



EXCEPTIONAL CASE

The potential role of complements in cocaine-induced thrombotic microangiopathy

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Abstract

Thrombotic microangiopathy (TMA) is a rare disorder characterized by microvascular injury and occlusion resulting in tissue ischemia and dysfunction. TMA occurs in a variety of settings including cocaine use. Although cocaine is widely used in the United States, cocaine-associated TMA is only rarely reported. Therefore, other factors may predispose cocaine users to the development of TMA. Emerging evidence indicates that cocaine activates complements. Therefore, complement activation may contribute to the development of cocaine-induced TMA. Here, we report a cocaine user who presented with renal failure. Renal biopsy demonstrated TMA. Laboratory tests revealed reduced serum complement C3 and normal complement C4 levels indicative of alternative complement activation. We postulate that complement activation is involved in the pathogenesis of cocaine-induced TMA.

Key words: cocaine, complements, endothelial injury, thrombotic microangiopathy

Introduction

Cocaine use remains a serious public health concern. Although cocaine can adversely affect the function of almost every organ system, the effects of cocaine on the vasculature including those of the kidney, the coagulation system and complements are of particular interest to this report [1]. Cocaine causes endothelial dysfunction characterized by increased endothelin-1 (vasoconstrictor) and reduced nitric oxide (vasodilator) release, thereby promoting vasoconstriction. Cocaine stimulates platelet activation and aggregation. It further promotes coagulation by increasing the activity of plasminogen activator inhibitor and raising the plasma levels of fibrinogen and von Willebrand

factor. Accumulating evidence indicates that cocaine and its adulterant levamisole may also activate complements [2–4]. Increased complement activity may cause endothelial injury and thrombotic microangiopathy (TMA) [5, 6].

Cocaine use may cause kidney injury secondary to ischemia, infarction, rhabdomyolysis, malignant hypertension and TMA. Although cocaine is in widespread use in the United States, cocaine-induced TMA is only rarely observed [7–9]. Therefore, other factors such as increased complement activity may predispose cocaine users to TMA. Here, we report a middle-aged cocaine user who developed TMA accompanied by complement abnormalities suggestive of alternative complement activation.

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We postulate that complement activation is involved in the pathogenesis of cocaine-induced TMA.

Case presentation

A 54-year-old man with a history of polysubstance abuse presented with altered mental status. His past medical history was notable for treatment-naïve hepatitis C infection. Family history was notable for a sister who was diagnosed with renal failure of obscure etiology requiring dialysis at the age of 45 years. On examination, the patient was found to be afebrile, drowsy and hypertensive (172/110 mmHg). Jugular veins were distended. There were crackles at the lung bases. Blood tests revealed creatinine 16.0 mg/dL, blood urea nitrogen 99 mg/dL, hemoglobin 11.3 g/dL, platelets 222 000/mm³, LDH 907 (84–246 IU/L) and haptoglobin 171 (30–200 mg/dL). Urinalysis showed proteinuria. A blood film revealed rare schistocytes. Random urine protein-to-creatinine ratio was 1.9. Urine toxicology revealed cocaine and its metabolites. Routine blood and urine cultures showed no growth. Serologic tests showed reduced complement C3 level of 71 (90–180 mg/dL) and normal C4 level of 32 (10–40 mg/dL). C3 hypocomplementemia persisted throughout hospitalization. There were no antibodies against HIV 1/2. Ultrasonography showed echogenic kidneys measuring 9.8 cm (right) and 10.3 cm (left). A renal biopsy was performed 9 days following admission. It contained 62 glomeruli, 51 of which showed global sclerosis.

In all, 11 glomeruli appeared bloodless and demonstrated tuft wrinkling as well as focal and segmental sclerosis. There were severe (80%) interstitial fibrosis and tubular atrophy. There was severe diffuse acute tubular epithelial cell injury. Arteries demonstrated moderate arteriosclerosis with foci of superimposed edematous intimal expansion resulting in luminal narrowing or occlusion (Figure 1A and B). Arterioles showed hyperplastic arteriolosclerosis (Figure 1C). Direct immunofluorescence microscopy showed no immunoreactants. Ultrastructural examination of glomeruli revealed subendothelial widening by finely granular and fibrillar material. The hospital course was notable for lack of renal recovery and uremia resulting in initiation of hemodialysis. Considering the patient's psychosocial status and the severity of renal fibrosis, eculizumab therapy was not considered. The patient was discharged from the hospital to receive hemodialysis in a dialysis center in the community.

Discussion

Here, we report a cocaine user who developed TMA. TMA is a rare complication of cocaine use. Gu and Herrera observed histopathological features of TMA in 0.9% of 2750 kidney biopsies [7]. They noted TMA associated with cocaine use and severe hypertension in only 2 (0.07%) biopsies. The authors argued that the presence of severe hypertension alone does not appear to

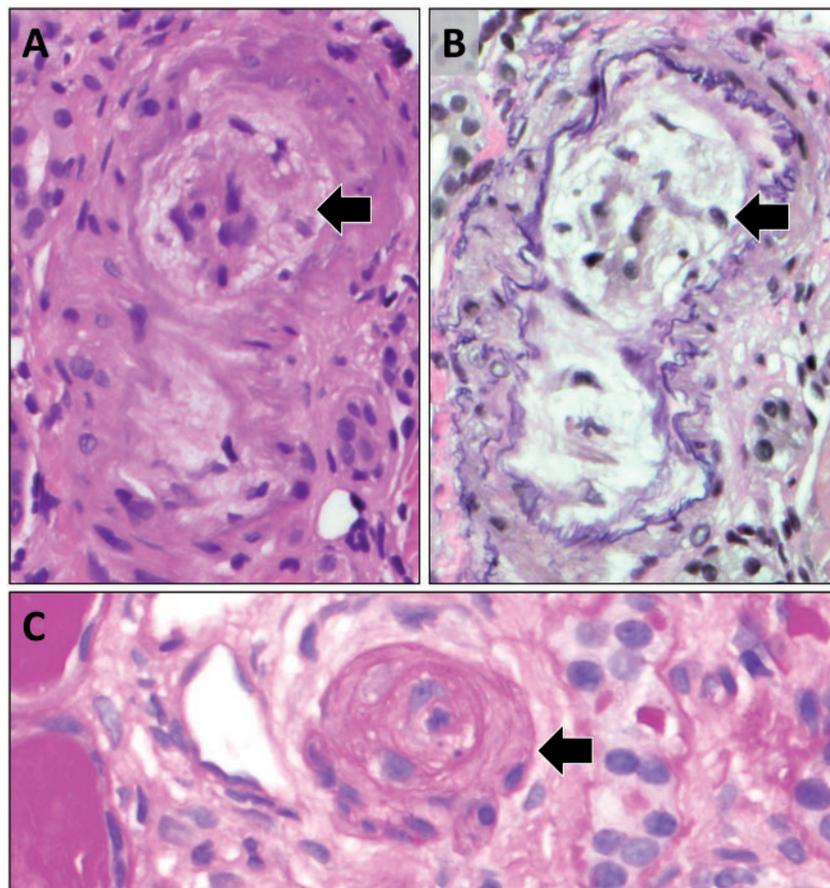


Fig. 1. Vascular histopathology. (A) An artery in the kidney showing luminal occlusion secondary to edematous intimal expansion (arrow) (hematoxylin and eosin stain). (B) Same artery as (A), demonstrating the absence of elastic fibers in the expanded intima (arrow) (Verhoeff's Van Gieson elastin stain). (C) An arteriole demonstrating onion skin-like smooth muscle cell hyperplasia (hyperplastic arteriolopathy) (arrow) (periodic acid-Schiff stain).

be sufficient for the development of TMA associated with cocaine use. Similar to our case, neither case demonstrated marked anemia or absolute thrombocytopenia. Volcy et al. reported a 38-year-old woman who presented with renal failure along with hematological and histopathological features of TMA following inhalation of crack cocaine [8]. Balaguer et al. reported a 22-year-old woman with a history of hepatitis C infection who developed acute hepatitis and renal failure following ethanol and intravenous cocaine use [9]. They diagnosed TMA based on clinical and hematological findings.

Because the vast majority of cocaine users do not develop TMA, there must be hitherto poorly understood contributing factor(s) that are crucial for the development of cocaine-induced TMA. Much is known about the role of complements in the pathogenesis of atypical hemolytic-uremic syndrome (aHUS), which is a life-threatening form of TMA [5]. In aHUS, loss-of-function mutations affecting complement regulatory genes lead to increased complement activity and complement-mediated endothelial injury. Conditions that further augment complement activity (complement amplifying conditions) or disturb endothelial homeostasis may result in severe microvascular injury and thrombosis in genetically susceptible individuals [10]. Emerging evidence indicates that cocaine and levamisole (a cocaine adulterant) activate the complement system. Tanhehco et al. showed that cocaine increased the gene expression of several complement components and the protein expression of the terminal complement complex C5b-9 in the rabbit heart [2]. Magro et al. reported extensive vascular C5b-9 deposition in cocaine-induced retiform purpura that is characterized by skin necrosis secondary to cutaneous TMA [3]. Durán et al. reported a 28-year-old man with complement factor H deficiency who developed TMA (aHUS) triggered by cocaine use [11]. Kondo et al. explored the effects of levamisole on complements in human subjects [4]. They demonstrated that levamisole led to complement activation via both classical and alternative pathways. Therefore, we speculate that cocaine-induced complement activation can lead to microvascular injury and thrombosis in genetically susceptible individuals.

Our patient had a history of hepatitis C infection. The serum C3 protein level can be reduced in patients chronically infected with hepatitis C compared with healthy individuals. This is in part secondary to hepatitis C-induced suppression of C3 production in hepatocytes [12]. However, several reports have shown that hepatitis C infection also reduces complement C4 expression and serum levels. Therefore, we believe that normal serum C4 levels argue against hepatitis C

infection as the cause of alternative complement activation in our case. In conclusion, we argue that alternative complement activation induced by cocaine and its adulterant levamisole can cause TMA.

Conflict of interest statement

None declared.

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