

Indinavir-induced nephrolithiasis three and one-half years after cessation of indinavir therapy

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Abstract Nephrolithiasis is a known side effect of indinavir sulfate, a protease inhibitor used in the treatment of human immunodeficiency virus (HIV). The duration of its side effects, however, has not been well defined. We present a case where a patient presented with symptomatic indinavir-induced nephrolithiasis 3.5 years after discontinuing indinavir. We use this case to illustrate the pathophysiology of indinavir stones and hypothesize how they can occur years after discontinuation by discussing the pharmacokinetics of the drug.

Background

Indinavir sulfate is a protease inhibitor used in the treatment of HIV by inhibiting the cleavage of precursor polyproteins into functional infectious proteins. Indinavir-induced nephrolithiasis is a well-reported side effect of the medication, with an incidence of approximately 12.4% necessitating discontinuation of the drug and altering the antiretroviral regimen in a considerable number of individuals [1]. However, little is known regarding the occurrence of indinavir-induced nephrolithiasis after cessation of indinavir therapy. Case reports have suggested that indinavir nephrolithiasis can occur up to 11 months after discontinuation of the drug [2]. We describe a patient who presents with gross hematuria where eventual workup revealed indinavir-induced nephrolithiasis 3.5 years after the cessation of indinavir.

Case history

A 49-year-old man with HIV presented with gross hematuria and powdery penile discharge with urination for the past 1 year. The patient also complained of mild lower back/flank pain but denied a history of dysuria, fevers, or chills. He attributed these symptoms to fatigue and long-distance air flights.

The patient was diagnosed with HIV in 1989 and treated with a highly active anti-retroviral therapy (HAART) regimen that included indinavir at a dose

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of 800 mg PO TID for 8 years. The indinavir was discontinued in February 2005 when he developed nephrolithiasis presumably due to indinavir stones (no stones were retained for analysis). At the time, he presented with gross hematuria and flank pain. He underwent a computed tomography imaging of kidney ureter bladder (CT KUB) which demonstrated mild bilateral hydronephrosis and right hydroureter consistent with obstruction although no radioopaque calculi were seen. Indinavir was subsequently discontinued and the patient's symptoms resolved with conservative management. A follow-up renal furosemide washout scan showed no evidence of stone or obstruction suggesting that the patient had passed the stones resulting in resolution of symptoms.

In September 2006, the patient underwent a kidney biopsy for a persistently elevated creatinine of 1.6 mg/dl. The biopsy revealed crystal-induced tubular injury with rupture, acute tubular necrosis, and arterial and arteriolar nephrosclerosis (Fig. 1). On electron microscopy, granulomatous giant cell reaction with indinavir crystals within the lumen was seen (Fig. 2).

The patient again presented with gross hematuria and right flank pain in September 2008. A urine analysis revealed pH 6.5, 3+ hemoglobin, 1+ protein, positive leukocyte esterase, and a negative urine culture. Serum creatinine was 2.3 mg/dl. A CT KUB showed complete resolution of the previously mentioned left hydronephrosis but moderate dilatation of the right intrarenal collecting system and right ureter and again no evidence of calculi. The patient eventually passed multiple stones with resolution of symptoms and improvement of serum creatinine to

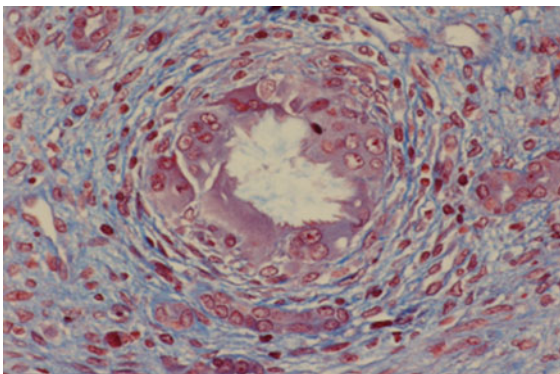


Fig. 1 Kidney biopsy showing crystal-induced tubular injury with rupture

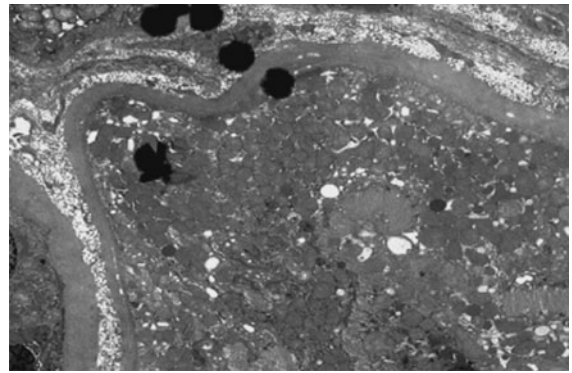


Fig. 2 Electron microscopy showing granulomatous giant cell reaction with crystals within the lumen

1.8 mg/dl. Stone analysis performed this time revealed indinavir as the primary composition. The patient had last taken indinavir 3.5 years ago.

Discussion

Indinavir is primarily metabolized by the liver with 20% eliminated through urine, approximately half of which is unchanged [1]. Indinavir crystallization occurs at a urine concentration of 100 mg/l which corresponds to a plasma concentration of 6.4 mg/l [2]. The peak plasma concentration of indinavir in patients at the recommended dose of 400–800 mg is already 8–10 mg/l [3]. Within 3 h after a typical indinavir dosage of 800 mg orally in a patient averaging 1.5 l urine output daily, the urine concentration already exceeds the limits of solubility at 200–300 mg/l making crystal formation likely common [3]. Current recommendations to prevent nephrolithiasis include hydration with at least 1.5 l of fluids daily to increase the clearance of indinavir [2].

In the clinical setting, many factors may increase the risk of indinavir crystallization in urine with the most important being volume depletion leading to higher urine drug concentration. Other cited risk factors include variations in individual pharmacokinetics of indinavir, hepatic insufficiency leading to greater dependence on renal clearance, differences in plasma protein binding of indinavir, low urinary pH decreasing indinavir solubility, renal insufficiency, renal tubular cell injury as a predisposition for crystal adherence and agglomeration, and low lean body mass [3, 4]. It is important to note that the effect of

renal insufficiency on the pharmacokinetics of indinavir has not been studied well.

In the patient presented, a kidney biopsy demonstrated crystal-induced tubular injury with rupture and electron microscopy revealed granulomatous giant cell reaction with crystals within the lumen. Even though the patient had discontinued indinavir for 1.5 years by the time of renal biopsy, the crystals remained in the renal tubules. One hypothesis of stone formation long after discontinuation of indinavir is that the soft, gelatinous nature of indinavir crystals allows it to gradually collect and build up within the renal tubules with time and when a critical mass of indinavir crystals develops, it precipitates into an obstructing stone [5].

A second hypothesis for stone formation centers on low lean body mass that results in a low distribution volume of indinavir and hence a higher plasma concentration of indinavir [4]. Since dosing of indinavir is independent of body mass, plasma concentrations of indinavir may vary greatly among patients on the same dose. The higher plasma concentration leads to a higher urinary concentration of indinavir that increases the risk of crystal and stone formation.

The detection of indinavir itself poses another challenge as no single imaging modality proves superior in definitively diagnosing indinavir stones. One study found that no abdominal imaging study is diagnostic, intravenous pyelogram detects less than 8% of indinavir stones, renal ultrasounds demonstrated obstruction in 82% of cases, and CT imaging revealed obstruction with no stones in over 50% of the cases [4]. Stones that were visible on CT were more likely of mixed composition, containing indinavir with radioopaque substances such as calcium or uric acid [4]. Accurate diagnosis is important as conservative management is often effective, but some cases may require ureteral stenting to relieve obstruction [6].

Conclusion

This case is an important illustration of how indinavir-induced nephrolithiasis can present many years after the discontinuation of therapy. Nephrolithiasis is an important differential diagnosis for any patient with a history of indinavir use presenting with symptoms of flank pain and/or hematuria. Typical means of imaging may not be diagnostic and failure to visualize a stone insufficient to rule out nephrolithiasis. Since urinary concentrations may vary from patient to patient on similar dosages of indinavir, future management may require titrating dosages to yield urinary concentrations below the maximum solubility of indinavir to minimize risk of nephrolithiasis.

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References

1. Daudon M, Estepa L, Viard JP, Joly D, Jungers P (1997) Urinary stones in HIV-1-positive patients treated with indinavir. *Lancet* 349:1294–1295
2. Polhemus ME, Aronson NE (1998) Persistent nephrolithiasis after discontinuation of indinavir therapy. *Clin Infect Dis* 27:1536–1537
3. Salahuddin S, Kok DK, Buchholz NNP (2007) Influence of body temperature on indinavir crystallization under loop of Henle conditions. *J Antimicrobial Chemother* 59:114–117
4. Nadler RB, Rubenstein JN, Eggener SE, Loor MM, Smith ND (2003) The etiology of urolithiasis in HIV infected patients. *Am Urolog Assoc* 169:475–477
5. Kohan AD, Armenakas NA, Fracchia JA (1999) Indinavir urolithiasis: an emerging cause of renal colic in patients with human immunodeficiency syndrome. *J Urol* 161:1765–1768
6. Gentle DL, Stroller ML, Jarrett TW, Ward FJ, Geib KS, Wood AF (1997) Protease inhibitor-induced urolithiasis. *Urology* 50(4):508–511