Journal of Nephropathology

Cocaine-induced acute interstitial nephritis: A case report and review of the literature

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ARTICLE INFO

ABSTRACT

Background: Acute tubular necrosis and pigment induced kidney injury are well described consequences of cocaine abuse. However, acute interstitial nephritis associated with cocaine use has been previously reported in only three patients.
Case presentation: We present the case of a 49-year-old man who developed acute kidney injury from biopsy-proven interstitial nephritis after nasal insufflation of cocaine. Unlike prior reports, our patient remained non-oliguric and did not require renal replacement therapy.
Conclusions: Interstitial nephritis should be considered as a potential cause of acute kidney injury associated with cocaine use. The approach to management of cocaine associated acute kidney injury (AKI) may be different in patients with interstitial nephritis than for those with tubular necrosis or pigment induced renal injury.

Implication for health policy/practice/research/medical education:
Interstitial nephritis should be considered as a potential cause of acute kidney injury associated with cocaine use. The approach to management of cocaine associated acute kidney injury (AKI) may be different in patients with interstitial nephritis than for those with tubular necrosis or pigment induced renal injury.

Introduction

Kidney injury associated with cocaine abuse has been previously described. Ischemic acute tubular necrosis (ATN) from severe vasoconstriction (1, 2) and direct proximal tubular toxicity from pigment deposition (3, 4) are frequently associated with cocaine use. However, acute interstitial nephritis (AIN) is seldom recognized as a potential cause of acute kidney injury (AKI) in cocaine users. We present a patient who developed AKI from AIN after nasal insufflation

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of cocaine and we review the existing literature on the association between cocaine use and the development of AIN. Recognition of cocaine induced AIN is important because the clinical management of AKI may be substantially different than in cocaine users with pigment-induced tubular necrosis.

Case

A 49-year-old African American man presented to the emergency department with a four-day history of diffuse abdominal pain associated with fatigue, anorexia and malaise. He had a past history of nephrolithiasis and hypertension treated with amlodipine for two years. He had smoked marijuana and snorted cocaine within the two weeks prior to his presentation.

The physical examination revealed a blood pressure of 170/95 mmHg in both arms, pulse 92 beats per minute, respiratory rate 18 per minute, and axillary temperature 36.2C. Fundoscopic examination revealed no hemorrhages or papilledema. Both the chest and cardiac exams were normal. His abdomen had normoactive bowel sounds; it was diffusely tender to palpation but there was no rebound tenderness, guarding or organomegaly. There was no peripheral edema, petechiae, palpable purpura or rash.

At the time of admission, his blood urea nitrogen was 69 mg/dL (24.6 mmol/L) and his serum creatinine was 10.8 mg/dL (954.7μmol/L). Previous laboratory records documented a serum creatinine of 0.8 mg/dL (70.72 μmol/L) and 2.3 mg/dL (203.3 μmol/L), 6 months and 2 weeks previously, respectively. The urinalysis showed moderate blood but no red blood cells and 10-14 white blood cells/HPF. There were no pigmented granular casts or urinary eosinophils present. .Proteinuria was present (>0.3g/dL [3 g/L]) by dipstick, but the urine protein/creatinine ratio

was less than 0.5 g/g. The urinary sodium concentration was 53 mEq/L (53 mmol/L). A urine toxicology screen was positive for marijuana and cocaine. Serum total CK was 621 U/L. Anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmatic antibodies (ANCA), hepatitis, human immunodeficiency virus (HIV), and anti-glomerular basement membrane (GMB) antibodies were all negative. C3 and C4 complement levels were normal and the rapid plasma reagin test (RPR) was non-reactive. A renal ultrasound demonstrated normal sized kidneys (right 11.6 cm and left 12.1 cm) without evidence of hydronephrosis or nephrolithiasis.

Blood pressure control was achieved over the next 3 days with oral medications including amlodipine and metoprolol. A kidney biopsy was performed on the third hospital day, when the serum creatinine peaked at 11.2 mg/dL (990 μmol/L). The biopsy showed patchy areas of interstitial edema with interstitial lymphocytic and eosinophilic infiltrates (Figure 1A) with tubulitis and focal acute tubular injury with granular casts (Figure 1B) consistent with AIN. Mild interstitial fibrosis, mild thickening of the tunica media and hyalinosis of arterioles was also present.
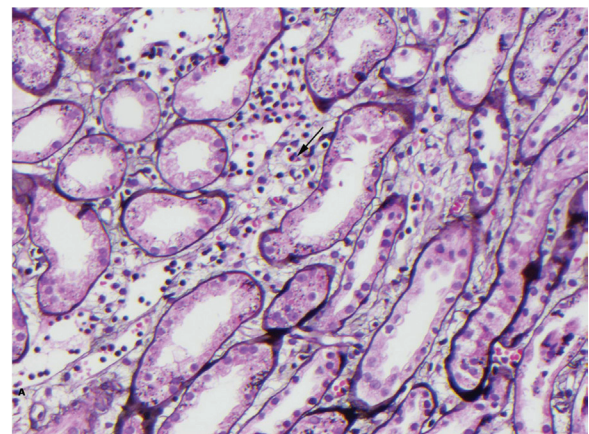

Figure 1. A. Focal interstitial lymphocytic infiltrate with interstitial edema and occasional interstitial eosinophils (arrow) (Jones stain, x 400).
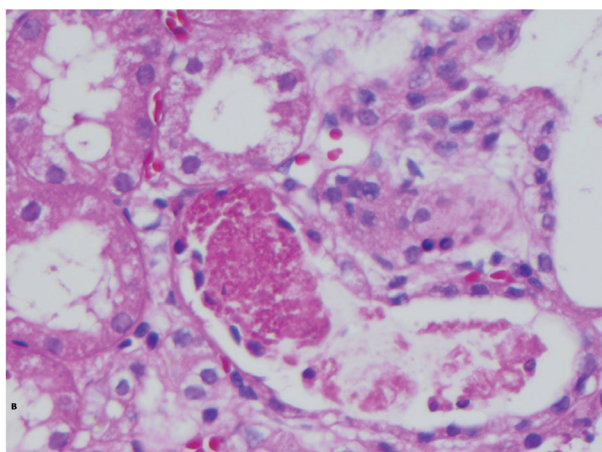
Figure 1. B. Acute tubular injury with granular casts (H&E stain, x 400).

Renal replacement therapy was not required and corticosteroids were not given. Kidney function improved and the patient was discharged on the eighth hospital day with a serum creatinine of 2.1 mg/dL (185.4 μmol/L). Two months following hospital discharge, his serum creatinine was 1.0 mg/dL (88.4μmol/L).

Discussion

In addition to our case report, there are only three previously reported cases of cocaine induced acute interstitial nephritis. Table 1 summarizes the relevant clinical characteristics. All four patients were African American men with a mean age of 40 years at presentation. All patients complained of abdominal pain and had hematuria and mild proteinuria. The magnitude of the serum creatinine elevation at presentation suggests that kidney injury had been present for several days in all of the reported cases. Except for our patient, all patients were oliguric and required renal replacement therapy (29-31). None had signs of systemic allergy. All recovered kidney function within a few weeks and did not require chronic dialysis.

Table 1. Clinical characteristics of cocaine induced acute interstitial nephritis.

	Alvarez (29)	Decelle (30)	Wojciechowki (31)	Alfaro
Drug	Alkaloid Cocaine	Hydrochloride Cocaine	Hydrochloride Cocaine	Hydrochloride Cocaine
Sex	Male	Male	Male	Male
Age (years)	34	42	38	49
Abdominal Pain	Yes	Yes	Yes	Yes
Oliguria	Yes	Yes	Yes	No
Hematuria	Yes	Yes	Yes	Yes
Proteinuria	3+	1+	2+	1+
Eosinophiluria	No	No	Yes	No
Urea Nitrogen (mg/dl)	113	332	91	84
Creatinine (mg/dl)	12.5	20.5	13	12.8
Dialysis	Yes	Yes	Yes	No
Steroids	No	Yes (IV)	Yes (PO)	No
Recovery to baseline kidney function	Yes	Yes	Yes	Yes

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to mmol/L, ×0.357.

AIN may be an under recognized cause of acute kidney injury in patients with cocaine use. As with other causes of AIN, withdrawing the offending agent is the corner stone of treatment. The efficacy of corticosteroid administration remains unclear. We cannot determine if the patient who received steroids had a faster recovery than those who did not.

Renal histology at autopsy of cocaine users shows periglomerular fibrosis and mononuclear interstitial infiltrates (16) suggestive of chronic interstitial nephritis. This observation suggests that some of these patients may have also experi-

enced AIN. It is unclear if the allergic response is directly to cocaine, its metabolites or some of the diluents or contaminants found.

The pathogenesis of AIN involves an idiosyncratic allergic response. AIN typically presents 7-10 days after drug exposure (22). Drug-induced AIN is believed to have an immunological basis, suggested by the dose-independent nature of the presentation, the extrarenal manifestations, and the recurrence after re-exposure (25). Cell-mediated immunity seems to a play important role in the development of AIN (25). Animal models suggest the presence of several proteins in the brush border of proximal tubular cells and others in tubular basement membrane (TBM) that can act as endogenous antigens associated with the development of AIN (23, 24).

A definitive diagnosis of drug-induced AIN requires a renal biopsy. Interstitial edema with patchy or diffuse infiltrates, characterized by predominantly CD4+ T cells and tubulitis, are the hallmarks of AIN. Macrophages, eosinophils and plasma cells can also be present (26). Tubulitis is characterized by infiltration of inflammatory cells into the TBM and may be associated with tubular degenerative changes including luminal ectasia, irregular luminal contours, prominent nucleoli, loss of the brush border, and apoptosis of tubular cells (22). Immunofluorescence and electron microscopy typically do not add to the light microscopic diagnosis (27, 28).

Cocaine is one of the most frequently abused drugs in the United States. It exists in two chemical forms that confer characteristic pharmacokinetic properties (5). Cocaine hydrochloride is water soluble and inactivated at low temperatures (95° F). It can be used through nasal, oral or intravenous ingestion. The onset of action is 1-5 minutes with a peak effect occurring in 20 minutes and a half-life of 75 minutes. The alkaloid

form is water insoluble but resistant to heat (195° F) and it vaporizes before degradation, which allows for inhalation. The onset of action occurs within seconds and it peaks within one minute with a half-life of 45 to 90 minutes (6, 7). Cocaine ingested by either route is metabolized by the liver to nearly a dozen metabolites. Only a small amount is excreted unchanged in the urine after 4 to 6 hours, while the metabolites are detected up to 14 days after ingestion in heavy users (7, 8). Illicit cocaine circulating in the United States is estimated to be only 40% pure and is usually mixed with multiple diluents and contaminants (9).

Cocaine causes acute and chronic kidney injury by different mechanisms. It is a potent vasoconstrictor and endothelins (ET) are implicated in cocaine-induced vascular dysfunction (10). ET-1 receptors are up-regulated by cocaine, and it has been suggested that this effect decreases renal blood flow and glomerular filtration rate by activating the renin-angiotensin-aldosterone system (10-14).

The most common mechanisms associated with AKI include ATN as a consequence of severe vasoconstriction and rhabdomyolysis. Rhabdomyolysis was first recognized as a cause of AKI associated with cocaine intoxication in the 1980's (17, 18). Kidney injury is present in up to 33% of these patients, and half of them will develop oliguria requiring renal replacement therapy (19).

Accelerated malignant hypertension (AMH) has been implicated as a possible cause of AKI among cocaine users. These patients present with pulmonary edema, papilledema, increased creatinine and proteinuria with characteristic changes associated with AMH (1). Renal infarction due to severe vasoconstriction has also been reported to cause AKI in cocaine users; it is uncommon and is associated with severe vasoconstriction (20).

Clinical presentation includes severe flank pain, fever, leukocytosis, hematuria and high LDH. Henoch-Schönlein purpura and anti-GBM disease are among the glomerular diseases reported to be associated with cocaine use (21).

Vupputuri and colleagues established that cocaine use is an independent risk factor for developing chronic kidney disease. They estimated a threefold increased risk of declining kidney function among hypertensive cocaine users (15). These findings correlate with the prevalence of hypertension related end stage renal disease (ESRD) among 89.1% of patients on outpatient hemodialysis with history of cocaine use as compared to 46.5% of nonusers. Cocaine users were younger and had a shorter duration of hypertension before initiation of dialysis (2).

Recognition of AIN as a cause of AKI in cocaine users is important and should be considered in patients with AKI and a history of cocaine use or a positive drug test for cocaine, hematuria, abdominal pain, and a serum creatinine elevation sufficient to suggest AKI of several days duration. The presentation and clinical course of cocaine induced AIN described in these four cases is similar to that reported in patients with other causes of drug induced AIN (32).

Authors' contributions

GRA prepared the primary draft. PP reported the pathology. GTH and NV provided extensive intellectual contribution. RA prepared the final manuscript.

Conflict of interest

The author declared no competing interests.

Funding/Support

None declared

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