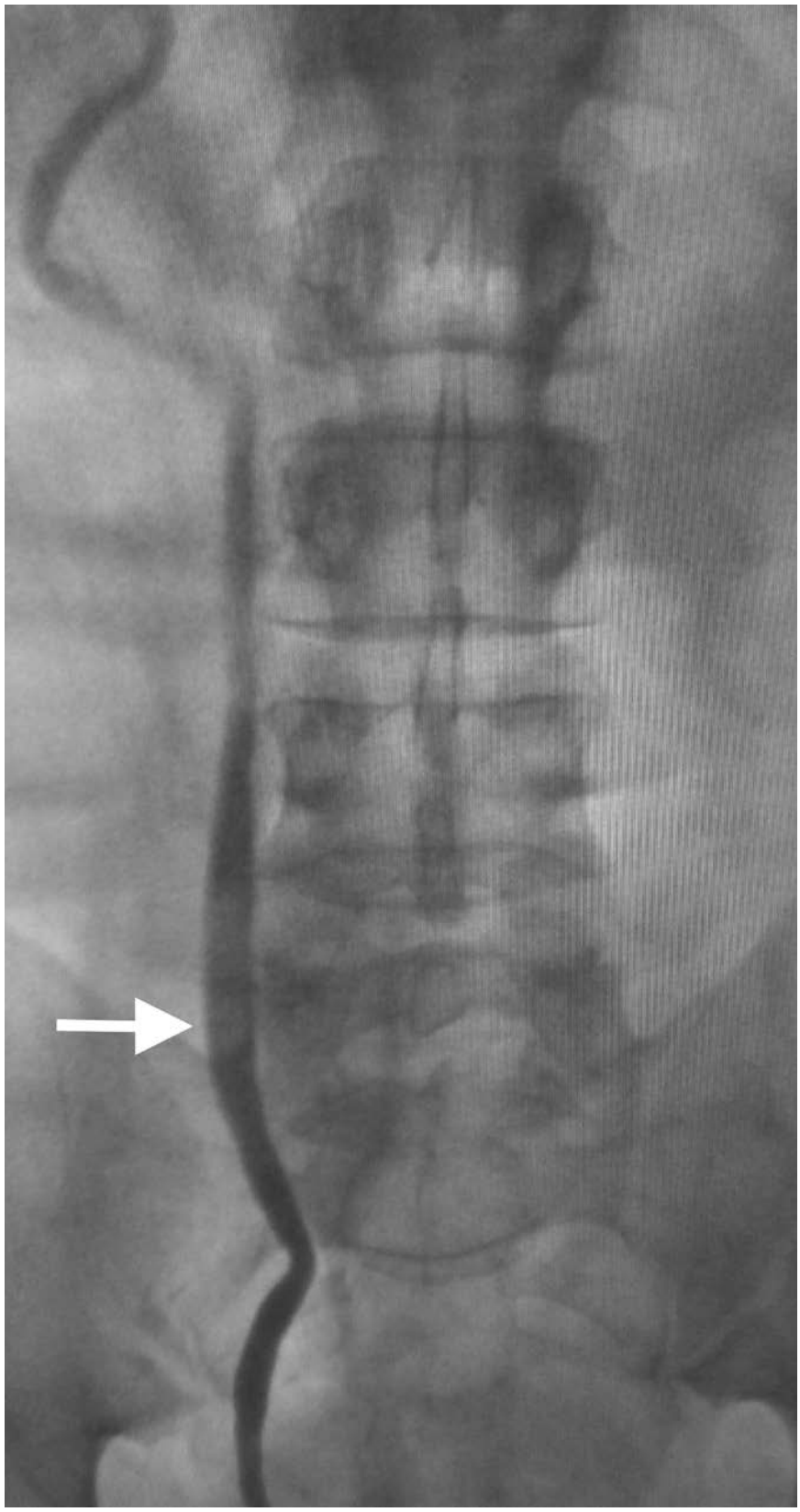

Figure. Initial retrograde pyelogram with right hydroureter.

The creatinine level was 2.3 mg/dL (the patient's baseline was 1.6 mg/dL). Urinalysis findings included +1 blood and 3 red blood cells per high-power field.

Renal ultrasonography demonstrated mild right hydronephrosis without nephrolithiasis.

MANAGEMENT

The patient was treated with intravenous fluid and morphine via patient-controlled analgesia. A consultant urologist performed cystoscopy with retrograde pyelography. The pyelogram showed right hydroureter without a definitive stone (**Figure**). Cystoscopy revealed brown debris in the right ureteral orifice. The debris was removed, and a ureteral stent was placed. The man's symptoms rapidly improved, and he was discharged the next day.

Cystoureteroscopy and pyelogram were performed again several weeks later. The ureteral stent was removed, and the pyelogram showed a right mid-ureteral filling defect. Ureteroscopy revealed a 5- to 6-mm yellow stone, which was retrieved. Analysis of the stone showed it to be pure atazanavir.

DISCUSSION

Nephrolithiasis is a commonly encountered problem in primary care. Diagnosis generally involves radiologic imaging in the context of the patient's history, examination finding, and laboratory study results. Several imaging modalities are available, each with different strengths and weaknesses (**Table**).[1,2]

Plain film is widely available, uses minimal radiation, and is inexpensive. However, plain film has low sensitivity due to challenges posed by body habitus and bowel gas. Additionally, a number of types of stones are radiolucent on plain film, including uric acid stones and medication-related stones such as those made of pseudoephedrine,[3] guaifenesin,[3] and protease inhibitors (PIs). Plain films also lack information on patient anatomy, including urinary tract obstruction.

Ultrasonography also is widely available, is inexpensive, and involves no radiation exposure. This modality identifies more types of stones than does plain film, and it can provide evidence of obstruction, such as hydronephrosis and hydroureter. Ultrasonography poses difficulty, however, in visualizing ureteral (especially mid-ureteral) and very small (<5 mm) renal stones.

Magnetic resonance (MR) urography is the most recent imaging modality for stone disease. It involves no radiation and can provide very good anatomic detail, but it is expensive, time-consuming, and is still not available at all centers. Additionally, MR urography detects all intraureteral findings as a signal void and thus cannot reliably differentiate a stone from a tumor or clot.

Noncontrast helical CT has become the most common initial imaging test, since it has the highest sensitivity and specificity of all imaging modalities. CT detects the vast majority of urinary stones, including uric acid stones and most medication stones. Disadvantages include significant radiation exposure, greater cost, and frequently encountered incidental findings that must then be addressed.[4,5] Despite the higher sensitivity of CT, a recent large randomized, controlled trial comparing bedside ultrasonography, ultrasonography by radiology, and CT for initial imaging of suspected nephrolithiasis found no difference in frequency of high-risk diagnoses, although it should be noted that 40.7% of the bedside ultrasonography group and 27% of the radiology ultrasonography group still underwent CT during the initial visit.[6]

PI stones are a well-reported cause of nephrolithiasis in patients receiving antiretroviral therapy. They often pose a particular diagnostic challenge because they are difficult to visualize using any imaging modality, including CT. Indinavir is the PI most widely associated with stone disease, with an occurrence rate of 4% to 13%,[7,8] but atazanavir recently has been highly associated, as well.[9] In a study of HIV patients on PIs, those taking ritonavir-boosted atazanavir were 10 times more likely to develop stones than those taking other PIs.[10]

The pathophysiology of PI stones is drug crystallization in the urine due to high urinary excretion of the unmetabolized drug, combined with poor solubility of the drug at physiologic urinary pH. The recovered stones generally are pure drug compound, as in our case. Definitive diagnosis requires stone analysis. In patients with small (<5 mm) ureteral stones but without signs of infection or refractory vomiting, a trial of spontaneous stone passage with hydration and tamsulosin therapy may be attempted.[11] Patients with recurrent symptomatic stones may require a change in antiretroviral therapy.

In summary, general practitioners should be aware of the limitations of radiologic imaging for certain types of urinary stones, including PI stones. Ritonavir-boosted atazanavir appears to confer a significantly increased risk of stone formation, so urologic complaints from patients taking these medications should prompt a high index of suspicion for stone disease, even in the presence of unremarkable imaging. Sound knowledge of radiologic study qualities and the PI association with radiolucent stones will facilitate timely diagnosis and treatment. ■

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REFERENCES:

1. Mandeville JA, Gnessin E, Lingeman JE. Imaging evaluation in the patient with renal stone disease. *Semin Nephrol.* 2011;31(3):254-258.
2. Dhar M, Denstedt JD. Imaging in diagnosis, treatment, and follow-up of stone patients. *Adv Chronic Kidney Dis.* 2009;16(1):39-47.
3. Song GY, Lockhart ME, Smith JK, Burns JR, Kenney PJ. Pseudoephedrine and guaifenesin urolithiasis: widening the differential diagnosis of radiolucent calculi on abdominal radiograph. *Abdom Imaging.* 2005;30(5):644-646.
4. Lumbreras B, Donat L, Hernández-Aguado I. Incidental findings in imaging diagnostic tests: a systematic review. *Br J Radiol.* 2010;83(988):276-289.
5. Thompson RJ, Wojcik SM, Grant WD, Ko PY. Incidental findings on CT scans in the emergency department. *Emerg Med Int.* 2011;2011:624847.
6. Smith-Bindman R, Aubin C, Bailitz J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. *N Engl J Med.* 2014;371(12):1100-1110.
7. Dieleman JP, Sturkenboom MC, Jambroes M, et al; ATHENA Study Group. Risk factors for urological symptoms in a cohort of users of the HIV protease inhibitor indinavir sulfate: the ATHENA cohort. *Arch Intern Med.* 2002;162(13):1493-1501.
8. Wu DS-W, Stoller ML. Indinavir urolithiasis. *Curr Opin Urol.* 2000;10(6):557-561.
9. Wang LC, Osterberg EC, David SG, Rosoff JS. Recurrent nephrolithiasis associated with atazanavir use. *BMJ Case Rep.* 2014;2014. doi:10.1136/bcr-2013-201565.
10. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis.* 2012;55(9):1262-1269.
11. Hollingsworth JM, Rogers MAM, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet.* 2006;368(9542):1171-1179.