Thrombotic Microangiopathy in Cocaine Abuse–Associated Malignant Hypertension

Report of 2 Cases With Review of the Literature

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Cocaine is one of the most commonly used illicit drugs. Acute renal failure is an emergent complication in patients with acute cocaine intoxication. It is well known that rhabdomyolysis and vasoconstriction can be important pathogenetic mechanisms resulting in acute renal failure in these patients. Clinically, although cocaine abuse is associated with elevated blood pressure, persistent accelerated hypertension reaching levels diagnostic of malignant hypertension is uncommon. Cocaine-induced malignant hypertension associated with morphologic features of thrombotic macroangiopathy has been rarely mentioned in the literature. We report 2 cases of cocaine abuse–associated malignant hypertension with renal failure. Kidney biopsies revealed thrombotic microangiopathy with fibrinoid necrosis of arterioles and glomerular tufts. Cocaine-mediated endothelial injury and platelet activation may play important pathogenic roles in cocaine abusers who develop acute renal failure and malignant hypertension. (Arch Pathol Lab Med. 2007;131:1817–1820)

Acute renal failure is well described in cocaine-induced acute intoxication. The cause is multifactorial. In most cases reported, acute renal failure was associated with rhabdomyolysis, direct vasoconstriction, and alteration of systemic hemodynamics. In recent in vitro studies, cocaine-induced direct or indirect diffuse injury to endothelial cells has also been described. Clinically, cardiovascular symptoms with elevated blood pressure are common findings in patients with acute cocaine intoxication. However, significant elevation of blood pressure reaching malignant hypertension is infrequent. We report 2 cases of cocaine-induced malignant hypertension with acute renal failure. Renal biopsies revealed typical pathologic features of thrombotic microangiopathy (TMA) with fibrinoid necrosis of glomerular arterioles and segmental fibrinoid necrosis of glomeruli. Cocaine toxicity not only induces vasoconstriction but may also precipitate diffuse endothelial injury as a result of malignant hypertension and, eventually, acute renal failure.

REPORT OF CASES

Case 1

A 48-year-old man came to the emergency department for bleeding from the left ear because of trauma. He had no chest pain, shortness of breath, or other complaints. During physical examination, he was found to have an elevated blood pressure (210/110 mm Hg). Laboratory tests revealed a serum creatinine of 11 mg/dL and blood urea nitrogen of 90 mg/dL. Platelet counts and lactate dehydrogenase levels were within normal limits, and schistocytes were less than 1% in the peripheral blood smear. The patient had a history of hypertension for 1 year and was taking antihypertensive medications. His last known serum creatinine (1 year ago) was 1.2 mg/dL. Serology tests for hepatitis, antineutrophil cytoplasmic antibodies, and rheumatoid factor were all negative. Twenty-four-hour urine protein was measured at 2 g. A kidney biopsy was done for worsening renal function with uncertain etiology. Prebiopsy, the patient denied using illegal drugs. When the nephrologist discussed the biopsy report with the patient, he admitted that he had used cocaine a few days before his admission. The patient's renal function was improved after his hypertension was controlled using multiple antihypertensive medications. However, he remained in chronic renal insufficiency with elevated creatinine (3–4 mg/dL) after 1 year.

Kidney biopsy revealed small arteries with hyperplastic change (onion-skinning) and myxoid intimal change. Segmental fibrinoid necrosis of vascular walls with fragmented red blood cells was also present. The glomeruli revealed segmental fibrinoid necrosis of capillary tufts. Moderate interstitial fibrosis with tubular atrophy and dropout was also present (Figures 1 through 3). Immunostain for cocaine metabolites was positive in the cytoplasm of proximal tubular cells (Figure 4) proving that indeed cocaine use prior to the renal biopsy had occurred.

Case 2

A 39-year-old man visited the hospital and complained of a 2-day history of headache with blurred vision. The patient had no significant medical history. He appeared agitated but not confused. Physical examination revealed a normal heart rate and regular rhythm with no signs of congestive heart failure. The blood pressure was elevated (200/110 mm Hg). He denied illicit drug use. Laboratory tests revealed an elevated serum creatinine (9 mg/dL). He was given dialysis for acute renal failure. A kidney biopsy was performed for acute renal failure with unknown etiology. Drug abuse was suspected. Urine chemical analysis revealed cocaine metabolites. The patient was lost to follow-up.

Kidney biopsy revealed segmental glomerular fibrinoid necrosis and prominent fibrinoid necrosis of afferent and efferent arterioles with fibrinoid necrosis of glomerular capillary tufts. Immunostain for cocaine metabolites was positive in the cytoplasm of proximal tubular cells (Figure 4) proving that indeed cocaine use prior to the renal biopsy had occurred.

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Figure 1. Case 1. Fibrinoid necrosis of arterioles (hematoxylin-eosin, original magnification ×500).

Figure 2. Case 1. Fibrinoid necrosis of glomerular capillary tufts (hematoxylin-eosin, original magnification ×150).

Figure 3. Case 1. Fibrinoid necrosis of arteriole with collapse of capillary loops (hematoxylin-eosin, original magnification ×350).

Figure 4. Case 1. Immunohistochemical stain for cocaine metabolites; peroxidase-anticocaine–cocaine amphetamine regulatory transcripts as marker. Proximal tubular damage with vacuolization, apical blebs, desquamation and fragmentation of tubular cells, and staining in their cytoplasm for cocaine metabolites (original magnification ×500).

Figure 5. Case 2. Fibrinoid necrosis of glomerular arteriole and capillary tufts with fragmented red blood cells (hematoxylin-eosin, original magnification ×500).

Figure 6. Case 2. Segmental fibrinoid necrosis of glomerulus with fragmented red blood cells (hematoxylin-eosin, original magnification ×500).
teriolar and interstitial compartments were unremarkable. There was no significant interstitial fibrosis or vascular sclerosis (Figures 5 and 6).

**COMMENT**

Cocaine is a stimulant extracted from the leaf of the *Erythroxylon coca* plant and is available as a hydrochloride salt for intravenous or intranasal administration or as "freebase" for smoking. The major pharmacologic effects of cocaine include blockage of norepinephrine reuptake and release of catecholamines from adrenal glands.6,8 The pathogenesis of cocaine-induced acute renal failure is multifactorial and includes rhabdomyolysis, acute ischemia because of vascular constriction, and direct toxicity.10–13 Most cocaine is metabolized by the plasma and liver cholinesterases to water-soluble metabolites. This enzyme is responsible for the detoxification of cocaine in the body, and it has been shown that patients with life-threatening cocaine toxicity have lower plasma cholinesterase activity than those who have non-life-threatening toxicity.14 Most cocaine metabolites are eliminated through the urine.15 Cocaine and its metabolites often combine with cocaine amphetamine regulatory transcripts and can be detected in the urine or blood and can also be found in renal tubular epithelial cells using an immunohistochemical stain, as seen in case 1. Because the transcripts are quickly absorbed and metabolized, presence of strong positive staining in the tubular epithelial cells indicates recent use of cocaine.

The first reports of cocaine abuse–related acute renal failure were associated with rhabdomyolysis.6,16,17 It is still the most common renal complication of cocaine abuse. Cocaine-related rhabdomyolysis has a high mortality. In 1 report,16 13 of 39 patients with cocaine-related rhabdomyolysis developed acute renal failure. Among those patients with acute renal failure, 6 died. The mechanism of cocaine-induced rhabdomyolysis is unclear. Increased muscle activity resulting from sustained and repetitive sympathetic stimulation, ischemia because of vasoconstriction, and direct toxicity are potential causes of cocaine-related rhabdomyolysis.

Myocardial and cerebral ischemia because of cocaine-induced vasoconstriction has been well documented in many clinical and experimental studies. The vasoconstriction effects are mediated via competitive antagonism of norepinephrine reuptake.8 In animal studies, the cocaine effects on various blood vessels and vascular beds are different, suggesting variable distribution of catecholamine loci and their receptors.9 Although there is no direct evidence of cocaine inducing renal vascular constriction in humans, clinical reports of acute tubular necrosis and kidney infarcts following cocaine abuse strongly suggest that vasoconstriction most likely occurs in the renal circulation.11 The result of renal vasoconstriction is commonly acute tubular necrosis, but there may be a direct toxic effect of cocaine metabolites on the proximal epithelial cells.12,19

Acute renal failure with accelerated or malignant hypertension is occasionally seen in cocaine abusers. Thakur and colleagues20 reported 2 chronic hypertensive patients who developed accelerated hypertension with renal failure after consuming cocaine. Histologic examination of kidney biopsies from these patients revealed typical hyperplastic vasculopathy with onion-skinning of the interlobular arteries and ischemic changes of glomeruli with cerebiform waviness of glomerular basement membranes. Segmental fibrinoid necrosis of an interlobular artery was also noted.

Reported cocaine-associated TMA is rare, with only 2 previously reported cases in the literature.21,22 In those reported cases, patients presented with hemolysis, thrombocytopenia, renal failure, and other systemic manifestations mimicking thrombotic thrombocytopenic purpura. Herein we have reported 2 cases of cocaine abuse-associated acute renal failure in patients who denied illicit drug use. The kidney biopsies revealed typical features of TMA. Clinically, these 2 patients presented with headache and significantly elevated blood pressure in the malignant hypertension range. Symptoms and signs of cardiac or cerebral ischemia were not present. Laboratory tests ruled out rhabdomyolysis. There were also no clinical indications and laboratory results to support thrombotic thrombocytopenic purpura or scleroderma. The renal biopsy from patient 1 revealed not only fibrinoid necrosis of arterioles and glomeruli but also evidence of vascular sclerosis and glomerulosclerosis. In case 2, the patient had no significant medical history, and the renal biopsy revealed prominent fibrinoid necrosis of glomerular arterioles and capillary tufts. The chronic changes of interstitium and vasculature were rather mild. Abuse of cocaine was confirmed by positive cocaine metabolites in urine by chemical analysis and by the finding of cocaine metabolites in proximal tubular cells.  

Thrombotic microangiopathy is not a specific entity but a lesion seen in many conditions, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, scleroderma, malignant hypertension, and toxicity related to various drugs and radiation nephritis. In our last 5-year renal biopsy archives, 24 (0.9%) of 2750 kidney biopsies were diagnosed as TMA. In these 22 cases, 6 presented clinically as malignant hypertension, and 2 of these 6 cases, as we have reported here, were cocaine related with clear laboratory evidence of abuse cocaine. The other 4 cases include 2 young females with preeclampsia and 2 chronic hypertensive patients with accelerated malignant hypertension. In these 4 patients, the blood pressures reached as high as 220 to 240 over 120 to 140 mm Hg, slightly higher than what we found in patients with cocaine abuse.

The pathogenesis of TMA is unclear. Proposed mechanisms suggest direct damage of vascular endothelium such as occurring in malignant hypertension, preeclampsia, chemotherapy-associated toxicity, and burns.23,24 In animal studies, cocaine abuse has been shown to induce a marked pressor response, which is mediated by sympathetic activation and α1-adrenoceptor stimulation.25 However, this hypertensive effect was short lasting because of the rapid recruitment of compensatory mechanisms that quickly normalize blood pressure, such as β-adrenoceptor-mediated relaxation of vascular smooth muscle cells. Clinically, most cocaine-intoxicated patients have short-lasting hypertension with no significant renal impairment. The hypertension is generally controlled by administration of medications that directly target the central effects of cocaine, such as the benzodiazepines.2,26 Therefore, hypertension alone appears to be insufficient for inducing TMA in cocaine-associated acute renal failure.

As indicated in several in vitro studies, cocaine is toxic to endothelial cells and can directly or indirectly injure the endothelium.5,6 Enhancement of catecholamines has
been demonstrated to be an effect of cocaine. Exposure to catecholamines has been suggested to induce endothelial injury and affect the permeability of small blood vessels in animal models. Clinically, disseminated intravascular coagulopathy is not an uncommon finding in patients who have died from cocaine abuse.11 These findings imply that either direct or indirect cocaine toxicity may damage endothelial cells and induce a vasculopathy with TMA features.

In addition, platelet activation and thrombus formation also occur secondary to cocaine. Platelets can be directly activated by cocaine27 and indirectly activated through an α-adrenergic–mediated increase in platelet aggregation.28 In the presence of cocaine, adenosine diphosphate–induced platelet aggregation is enhanced,29 and tissue plasminogen activator inhibitor is increased.30 It is likely that cocaine-induced toxicity and the hypertensive effect resulted in injury of endothelial cells in the 2 cases presented. Damage to the endothelium and activation of platelets further triggered thrombosis and fibrinoid necrosis in small vessels and capillaries and resulted in the morphologic changes characteristic of TMA. Other factors, such as chronic hypertension, arteriolosclerosis, and low cholinesterase activity, may also be involved in selected cases.

In most cases, a history of cocaine abuse is not readily available. A high index of clinical suspicion is necessary when patients present with acute renal failure associated with significantly elevated blood pressure and poor response to conventional treatment. Serum and urine testing for cocaine and cocaine metabolites are indicated in this clinical situation. Ancillary diagnostic techniques are often helpful in working out acute renal failure in suspicious cocaine abuse cases if a renal biopsy is performed. In some cases associated with cocaine use, the main renal lesion is infarct or necrosis,31,32 in others myoglobinuria-related,33 and in another group associated with acute tubular necrosis resulting from vasoconstriction and possibly as a direct toxic effect on proximal tubular cells by cocaine metabolites.19 In conclusion, 2 cases of cocaine-induced acute renal failure with no rhabdomyolysis or ischemic or toxic-induced acute tubular necrosis are reported. Renal insufficiency with malignant hypertension was the major clinical presentation. The histologic features are those of TMA with conspicuous fibrinoid necrosis of glomerular capillary tufts and arterioles. The mechanisms responsible for these pathologic changes are unclear but most likely multifactorial. Diffuse vascular endothelial injury because of direct toxicity or cocaine-enhanced catecholamine release is likely a major contributor to the renal pathology noted in the 2 reported cases. It remains imperative to recognize that acute renal failure following cocaine abuse can occur in the absence of concomitant rhabdomyolysis.

References