

Cocaine-Levamisole Causing ANCAS Associated Vasculitis with Diffuse Alveolar Hemorrhage and Crescentic Membranous Glomerulonephritis

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Abstract

We present a 45-year-old female who presents with diffuse alveolar hemorrhage and acute kidney injury and positive MPO-ANCA serology induced by adulterated cocaine with levamisole, an antiparasitic molecule. The discussion includes clinical, laboratories, imaging pathophysiology, and treatment components.

Keywords: *Adulterated Cocaine-Levamisole; ANCAS Associated Vasculitis; Diffuse Alveolar Hemorrhage; Crescentic Membranous Glomerulonephritis*

Abbreviations

ANCA: Anti-Neutrophilic Cytoplasmic Antibody; AAV: ANCAS Associated Vasculitis; NETSs: Neutrophil Extracellular Traps; MPO: Myeloperoxidase; P-ANCA: Perinuclear Anti-Neutrophilic Cytoplasmic Antibody; PR3: Proteinase-3; C-ANCA: Cytoplasmic Anti-Neutrophilic Cytoplasmic Antibody; CIMDL: Cocaine-Induced Midline Destructive Lesions; CT: Computerized Tomography

Introduction

Cocaine abuse affects around 6.2 million persons in the United States of America as of 2009 [3]. The complications of this abuse in the respiratory are vast and varied, with a spectrum including severe epistaxis, nasal septum perforation, to non-hydrostatic pulmonary edema, or acute pulmonary hypertension, amongst many others.

Levamisole was originally formulated and marketed as an anti-helminthic to treat both humans and animals, originally Relcan under the brand name Ergamisol. Unfortunately, due to its unique properties in its powder formulation, makes the distinction between cocaine and levamisole impossible to distinguish between one or the other at first glance. Hence in the first decade, it started to be used as a “bulk” or “cutting” agent by drug dealers and is believed to adulterate at least 70% of cocaine [1,3].

Levamisole caused ANCAS associated vasculitis (AAV) in cocaine users’ kidney biopsies. AAV relapse in 50% of patients after successful treatment but the mortality decreased from 80% (untreated) to 25% in 5 years with treatment [2]. Only two autopsies cases of levamisole showed AAV in the medical literature. The pulmonary-renal syndrome associated with AAV is well known, but after an extensive search, we found no clinical cases documented with adulterated cocaine-levamisole causing diffuse alveolar hemorrhage due to AAV.

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Case Narrative

We present a 45 years old woman with a diagnosis of systemic lupus erythematosus with predominantly cutaneous vasculitis, fibromyalgia, arthralgias in the past with remission for the last three years. She presented to the Emergency Department with dyspnea and hemoptysis for the last five days prior to admission. She has been using inhaling cocaine actively for the last 20 years.

Physical exam showed two significant factors on initial presentation; one was her saddle nose deformity initially thought to be from long term heavy cocaine use and two, her violaceous purpuric plaques predominantly at upper and lower extremities. The lungs have scattered fine inspiratory crackles at both lungs. The heart had normal sounds without murmurs. There was no organomegaly in the abdomen. The patient denied chest pain, epistaxis, hematuria, hepatitis, trauma, intravenous drug abuse.

She was found to have severe anemia requiring 2 units of red blood cells transfusion. Initial CT chest showed diffuse pulmonary infiltrates without cavitary lesions (Figure 1).

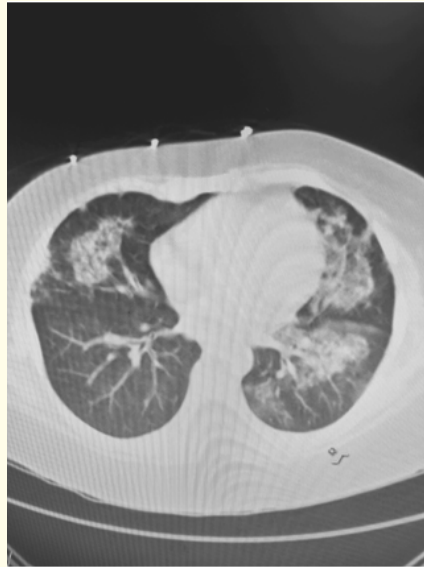


Figure 1: CT scan of the chest in a patient with cocaine inhalation and hemoptysis

The electrocardiogram was unremarkable with negative cardiac enzymes. The echocardiogram showed mild pulmonary hypertension with normal left ventricular function and cardiac valves function and anatomy. The patient required multiple transfusions over the hospital course but never developed hypotension or needed mechanical ventilation. A bronchoscopy showed diffuse alveolar without infectious organisms or eosinophilia. A fluoroscopy-guided transbronchial biopsy showed only hemosiderin-laden macrophages despite adequate sampling.

The renal function deteriorated acutely with a creatinine clearance of 15ml/min without response to intravenous fluids. The urinalysis showed hematuria with large red blood cells numbers, but no red blood cell casts. The urinary drug screen was positive for cocaine. In the serology, the MPO Ab titers were 531.5, strongly positive with P-ANCA titers > 1:640. The Proteinase 3, anti-glomerular basement antibodies, cardiolipin antibodies, antistreptolysin O antibodies were negative. Surprisingly, the serology for ANA (Antinuclear antibodies), DS-DNA (double-stranded DNA) for systemic lupus erythematosus were negative. Hepatitis B and C antibodies were negative.

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The patient received pulses of methylprednisolone one gram daily for three days earlier, followed by Prednisone 60 mg orally daily. After three days, she initiated Cyclophosphamide induction therapy, which the patient tolerated very well. The hypoxemia and hemoptysis resolved at the end of the hospitalization.

The kidney biopsies showed subsegmental crescentic glomerulonephritis with necrosis associated with granular immunofluorescence and membranous nephropathy (Figures 2-5).

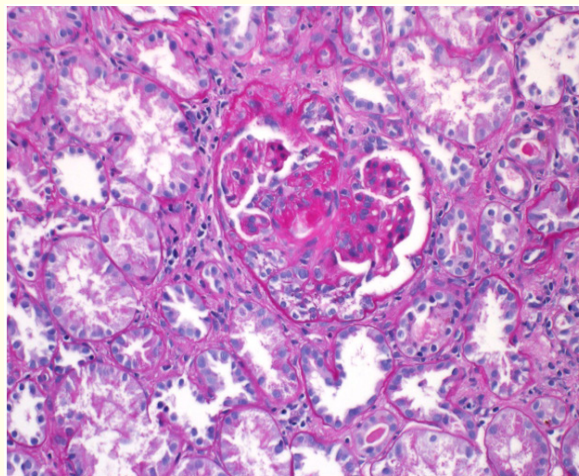


Figure 2: Kidney biopsy showed crescentic glomerulonephritis in cocaine-levamisole induced vasculitis.

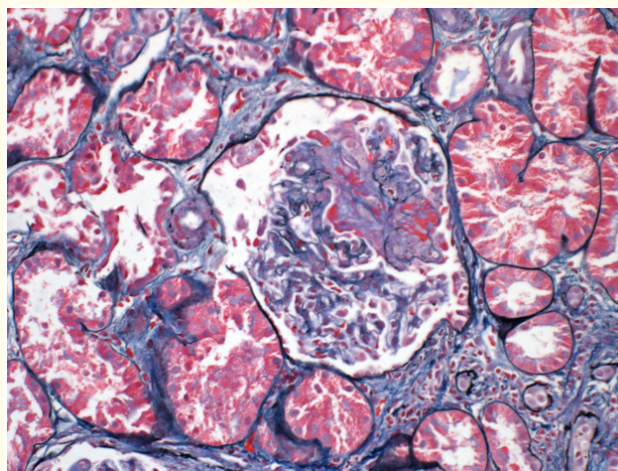


Figure 3: Necrotizing Glomerulonephritis in kidney biopsy of cocaine-levamisole induced vasculitis

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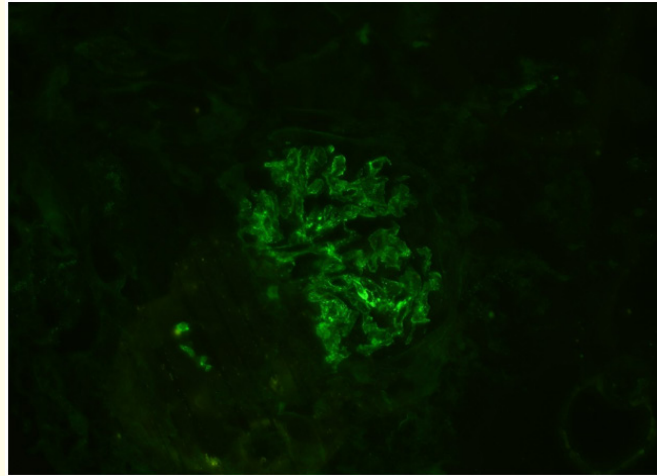


Figure 4: Kidney biopsy showing IgG immunofluorescence fine granular pattern of glomerular capillary loops of ANCA vasculitis by cocaine-levamisole.

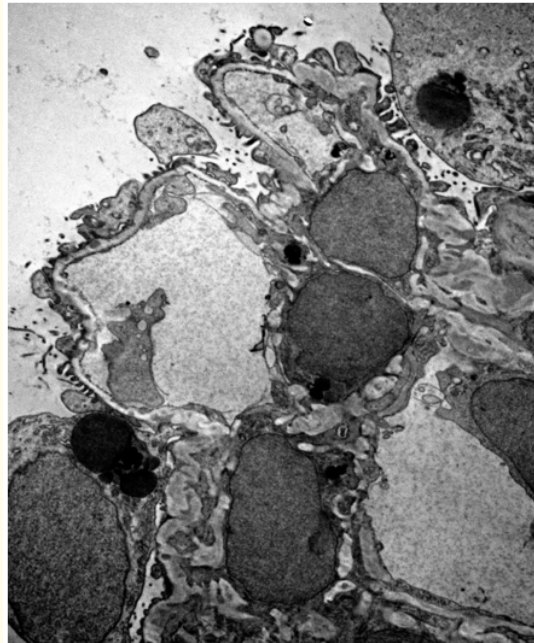


Figure 5: Electron microscopy of kidney biopsy showing minute subepithelial and mesangial deposits of membranous nephropathy in ANCAS vasculitis induced by cocaine-levamisole.

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Discussion

There were 1.5 million cocaine users in the United States of America in 2014, according to the National Survey on Drug Use and Health. Levamisole was detected in seized samples by the US Drug Enforcement Administration in 2003 [3]. The first reports of levamisole-induced ANCA vasculitis involved 30 patients in 2011 [4].

Levamisole is an anthelmintic veterinary drug once used in humans as a chemotherapy adjuvant in colon adenocarcinoma, steroid-resistant pediatric nephrotic syndrome, and rheumatoid arthritis. The drug was removed from the US market in 1999 due to agranulocytosis during long term use [5,6]. The CDC reports that nearly 70% of all cocaine products sold in the US include levamisole [7]. Levamisole prolongs the effects of cocaine by its metabolite Aminorex. Aminorex and its metabolites have an amphetamine-like pharmacological activity with high abuse potential with a longer half-life than cocaine [1,8,9]. Aminorex was discontinued from the market as an anorectic agent due to pulmonary hypertension adverse effect.

Tests for the presence of levamisole itself in patients is challenging to perform [10], so it is expected to have a high number of false-negative tests. The vasculitis that arises from Levamisole use is uniquely capable of creating positivity for both myeloperoxidase (MPO formerly P-ANCA) and proteinase-3 (PR3 formerly C-ANCA), however most predominantly MPO-ANCAS.

The patient had a saddle nose deformity attributed to cocaine-induced midline destructive lesion (CIMDL). The CIMDL involves septal cartilage ischemic necrosis, nasal septal perforation similar to Wegener's granulomatosis [11]. Pulmonary vasculitis associated with cocaine adulterated with levamisole was identified in 2 autopsies in the medical literature [12]. Cocaine may produce acute pulmonary edema by coronary artery vasoconstriction. An eosinophilic inflammatory coronary artery pathology associated with cocaine/levamisole with possible clinically linked coronary artery dissection, hypersensitivity coronary syndrome and vasospastic allergic angina may be present in clinically linked eosinophilic coronary syndromes [13]. Laboratory abnormalities with adulterated cocaine may include positive ANA, ANCA, and phospholipid antibodies [14].

Levamisole propagates multiple direct tissue inflammatory effects through a myriad of pathways. One is through its effect on neutrophil extracellular traps (NETs), a cell death mechanism used by neutrophils culminating in an extrusion of DNA that surrounds and kills/immobilizes bacteria, protozoa, and helminths. NETs produce endothelial inflammation by activating the complement systems using MPO and PR3 ANCA via proinflammatory proteins [15]. Levamisole activates the NET pathway by activating nicotinamide-adenine dinucleotide phosphate oxidase and peptidyl deaminase-dependent pathways, as well as M3 muscarinic receptors, specifically in the areas of vasculitis inflammation/thrombosis. This mechanism is toxic to endothelial cells, impairing endothelium-dependent vasorelaxation [16]. Vasculitis skin lesion from cocaine users showed NETs in medical reports.

Levamisole causes a pauci-immune focal necrotizing and crescentic glomerulonephritis as well as mesangial deposits of immunoglobulin A, immunoglobulin G, immunoglobulin M, and C3. The exact method whereby levamisole brings about its nephrotoxic effects is poorly understood, however it has been proposed that it forms an MPO-levamisole antigen which induces antibodies accounting for the ANCA vasculitis as well as crescentic glomerulonephritis, and then implanting preferentially in the kidney subepithelium to induce a secondary membranous nephropathy [17-19].

Conclusion

Pulmonary-renal syndrome with alveolar hemorrhage may occur with adulterated cocaine with levamisole. MPO-ANCAS vasculitis associated with cocaine-levamisole may affect the lung causing severe hemoptysis. A bronchoscopy may identify pulmonary alveolar hemorrhage -but the transbronchial biopsy is probably not useful as described in cases of pulmonary vasculitis.

The treatment with pulse corticosteroids and cyclophosphamide was effective in resolving the symptoms.

Disclosure

The authors have no conflict of interest or bias corresponding to this article.

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