ANCA Associated Vasculitis Secondary to Levamisole-Adulterated Cocaine with Associated Membranous Nephropathy: A Case Series

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Keywords

Levamisole-adulterated cocaine · ANCA associated vasculitis · Membranous nephropathy

Abstract

Background: Cocaine is a risk factor for acute kidney injury and chronic kidney disease with progression to end-stage renal disease. Levamisole is an adulterant that is added to cocaine to enhance its euphoric effects. Levamisole-adulterated cocaine (LAC) is associated with the distinct clinical syndromes of agranulocytosis, leukocytoclastic vasculitis, cocaine-induced midline destructive lesions (CIMDL), and ANCA-associated vasculitis (AAV) with pauci-immune necrotizing glomerulonephritis. **Methods:** We reviewed all cases of AAV secondary to LAC at our institution. **Results:** We report 3 cases of AAV secondary to LAC and associated membranous nephropathy (MN). The first and second cases are concurrent AAV secondary to LAC and associated MN while the third case involves the development of MN after AAV secondary to LAC. **Conclusions:** Clinicians should be aware of this novel association of LAC with MN.

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Background

Cocaine is associated with a variety of renal manifestations including hyponatremia [1], hypertension (HTN) [2], rhabdomyolysis [3], thrombotic microangiopathy (TMA) [4], renal infarction [5], renal vein thrombosis [6], acute interstitial nephritis [7], AA amyloidosis [8], arteriosclerosis [9–11], chronic kidney disease [12–14], and end-stage renal disease (ESRD) [15]. Levamisole is a common adulterant that is added to cocaine to potentiate its euphoric effects [16–18] and is associated with distinct clinical syndromes including agranulocytosis [19], leukocytoclastic vasculitis (LCV) [20], cocaine-induced midline destructive lesions [21], and ANCA-associated vasculitis (AAV) with pauci-immune necrotizing glomerulonephritis (GN) [22]. AAV is associated with membranous nephropathy (MN) and MN is associated with crescents outside the setting of levamisole. We report our experience with 3 patients with AAV secondary to levamisole-adulterated cocaine (LAC) with associated MN.

Fig. 1. Cutaneous manifestations of case 1.

Case Presentations

Case 1

A 53-year-old Caucasian male with HTN, dyslipidemia, remote lumbar surgery, and a chronic pain syndrome was seen in the outpatient Nephrology clinic May 2014 with a 2 weeks history of lower extremity rash, hematuria, and a creatinine (Cr) of 150 $\mu\text{mol/L}$. Medications included prednisone 100 mg p.o. daily, rabeprazole 20 mg p.o. daily, and occasional ibuprofen. He smoked 1 pack of cigarettes per day, had a remote history of alcohol abuse, and was actively using crack cocaine up to the day prior to his clinic visit. He denied any other illicit drug use. On physical examination, blood pressure (BP) was 144/100 mm Hg with otherwise normal vitals. There were palpable purpura on his abdomen, thighs, and legs bilaterally (Fig. 1) as well as bilateral ear necrosis (Fig. 1). Relevant investigations are provided in Table 1.

A presumptive diagnosis of LAC-induced AAV was made and methylprednisolone 1 g IV q24h was initiated prior to renal biopsy (Fig. 2). The 34 glomeruli sampled for light microscopy (LM) showed an active focal crescentic and necrotizing GN with 4 glomeruli having active crescentic injury, 1 with segmental fibrinoid necrosis. There was also diffuse glomerular capillary wall thickening with epimembranous spikes seen on period acid methenamine stain. There was tubular epithelial injury with regeneration. Arteries sampled showed no active vasculitis. Immunofluorescence (IF) showed glomerular granular capillary loop IgG (2+), C3 (1+), kappa (2+), and lambda (3+). Glomeruli were negative for IgA, IgM, C1q, and fibrinogen. Staining for anti-phospholipase A2 receptor (anti-PLA2R) was negative in the glomerular deposits [23]. Electron microscopy (EM) of 2 glomeruli showed diffuse epithelial cell foot process effacement, and numerous subepithelial electron dense immune complex deposits. No mesangial deposits were

identified. Plasmapheresis was not performed. He was discharged with a prescription for prednisone 80 mg p.o. daily (1 mg/kg) with tapering and perindopril 4 mg p.o. daily. At the last follow-up of September 2015, Cr was 150 $\mu\text{mol/L}$, estimated glomerular filtration rate (eGFR) 50 mL/min/1.73 m^2 , and urine protein to Cr ratio (PCR) 160 mg/mmol with ongoing crack cocaine use.

Case 2

A 35-year-old Caucasian male with a 1 week history of distal symmetric polyarthrititis presented to his family physician in rural Manitoba, Canada, March 2013 and was prescribed prednisone 50 mg p.o. daily. Two days later, he presented to the emergency room with hemoptysis and iron deficiency anemia requiring blood transfusions. Computed tomography of his chest showed bilateral ground glass opacifications. Further history revealed chronic epistaxis for the last year. His Cr was 150 $\mu\text{mol/L}$, and urine PCR was 593.2 mg/mmol. A diagnosis of pulmonary renal syndrome (PRS) was made, and he was transferred to our tertiary center. He smoked half a pack of cigarettes and 4 g of marijuana per day, consumed 30 beers per week, and later disclosed intranasal cocaine and inhaled crack use. On physical examination, vitals were unremarkable and no abnormalities were noted including lymphadenopathy, mouth ulcers, uveitis, Raynaud's phenomenon, rashes, active joints, or neurologic symptoms. Relevant investigations are provided in Table 1.

A diagnosis of PRS secondary to LAC-induced AAV was made and a renal biopsy was performed (Fig. 2). There were 23 glomeruli for LM, up to 9 showing active segmental fibrinoid necrosis, and 3 with active crescentic injury. There was tubular epithelial injury with regeneration. Arteries sampled showed no active vasculitis. IF showed glomerular mesangial and capillary loop IgG (1–2+), IgM (1+), C3 (1+), trace C1q, and lambda (1+). Glomeru-

Table 1. Summary of cases

Case	Demographics	Clinical	Laboratory	Renal	Serology	Secondary MN investigations	Urine drug screen*	Treatment
1	53-year-old Caucasian male	Cutaneous	Na 137, K4.9, Cl 103, HCO3 21, albumin 28, albumin 28, P 1.65, normal LE's, normal LFT's, INR 1.2, PTT 34.3, WBC 5.8, HGB 81, PLT 296, C3 0.68, C4 0.10, SPEP N/O	Urea 24.8, Cr 449, U/A: protein 1.0 g/L, 51–100 RBC/HPF, UNa 65, FeNa >1%, PCR = 186.8, U/S R 12.2 cm, L 11.8 cm and increased echogenicity, anti-PLA2R negative	ANA -'ve, anti-dsDNA 15, ENA -'ve, Rf -'ve, c-ANCA -'ve, p-ANCA +'ve, PR3 8, MPO 167, anti-GBM 2, APLA IgM -'ve, APLA IgG -'ve, HIV -'ve, HCV -'ve, HIV -'ve	ANA -'ve, anti-dsDNA 15, HBV -'ve, HCV -'ve, normal CXR, normal skin exam, FOBTx3 negative, PSA normal, abdominal U/S normal, NSAID exposure	Cocaine metabolites LC-MS N/O	CS ACE inhibitor
<2	35-year-old Caucasian male	Arthralgias hemoptysis	Na 136, K 4, Cl 102, HCO3 21, albumin 28, Ca 2.40, Mg N/O, P 1.27, normal LE's, normal LFT's, INR 1.1, PTT 31.1, WBC 9.4, HGB 90, PLT 460, C3 1.56, C4 0.20, SPEP -'ve	Urea 7.1, Cr 150, U/A: protein 1–5 g/L, 4+ HGB, 21–50 RBC/HPF, occasional WBC, dysmorphic RBC, PCR 593.2, CrCl 60 mL/min, U/S N/O, anti-PLA2R testing N/O	ANA -'ve, anti-dsDNA Ab 9, Rf 11, p-ANCA +'ve, c-ANCA -'ve, PR3 24, MPO >200, anti-GBM 0, cryoglobulins -'ve, HBV -'ve, HCV -'ve, HIV -'ve	ANA -'ve, anti-dsDNA 15, HBV -'ve, HCV -'ve, normal CXR, normal skin exam, abdominal U/S normal, no NSAID exposure	Cocaine metabolites, LC-MS = cannabinoids, opiates, benzodiazepines, levamisole	CS + CYC then AZA ACE inhibitor
3	34-year-old Caucasian male	Cutaneous arthralgias edema	Na 140, K 4.4, HCO3 28, Cl 103, Ca 2.35, P 1.37, albumin 30, normal LE's, normal LFT's, INR 1.0, PTT 31.3, WBC 9.7, HGB 143, PLT 287, C3 1.15, C4 0.19, SPEP -'ve	Urea 4.6, Cr 71, U/A 1–5 g/L protein, 1+ HGB, 3–5 RBC/HPF, occasional dysmorphic RBC, PCR 369.5, PCR 449.9, U/S R 13.4 cm, L kidney 13.0 cm, anti-PLA2R testing N/O	ANA -'ve, anti-dsDNA 15, Rf 23.0, ENA -'ve, p-ANCA +'ve, c-ANCA -'ve, PR3 74 and MPO 91 at presentation with vasculitis, PR3 <20 and MPO 100 at time of renal biopsy, APLA IgM -'ve, APLA IgG -'ve, LI present, HBV -'ve, HCV -'ve, HIV -'ve	ANA -'ve, anti-dsDNA 15, HBV -'ve, HCV -'ve, normal CXR, normal skin exam, abdominal U/S normal, no NSAID exposure	Cocaine metabolites, LC-MS = opiates, benzodiazepines, levamisole	Conservative therapy then CS + CYC then CNI

MN, membranous nephropathy; Na, sodium (mmol/L); K, potassium (mmol/L); Cl, chloride (mmol/L); HCO₃, bicarbonate (mmol/L); Ca, calcium (mmol/L); P, phosphate (mmol/L); albumin (g/L); LE's, liver enzymes; LFT's, liver function tests; INR, international normalized ratio; PTT, prothrombin time (seconds); WBC, white blood cells; HGB, hemoglobin (g/L); PLT, platelets, C3 (0.88–2.10 g/L), C4 (0.16–0.47 g/L); SPEP, serum protein electrophoresis, urea (mmol/L); Cr, creatinine (μmol/L); U/A, urinalysis; RBC, red blood cells; HPF, high powered field; UNa, urine sodium (mmol/L); FeNa, fractional excretion of sodium; ACR, albumin to creatinine ratio (mg/mmol); PCR, protein to creatinine ratio (mg/mmol); CrCl, creatinine clearance (mL/min); U/S, ultrasound; anti-PLA2R, anti-phospholipase A2 receptor antibodies; ANA, anti-nuclear antibody; anti-dsDNA, anti-double stranded DNA antibody (IU/mL); Rf, rheumatoid factor (IU/mL); ANCA, anti-nuclear cytoplasmic antibody; p, peri-nuclear; c, cytoplasmic; PR3, proteinase 3 (RU/mL); MPO, myeloperoxidase (RU/mL); anti-GBM, anti-glomerular basement membrane antibody; APLA, antiphospholipid antibody; HBV'sAg, hepatitis B surface antigen; HBV'sAb, hepatitis B surface antibody; HCV, hepatitis C antibody; HIV, human immunodeficiency; LI, lupus inhibitor; CXR, chest X-ray; FOBT, fecal occult blood testing; PSA, prostate specific antigen; NSAID, non-steroidal anti-inflammatory drug; LC-MS, liquid chromatography; CS, corticosteroids; CYC, cyclophosphamide; CNI, calcineurin inhibitor; ACE, angiotensin converting enzyme; N/O, not obtained.

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

* CEDIA cocaine assay by thermo scientific for cocaine and cocaine metabolites. Urine samples were deproteinized by addition of acetonitrile also containing internal standards and subsequently diluted with mobile phase prior to analysis. Analysis was by liquid chromatography-mass spectrometry (Agilent 1200 HPLC/Sciex 3200 QTRAP mass spectrometer) using the method of scheduled MRM monitoring with enhanced product ion scanning. Drugs were identified as "present" when exceeding a minimum chromatographic area count in addition to being identified by retention time and matching of mass spectra to spectra within a library database of 350 drugs and metabolites using a minimum fit and purity score.

Fig. 2. Renal pathology. **a** Case 1 light microscopy PAS stain showing active crescent injury. **b** Case 1 light microscopy period acid methamine stain showing diffuse capillary wall thickening with epimembranous spikes. **c** Case 2 light microscopy trichrome stain showing segmental fibrinoid necrosis. **d** Case 3 light microscopy

PAS stain showing no significant abnormality. **e** Case 3 immunofluorescence showing granular capillary IgG staining. **f** Case 3 electron microscopy showing diffuse podocyte effacement, subepithelial electron dense deposits, spikes of glomerular basement membrane.

li were negative for IgA, fibrinogen, and kappa. EM of 1 glomerulus showed diffuse epithelial cell foot process effacement and subepithelial and intramembranous immune complex deposits, with no mesangial deposits identified.

Based on the history of alveolar hemorrhage, prednisone 40 mg p.o. b.i.d. (1 mg/kg) and cyclophosphamide (CYC) 1 g IV administration were started. No plasmapheresis was performed. He received induction therapy with CYC 750 mg IV q monthly for 6 months with corticosteroids followed by maintenance therapy with azathioprine (AZA) 100 mg p.o. daily (which he did not tolerate) with prednisone tapering and subsequent discontinuation May 2014. At his last clinic follow-up in June 2014, his Cr was 121 $\mu\text{mol/L}$, eGFR 59 mL/min/1.73 m^2 , albumin to Cr ratio 62.9 mg/mmol, MPO 91 IU/ml with enalapril 10 mg p.o. daily. He has been lost to follow-up.

Case 3

A 34-year-old Caucasian male with a history of LCV secondary to LAC-induced AAV in December 2010 treated with prednisone and AZA was referred to the outpatient Nephrology clinic in December 2011 for new onset proteinuria at a routine Rheumatology clinic visit. He had been feeling well other than fatigue and arthralgias. He did not have any new skin manifestations and was considered to be in AAV remission. Medications included AZA 150 mg p.o. daily, ramipril 5 mg p.o. daily, and acetaminophen p.r.n. He drank socially, was a lifelong non-smoker, "dabbled" in cocaine (denied recent use) but had no other illicit drug use. On physical examination, he was hypertensive with a BP of 167/81 mm Hg and morbidly obese. Examination was unremarkable other than diffusely tender joints, trace edema, and hyper-pigmented lesions consistent with healed LCV on his extremities. Relevant investigations are provided in Table 1.

A renal biopsy showed 15 glomeruli for LM, none were globally or segmentally sclerosed. There was no glomerular crescentic or necrotizing injury. Glomerular capillary walls appeared of normal thickness. Arteries showed no active vasculitis. IF showed glomerular granular capillary loop IgG (3+), C3 (2+), trace kappa, lambda (3+), and mesangial IgM (1+). Glomeruli were negative for IgA, C1q, and fibrinogen. EM of 3 glomeruli showed scattered subepithelial immune complex deposits showing no specific substructure, with focal intervening spikes of new basement membrane material. No mesangial deposits were identified.

Conservative therapy for secondary MN was pursued with irbesartan titrated to 150 mg p.o. daily. After 6 months, there was no improvement in proteinuria. AZA was replaced with CYC 150 mg p.o. daily and prednisone 60 mg p.o. daily. CYC therapy was complicated by leukopenia and hemorrhagic cystitis requiring discontinuation in September 2012. It was replaced with tacrolimus 4 mg p.o. b.i.d. and he attained a complete remission in November 2013. Tacrolimus was stopped in February 2014 and prednisone discontinued in November 2014 after tapering. Serology did not correlate to renal response and MPO titers remained elevated in follow-up. Unfortunately, he has since been admitted for recurrent cocaine use, LCV, and septic shock secondary to a polymicrobial skin and soft tissue infection with bacteremia requiring skin grafting. He was last seen in follow-up in April 2015 with Cr 57 $\mu\text{mol/L}$, eGFR >60 mL/min/1.73 m² and PCR 15.4 mg/mmol and has been abstaining from cocaine.

Conclusions

We report 3 cases of AAV secondary to LAC with associated MN including 2 concurrent cases of AAV and MN secondary to LAC (cases 1, 2) and 1 case of MN with previous AAV secondary to LAC (case 3).

The association between MN and crescents is not a new clinical entity [24–26] and is thought to be due to immune complex injury, MN with superimposed AAV, or anti-glomerular basement disease. Nasr et al. [25] described 14 patients without systemic lupus erythematosus (SLE) or known secondary AAV with biopsy-proven MN and pauci-immune necrotizing AAV (32% of which had crescents). The mean age was 58.7 years; acute kidney injury (AKI) and hematuria were frequent, and mean 24-h urine proteinuria was 6.5 g/day. Seven were P-ANCA positive, 5 were C-ANCA positive, 1 had atypical ANCA, and there were 5 MPO, 3 PR3, and 1 mixed pattern. The majority were treated with CYC and corticosteroids with a relatively poor prognosis with 50% reaching ESRD or death. Although cocaine use was not explicitly reported, no patient had a syndrome compatible with LAC. It was thought that the 2 glomerular processes were unrelated occurring only by chance. Rodriguez et al. [26] reported 19 patients with biopsy-proven MN and crescents who were ANCA and anti-GBM negative without any clinical

evidence of SLE. Mean age was 55 years, mean eGFR 39.7 mL/min/1.73 m², proteinuria 11.5 g/day, 84% had hematuria, and 25% crescents. Fourteen patients were treated with immunosuppression and 21% progressed to ESRD with dialysis independent patients having a mean eGFR 53.3 mL/min/1.73 m² and proteinuria 3.2 g/day. Six of 16 patients (38%) were anti-PLA2R staining positive [27, 28] suggesting primary MN and 2 patients developed MPO positivity in follow-up. Zou et al. [29] reported the largest retrospective series of biopsy-proven AAV with MN from China with 223 AAV patients of which 27 had combined AAV and MN and 30 matched primary MN controls. AAV with MN was associated with higher disease activity, Cr, proteinuria, nephrotic syndrome, ENT involvement but lower gross hematuria and overall worse renal survival at 1 year with varying pathology scores. In the cases in which it was measured, serum anti-PLA2R was present in 12.5 vs. 65%, $p = 0.028$, and glomerular staining in 6.6 vs. 66.6%, $p = 0.015$ in the combined AAV plus MN and MN control groups respectively.

In the 2000s, levamisole was identified as a cocaine adulterant (a pharmacologically active substance added to a drug in order to decrease the purity of the primary product without making the user aware) and is seen commonly worldwide [17, 18]. Levamisole was previously used as an immunomodulatory agent and as adjuvant chemotherapy, but is no longer used due to its toxicity [30–32]. As an adulterant, it is associated with AAV with renal involvement [22, 33]. As a secondary AAV, p-ANCA is more common than c-ANCA, and MPO more common than PR3 (although dual positivity may occur), with anti-phospholipid antibodies occasionally coexisting [16]. However, renal involvement by AAV is rare with a literature review revealing only 1 case of pauci-immune necrotizing and crescentic GN in 2011 [16]. McGrath et al. [22] reported the largest series of LAC-associated AAV including 18 patients with complete clinical and laboratory data (eliminating 12 others) from a total of 327 patients with new positive ANCA serology between 2009 and 2010 at Massachusetts General Hospital. Arthralgias, skin (LCV, TMA, panniculitis, necrosis), and head/neck involvement were common. Renal involvement was less common and was found in 8 patients with abnormal urinalyses (proteinuria, hematuria, red blood cell casts) and 2 patients with AKI (Cr 7.7, 5.6 mg/dL). Only 1 patient had a renal biopsy performed and did not have any evidence of MN. p-ANCA and MPO serology were positive in all patients and c-ANCA and PR3 were positive in 50% and both were generally in high titers in conjunction with other autoimmune serology.

There have been 3 previous case reports of MN in the setting of AAV presumably secondary to LAC but none confirmed levamisole exposure (online suppl. Table S1, see www.karger.com/doi/10.1159/000456553).

The pathogenesis of MN in the setting of LAC AAV is unclear. Induction of ANCA is thought to be due to an inflammatory event with an immune response against epitopes [34] of neutrophil granules influenced by genetic susceptibility [35] and environmental factors with neutrophil priming, epitope spreading and apoptosis with release of NETs [36] leading to vascular necrotizing inflammation, hemorrhage, and fibrin deposition [37]. Crescent formation occurs as a result of GBM injury and disruption leading to podocyte activation [38], cellular proliferation in Bowman's space with an infiltrate composed of monocytes, macrophages, parietal epithelial cells evolving to T cells and sclerosis. ANCA are predominantly IgG1 and IgG4 [39] and may lead to IC deposition detected by IF or EM in AAV [40] but is usually minimal (<2+ or "pauci-immune") with predominantly mesangial and rarely subepithelial deposits [40–42]. MN involves IgG antibodies against endogenous podocyte antigens or circulating IgG antibodies against antigens that are filtered across the GBM resulting in subepithelial immune deposits, complement activation, and diffuse granular IgG and C3 GBM staining and expansion. Primary MN is associated with IgG4 deposition while secondary MN is associated with IgG3 deposition in addition to mesangial deposits. Anti-PLA2R antibodies are thought to be the mechanism of injury in primary MN [43] with other antigens implicated including thrombospondin type I domain containing 7A [44] as well with etiology-specific antigens playing a role in secondary causes.

In AAV, ANCA may target endogenous podocyte antigens or lead to GBM injury and IC deposition along the GBM, leading to cryptic podocyte neoepitopes that could contribute to an immune response resulting in coexisting MN. MPO, for example, has been shown to co-localize with IgG and C3 along anionic glomerular capillary walls in crescentic AAV with MN [45, 46]. However, any significant injury to the GBM theoretically would result in significant pan-glomerular IC which would not be typically seen [40]. But what is it about levamisole that may potentiate whatever the underlying mechanism? It is known that LAC may contribute to the development on ANCA by inducing endothelial injury and the release of NET [47] so perhaps this vascular injury is implicated. Levamisole itself may actually be the antigen that induces MN but this remains to be proven with limited ultrastructural renal biopsy studies in the LAC [48].

We were able to confirm exposure to LAC unlike other previous reports [22, 33, 48–50] with all of our cases having compatible LAC AAV syndromes. Garg et al. [51] did report positive testing for LAC but the pathology was consistent with an immune complex GN rather than AAV with MN. Limitations of our cases include anti-PLA2R testing only case 1 (although not a standard clinical practice at the time of cases 2 and 3) but we are confident in our exclusion of traditional secondary MN etiologies despite NSAID exposure in case 1. We are confident in our description of this association and hope that it informs clinicians who might encounter it but ultimately cannot definitively prove causality.

Authors' Contributions

D.C. acquired the data and was a major contributor in writing the manuscript. D.C., C.S., K.R., M.K., K.B., and I.W.G. contributed to the conception of the study and revision of the manuscript. I.W.G. performed histological examination of the kidney. All authors read and approved the final manuscript.

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Disclosure Statement

The authors declare that they have no conflicts of interests.

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