A Case Report on Suspected Levamisole-Induced Pseudovasculitis

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ABSTRACT

Introduction: Levamisole-induced pseudovasculitis should be considered in patients with inconsistent anti-neutrophil cytoplasmic antibodies (ANCA) pattern and history of cocaine use.

Case Presentation: A 50-year-old man presented to the emergency department with symptoms of bilateral pulmonary emboli. His hospital course was complicated by multiple end organ failure, which improved dramatically with prednisone. Although he was diagnosed previously with granulomatosis with polyangiitis due to positive proteinase 3 (PR3), myeloperoxidase (MPO), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) and cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) markers, his longstanding cocaine use and history of skin ulcers, thrombotic events, and febrile illnesses suggested a diagnosis of levamisole-induced pseudovasculitis instead.

Discussion: Differentiating between vasculitides can be challenging due to similar clinical and laboratory findings. To differentiate the two, biopsies should be obtained. The absence of granulomas or leukocytoclasia, and the presence of vasculopathic purpura, should guide clinicians toward pseudovasculitis.

Conclusion: It is important to maintain a high index of suspicion for pseudovasculitis because long-term corticosteroid use to treat granulomatosis with polyangiitis can lead to detrimental effects.

CASE PRESENTATION

A 50-year-old man presented to the emergency department with increasing shortness of breath, fatigue, and dizziness. On review of symptoms, the patient denied the presence of fever, chills, chest pain, and headache. Vital signs showed a blood pressure of 118/89 mmHg, temperature of 97.5°F, heart rate of 111 beats per minute, respiratory rate of 19 breaths per minute, and saturation of 94% on room air.

Physical examination revealed general illness. Lung examination revealed significant diffuse and bilateral wheezing and +3 bilateral pitting edema was found on both upper and lower extremities. Significant laboratory parameters included a B-type natriuretic peptide of 15,604 pg/mL, a D-dimer of 12.39 mcg/mL, and a white blood cell count of 13.2 x $10^3/mm^3$. Cardiac biomarkers were negative. A computed tomography angiogram was performed, revealing lobar and segmental bilateral acute pulmonary emboli with increased left axillary, hilar, and mediastinal lymphadenopathy. Magnetic resonance imaging also was completed, which showed restricted diffusion throughout both cerebral hemispheres, concerning for a global anoxic event.

Past medical history was significant for hypertension, transient ischemic attack, heartburn, chronic kidney injury, deep vein thrombosis, and pulmonary emboli. During a prior admission, the patient presented with similar respiratory symptoms as well as chronic kidney injury and was suspected of having granulomatosis with polyangiitis due to proteinase 3 (PR3), myeloperoxidase (MPO), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), and cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) serum marker positivity (Table 1). He declined renal biopsy and was treated empirically with prednisone and rituximab. In addition, the patient had a history of provoked deep vein thrombosis in his legs after sustaining bilateral leg trauma and subsequently having difficulty with ambulation. Due to medication noncompliance, he continued to have sub-

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Table 1. History of Biomarker Results

Admission Date	P-ANCA	C-ANCA	MPO	PR3	Cocaine	Levamisole
Feb 2011					+	
Feb 2012	-	+			+	
Nov 2012	+	+	+	+		
Feb 2014				+		
March 2015					+	
May 2015	+		+	+	+	-
July 2015			+	-	+	

Abbreviations: P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3.

therapeutic international normalized ratios, which presumably led to the formation of pulmonary emboli. There was no record of a thrombophilia workup despite these aforementioned provoking factors.

Family history was noncontributory. Relevant social history included heavy use of cocaine.

To treat his bilateral pulmonary emboli, the patient was started on heparin and warfarin therapy. Forty milligrams of prednisone was continued to treat granulomatosis with polyangiitis but rituximab was discontinued. On the fifth day of admission, the patient desaturated and laboratory findings revealed leukocytosis with a white blood cell count of 21.7 x 10^3/mm^3 and a procalcitonin level of 0.12 μg/L, likely due to sepsis. Chest x-ray revealed bibasilar opacities consistent with possible hospital-acquired pneumonia; thus, the patient was started on triple antibiotic therapy with vancomycin, piperacillin/tazobactam, and levofloxacin. Since the patient was immunocompromised, sulfamethoxazole/trimethoprim was subsequently added to cover the possibility of pneumocystis pneumonia. However, he continued to decline and developed severe sepsis with liver, kidney, and respiratory failure. Since no evidence of methicillin-resistant Staphylococcus aureus was found on sputum culture, vancomycin was discontinued. Due to continued rises in procalcitonin and white count, the decision was made to replace piperacillin/tazobactam with meropenem for broader coverage. Clindamycin was added for possible aspiration pneumonia and voriconazole was added for possible fungal infection. Sulfamethoxazole/trimethoprim also was discontinued due to rising creatinine and worsening acute kidney injury and replaced with primaquine. After 2 weeks, all antibiotics except meropenem were discontinued as all cultures remained negative. Due to continued high suspicion for pneumonia, doxycycline was added.

During his hospital admission, a transthoracic echocardiogram was obtained due to clinical deterioration with nonsustained ventricular tachycardia. Results revealed acute systolic heart failure with an ejection fraction of 25% to 30% with global hypokinesis secondary to sepsis. At that time, the possibility of levamisole-induced pseudovasculitis was considered due to the patient's longstanding history of cocaine use. Positive P-ANCA, C-ANCA, MPO, and PR3 serology as well as past medical history of deep vein thrombosis, necrotizing pneumonia, and infectious ulcers also were suggestive of pseudovasculitis induced by a cocaine contaminant known as levamisole. Prednisone was increased to 60 milligrams a day to empirically treat suspected levamisole-induced pseudovasculitis. As the patient's condition began to improve, meropenem and doxycycline were discontinued. Throughout the course of 1 month, the patient slowly recovered from bilateral pulmonary emboli, hospital-acquired pneumonia, acute kidney injury, anion gap metabolic acidosis, hepatic congestion, and acute systolic heart failure. At discharge, his laboratory data and clinical findings were markedly improved compared to baseline.

DISCUSSION

Differentiating between granulomatosis with polyangiitis and its mimics is a challenging but necessary task to prevent the misuse of corticosteroids and immunosuppressant therapy. Use, and particularly overuse, of corticosteroids is associated with immunosuppression, an increased risk of fracture, development or exacerbation of cardiovascular disease, fluid retention, hypertension, and obesity.[1]

Pseudovasculitis is a disease process that mimics the presentation and laboratory findings of true vasculitis (Table 2). It does not, however, present with the typical histopathologic findings usually seen in vasculitis. Cocaine-induced midline destructive lesions should be considered in patients with positive ANCA serology, an atypical set of clinical findings, and a history of cocaine use. Levamisole, a contaminant found in 69% of cocaine,[2] also can cause its own myriad symptoms known as levamisole-induced pseudovasculitis.

Currently, there is no clear consensus for the treatment of cocaineor levamisole-induced pseudovasculitis. Treatments are primarily supportive. Steroids, anticoagulation, and withdrawal from cocaine use have been beneficial in varying degrees.[3] The natural history of levamisole-induced pseudovasculitis is spontaneous resolution without medical therapy. Thus, early recognition and cocaine cessation is the key for treatment.[3]

Overall, our patient presented with bilateral pulmonary emboli and was hospitalized with necrotizing pneumonia. These symptoms, along with a past history of skin ulcers, thrombotic events, and frequent episodes of myalgia, shortness of breath, and febrile illnesses, are suggestive of levamisole-induced pseudovasculitis. In addition, the patient had positive ANCA serology and a longstanding history of cocaine use. Despite these characteristic findings, our patient did not develop necrotic purpura on the helix of his ears or agranulocytosis, two distinctive findings consistent with levamisole-induced pseudovasculitis.

Table 2. Comparison of Granulomatosis With Polyangiitis, Cocaine-Induced Midline Destructive Lesions, and Levamisole-Induced Pseudovasculitis

	VASCULITIS	PSEUDOVASCULITIS	
	Granulomatosis With Polyangiitis[4]	**Cocaine-Induced Midline Destructive Lesions**[5]	**Levamisole-Induced Pseudovasculitis**[6]
Physical Findings	Fever, myalgia, arthralgia	Absent systemic symptoms	Fever, myalgia, arthralgia
Ear, Nose, Throat	Oral/nasal ulcers, sinusitis, rhinorrhea, purulent/bloody nasal discharge	Nasal ulcers, nasal septum perforation, facial ulcers	Purpura on ear helix, zygomatic arch, cheek
Cardiac	Pericarditis, coronary arteritis[7]	Myocarditis	Variable
Pulmonary	Cough, dyspnea, stridor, wheezing, hemoptysis, pleuritic pain	Pulmonary edema, bronchiolitis	Variable
Renal	Variable	Variable	Variable
Cutaneous	Lower extremity purpura, necrosis, ulceration, urticaria	Skin necrosis, urticaria	Skin necrosis, skin ulcers, lower extremity purpura Immunoglobin and complement deposits found in skin[8]
Vascular	Variable	Thrombosis	Thrombosis
Serology	PR3, C-ANCA, P-ANCA, MPO	PR3, P-ANCA, HNE	PR3, C-ANCA, P-ANCA, MPO, HNE, cathepsin G lactoferrin, elastase, lysozyme, agranulocytosis
Histology	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis Stromal granuloma with giant cells, micro-abscesses and deeply located necrosis	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis

Note: This is a partial list and not intended to be all inclusive.

Abbreviations: P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3; HNE, hydroxynonenal.

During a prior admission, he tested negative for levamisole after a positive cocaine screen (Table 1). However, testing for levamisole occurred after 48 hours. Ideally, the presence of levamisole should be tested immediately upon admission, as the half-life is 5.6 hours and only 3% to 5% of the drug can be detected in the urine within 48 hours of last use.[6] Since levamisole can only be detected in the urine for up to 48 hours, the negative levamisole result could not be used to rule out the use of levamisole-laced cocaine.[6] Retrospectively, a biopsy of his skin ulcer, testing for hydroxynonenal (HNE) antibodies, and urine toxicology screening for levamisole within 48 hours of admission would have allowed us to confidently make this diagnosis, which unfortunately was not done. On the other hand, a renal biopsy would have been able to confirm granulomatosis with polyangiitis. A high index of suspicion and early diagnosis in a patient with a history of cocaine use is crucial in order to minimize unnecessary treatment that may place the patient at a higher risk for immunosuppression.

CONCLUSION

While differentiating among various vasculitides can be challenging, we must take steps to confirm a patient's diagnosis before initiating treatment, as long-term corticosteroid use can lead to myriad undesirable effects. To differentiate between granulomatosis with polyangiitis and pseudovasculitis induced by cocaine and levamisole, kidney and skin biopsies must be obtained. It is also imperative to check HNE ANCA, Cathepsin G, lactoferrin, elastase, and lysozyme levels and screen for the presence of levamisole in the urine.

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