Original Report

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Nonopaque Crystal Deposition Causing Ureteric Obstruction in Patients with HIV Undergoing Indinavir Therapy

OBJECTIVE. We describe the unique CT features of ureteric calculi in six HIV-infected patients receiving indinavir, the most commonly used HIV protease inhibitor, which is associated with an increased incidence of urolithiasis.

CONCLUSION. Ureteric obstruction caused by precipitated indinavir crystals may be difficult to diagnose with unenhanced CT. The calculi are not opaque, and secondary signs of obstruction may be absent or minimal and should be sought carefully. Images may need to be obtained using IV contrast material to enable diagnosis of ureteric stones or obstruction in patients with HIV infection who receive indinavir therapy.

Almost all urinary calculi are visible on unenhanced CT, and this technique has become widely used for radiologic diagnosis of patients with suspected renal colic [1–6]. In most cases, secondary signs of ureteric obstruction are also seen [4, 6]. We have noted a group of patients with ureteric obstruction in whom no calculus was visible on unenhanced CT. All patients had advanced HIV infection and were being treated with indinavir sulfate (Crixivan; Merck, Rahway, NJ).

Indinavir sulfate is the most widely used of the HIV protease inhibitors [7, 8], which since their introduction in December 1995 have revolutionized the treatment and short-term prognosis of patients with advanced HIV infection. During clinical trials, urolithiasis developed in approximately 4% of patients receiving indinavir therapy at the recommended dose of 2400 mg per day (Crixivan package insert); this rate is similar to that found by other groups [7–10]. Studies have suggested that the calculi consist of precipitated crystals of indinavir base with associated deposits of calcium oxalate and phosphates [9].

To our knowledge, the CT findings in patients with symptoms of renal colic who are undergoing indinavir therapy have not been described.

Materials and Methods

During a 3-month period, six men (29–48 years old) with advanced HIV infection presented on seven occasions with a suspected diagnosis of renal colic. All were receiving treatment with 2400 mg of indinavir daily in divided doses and had complied with instructions regarding hydration. Three presented with right flank pain, two presented with left flank pain, and one presented on two occasions 3 weeks apart, once with pain on his right side and once with pain on his left. One patient had had a previous episode of similar pain 1 year earlier that had been attributed to indinavir urolithiasis and responded to temporary withdrawal of the drug and increased hydration; no imaging studies were performed. Another patient had documented bilateral renal calculi before the start of indinavir therapy but had not presented with renal colic.

All patients underwent a standardized CT protocol on an Advantage Scanner (General Electric Medical Systems, Milwaukee, WI) for suspected ureteric calculi. No contrast material was used. Helical scan-

Received February 5, 1998; accepted after revision March 27, 1998.

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AJR 1998;171:717–720

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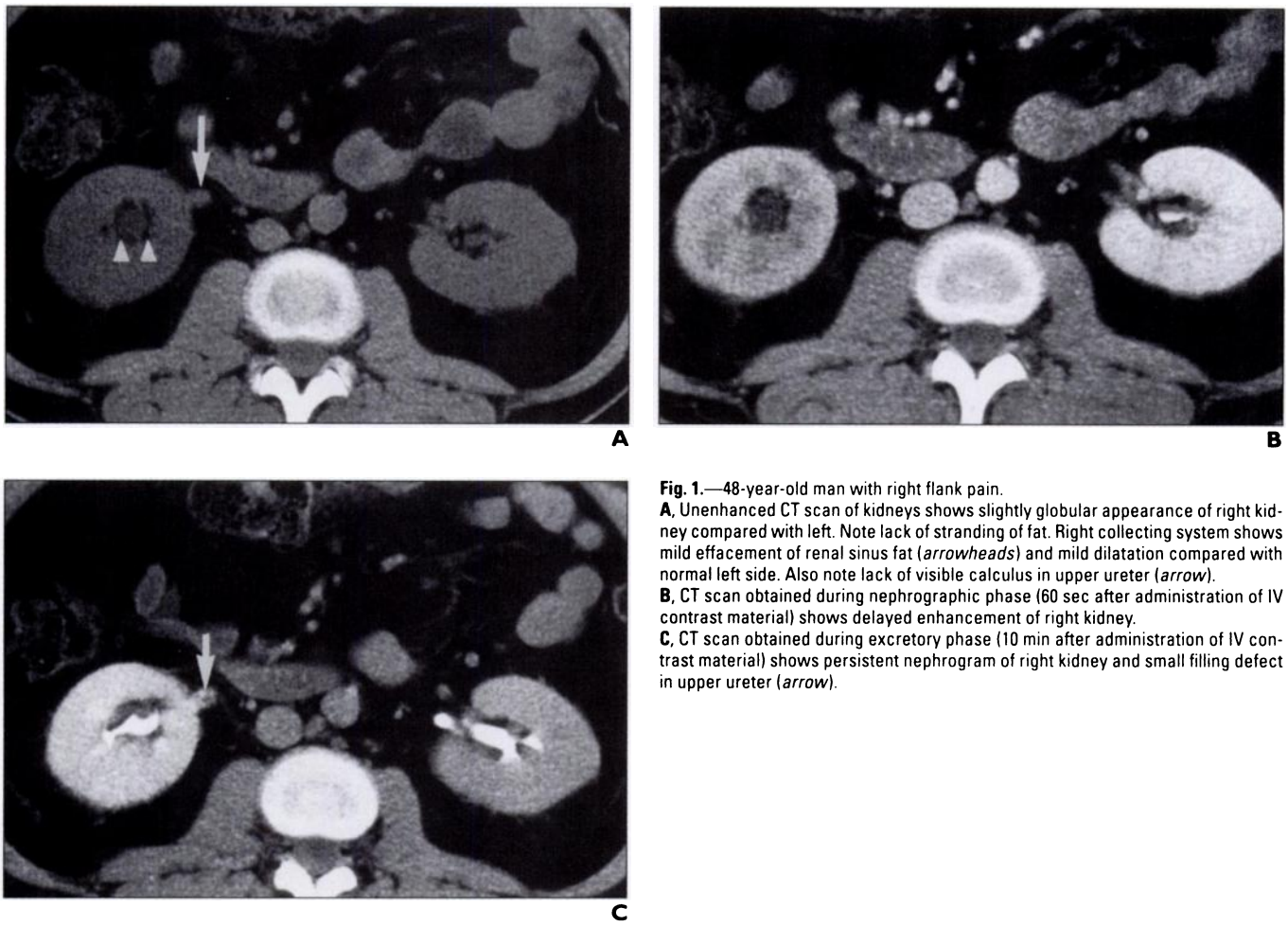


Fig. 1.—48-year-old man with right flank pain.
A, Unenhanced CT scan of kidneys shows slightly globular appearance of right kidney compared with left. Note lack of stranding of fat. Right collecting system shows mild effacement of renal sinus fat (*arrowheads*) and mild dilatation compared with normal left side. Also note lack of visible calculus in upper ureter (*arrow*).
B, CT scan obtained during nephrographic phase (60 sec after administration of IV contrast material) shows delayed enhancement of right kidney.
C, CT scan obtained during excretory phase (10 min after administration of IV contrast material) shows persistent nephrogram of right kidney and small filling defect in upper ureter (*arrow*).

ning at a pitch of 1 was performed from the top of the kidneys through the bladder base, with 7-mm collimation. The scan was performed during a single breath-hold. If the patient could not continue to hold his breath toward the end of the scan, he was instructed to slowly release it, with no other movement.

If no calculus was seen on the unenhanced study, a CT urogram was performed [11]. For this protocol, nephrographic phase images of the kidneys were obtained 60 sec after administration of 100 ml of IV contrast material, and delayed phase images of the kidneys, ureters, and bladder were obtained 10 min later during a bolus of a further 50 ml of contrast material. This series was obtained with 5-mm collimation at a pitch of 1.5 and prospectively reconstructed at 2.5-mm intervals. At the end of the study, a digital radiograph was obtained through the abdomen and pelvis.

Results

On the unenhanced scans, no patient had a visible ureteric calculus (Figs. 1 and 2A–2C). In one patient, we saw an area of subtly increased attenuation (25 H) in the upper ureter on CT scans performed during a second presentation 3 weeks after the first (Figs. 2D and 2E). In five of seven presentations, unenhanced CT revealed evidence of obstruction. Each of the affected kidneys had a globular or enlarged appearance with reduced attenuation compared with the opposite side. Unilateral hydronephrosis and hydroureter were seen in three patients. Blurring or effacement of the renal sinus fat (Fig. 1A and 2B), due to a combination of pelvicaliceal dilatation and swelling of the obstructed kidney, was also seen in three patients. Perinephric or periureteric fat stranding was seen in two patients (Fig. 2D). Perinephric and retroperitoneal fluid consistent with extravasated urine was seen in one patient.

In two patients, no abnormality was seen on the initial unenhanced CT study. In one patient, the renal pelvis and proximal ureter were mildly dilated, causing slight effacement of the renal sinus fat (Fig. 1A) when compared with the other side, but the dilatation was only noted in retrospect. In the other patient (Fig. 2A), unenhanced CT showed no abnormality of the kidney or ureter.

IV contrast material was given in six of the seven cases. In five cases the affected kidney was enlarged with persistent cortical enhancement, a persistent nephrogram, and delayed excretion. In the sixth patient, no abnormality was seen in the nephrographic phase.

On excretory phase imaging, a filling defect was seen in the contrast column on the affected side in three patients (Figs. 1C and 2C). In two other patients, a persistent column of contrast material was seen on 30-min delayed scans, which stopped abruptly above the ureterovesical junction. This was presumed to indicate complete obstruction by a nonopaque calculus. In one of these, the ureterovesical portion of the bladder wall was swollen (Fig. 3B). The other patient also had forniceal rupture with extravasation of contrast material into a small perinephric and retroperitoneal fluid collection.

In two patients IV contrast material was necessary to diagnose the ureteric calculus. In one patient, subtle signs of ureteric obstruction were seen in retrospect on the unenhanced CT study (Fig. 1A). The enhanced study revealed persistent cortical enhancement in the nephrographic phase and delayed excretion with an obstructed upper ureter in the excretory phase,

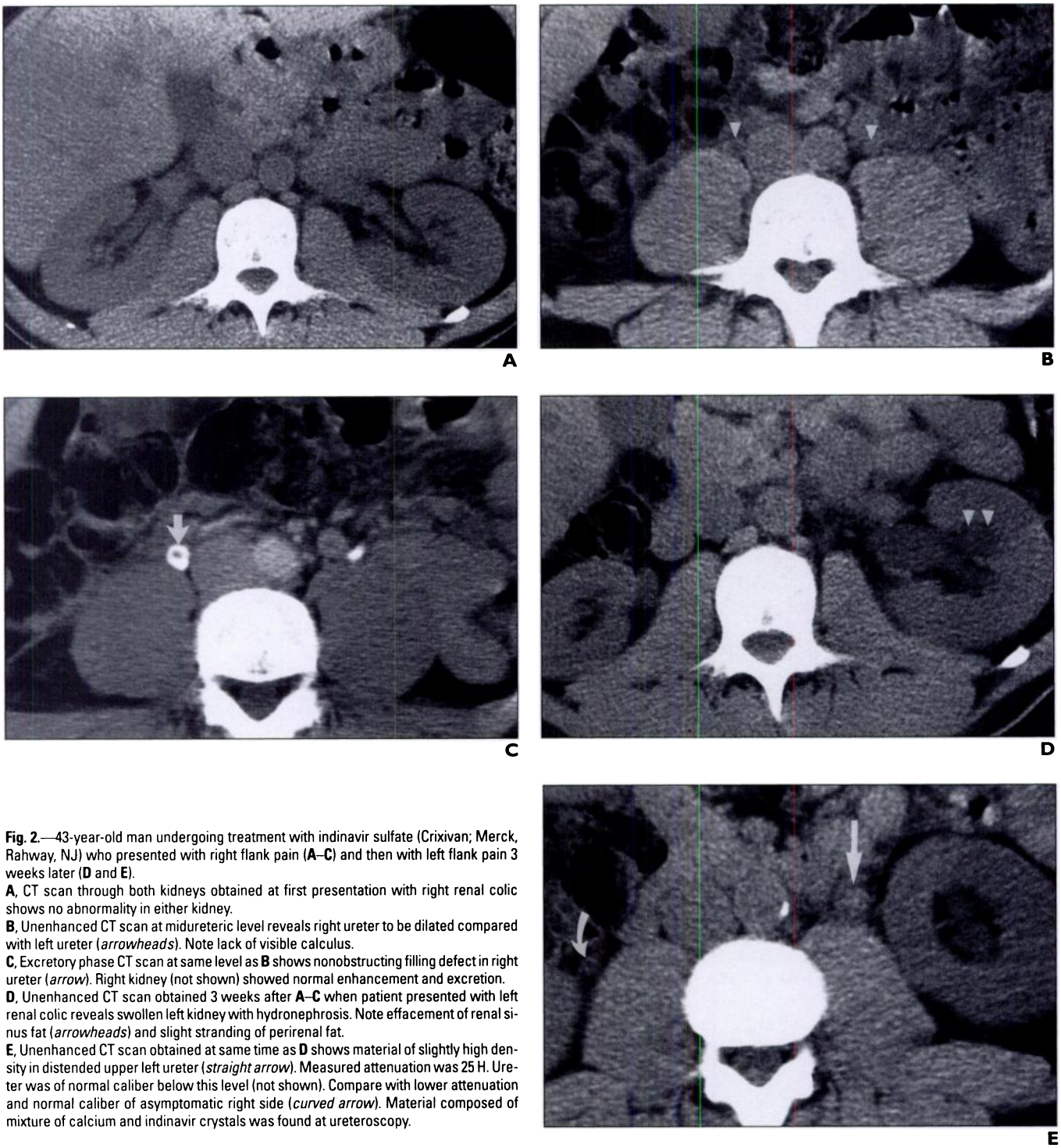


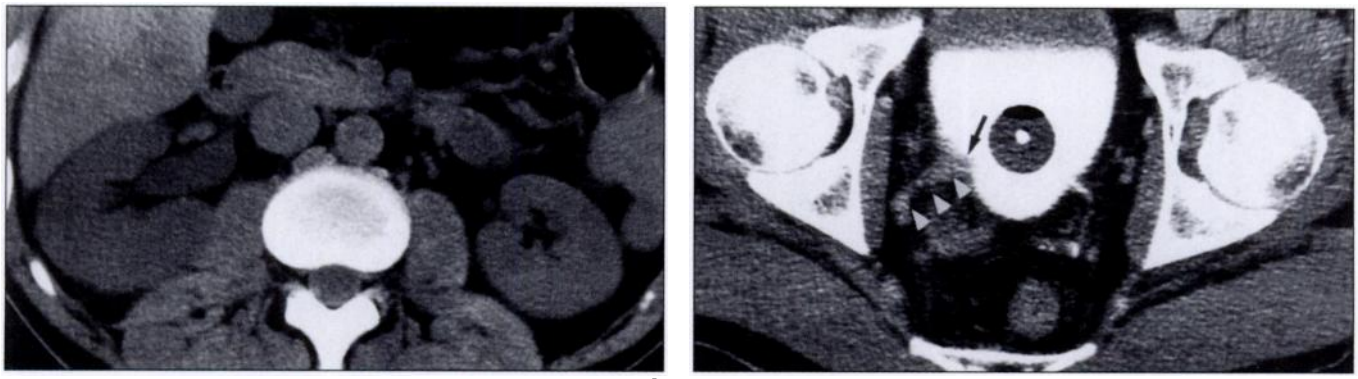
Fig. 2.—43-year-old man undergoing treatment with indinavir sulfate (Crixivan; Merck, Rahway, NJ) who presented with right flank pain (**A–C**) and then with left flank pain 3 weeks later (**D** and **E**).
A, CT scan through both kidneys obtained at first presentation with right renal colic shows no abnormality in either kidney.
B, Unenhanced CT scan at midureteric level reveals right ureter to be dilated compared with left ureter (*arrowheads*). Note lack of visible calculus.
C, Excretory phase CT scan at same level as **B** shows nonobstructing filling defect in right ureter (*arrow*). Right kidney (not shown) showed normal enhancement and excretion.
D, Unenhanced CT scan obtained 3 weeks after **A–C** when patient presented with left renal colic reveals swollen left kidney with hydronephrosis. Note effacement of renal sinus fat (*arrowheads*) and slight stranding of perirenal fat.
E, Unenhanced CT scan obtained at same time as **D** shows material of slightly high density in distended upper left ureter (*straight arrow*). Measured attenuation was 25 H. Ureter was of normal caliber below this level (not shown). Compare with lower attenuation and normal caliber of asymptomatic right side (*curved arrow*). Material composed of mixture of calcium and indinavir crystals was found at ureteroscopy.

with a small filling defect in the proximal ureter. In the other patient, we found no evidence of obstruction on the unenhanced images and he had a normal nephrogram after IV contrast material administration, with a nonobstructing calculus in the midureter, seen as a filling defect on excretory phase imaging (Fig. 2C).

All patients had evidence of indinavir crystals in the urine. In one, material was removed from the upper ureter at ureteroscopy, corresponding to the CT finding of an area of subtly increased attenuation within the upper ureter on unenhanced images (Fig. 2D). This material was composed of indinavir crystal and a small amount of calcium phosphate.

Discussion

Indinavir is the most commonly used HIV protease inhibitor in the United States and Western Europe and is generally well tolerated. Urolithiasis has an incidence between 2% and 5% in patients taking the drug [7–10], although some authors have reported higher rates [8]. Almost 19% of the drug is excreted in the urine, approximately half as metabolites and half unaltered [12]. Because of its low solubility, the drug is prone to precipitate out of solution and form crystals, causing sludging and ureteric obstruction. Crystal formation has



A B

Fig. 3.—43-year-old man with right flank pain.
A, Unenhanced CT scan of kidneys shows swollen right kidney with dilated renal pelvis. Attenuation of right kidney is lower (mean, 9 H) than that of unaffected left side (mean, 20 H). Note lack of changes in perinephric fat.
B, Excretory phase CT scan of bladder shows swelling of right ureterovesical junction (*arrow*) and lack of contrast material in distal ureter. Distal ureter (*arrowheads*) is mildly distended compared with asymptomatic side. Indinavir crystals were removed from this area at ureteroscopy.

also been described in the intrarenal collecting ducts in association with interstitial nephritis [13]. Studies analyzing the urine of patients being treated with indinavir have suggested that the obstructing calculi, although largely consisting of precipitated indinavir crystals, may also contain calcium oxalate and phosphate [9]. One of our patients had a mixture of indinavir crystals and a small amount of calcium phosphate in his urine.

The CT findings in such cases to our knowledge are not described in the radiology literature. Our experience shows that the calculi that cause ureteric obstruction have an attenuation that is the same as or slightly higher than that of soft tissue and are thus undetectable or barely detectable on unenhanced CT scans. Diagnosis may be made by secondary signs of ureteric obstruction in patients taking this medication. However, these signs may be subtle or absent. Secondary CT signs of ureteric obstruction have been described [1–6] and include hydroureter, hydronephrosis, perinephric stranding, increased size of the affected kidney, and reduced attenuation of affected kidney because of edema [6].

In our series, evidence of obstruction was found on the unenhanced CT scans in five of the seven episodes. Signs were obvious in three cases and subtle in two. In the remaining two cases, the diagnosis was difficult or impossible to make on the basis of the unenhanced study. In one, excretory phase imaging showed a 2-cm-long, 5-mm-diameter filling defect in the ureter. In the other case, subtle signs of ureteric obstruction could be seen in retrospect, but obstruction was obvious after the injection of IV contrast material when a small filling defect was seen in the upper ureter. Although six patients received IV contrast material, this protocol was probably not necessary in the three patients with clear signs of ureteric obstruction on unenhanced imaging. At that time, we were not as familiar with imaging these patients, and IV contrast material was given for further evaluation when no calculus was seen.

One patient had a documented history of nephrolithiasis before indinavir treatment. When he presented for the first time with renal colic, unenhanced CT showed the known bilateral renal stones but did not show a calculus in the midureter. This obstruction was subsequently seen as a negative filling defect on the excretory phase CT scan. Urinalysis confirmed indinavir crystals in his urine.

Patients undergoing indinavir therapy are known to be at risk for ureteric calculi composed of precipitated indinavir crystals. Treatment usually consists of analgesia and hydration, although ureteroscopy may be necessary to remove the obstructing material. Our experience is that these calculi are of soft-tissue attenuation and are usually not seen with unenhanced CT. If a patient taking indinavir presents with a clinical picture suggesting renal colic, ureteric obstruction caused by a nonopaque calculus should be suspected and may be diagnosed on an unenhanced CT scan even if a calculus is not seen. The signs may be subtle and should be sought carefully. Subtle signs include a globular appearance to the affected kidney indicating slight enlargement. Mild dilatation of the renal pelvis resulting in effacement of the renal sinus fat when compared with the contralateral side may also be seen. These may be the only signs of obstruction. Mild perinephric, peripelvic, or periureteric fat stranding may also be seen. If no evidence of ureteric obstruction can be found on unenhanced CT scans, IV contrast material may be useful to show a ureteric filling defect, delayed excretion, or persistent nephrogram on the affected side.

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