



# The Creative Clinician

## A New Low for an Old High: Neutropenia Induced by Levamisole-Adulterated Cocaine

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**Recently, both the media and medical literature have directed attention towards neutropenia associated with levamisole-adulterated cocaine.** Levamisole, available in South America as an anti-helminthic veterinary agent, was previously used in the **United States (US)** for treatment of colon cancer and rheumatoid arthritis. Due to its well-established adverse effect of reversible neutropenia in approximately 20% of patients exposed,<sup>1</sup> levamisole was voluntarily removed from the US market in 2000.<sup>2</sup> Despite this known complication, levamisole has been isolated in up to 70% of cocaine seized by the **Drug Enforcement Administration (DEA)** in recent years.<sup>3</sup> Evidence suggests traffickers in supply countries adulterate cocaine with levamisole, likely due to a known stimulatory synergism between the two drugs.<sup>2,4</sup>

Since 2009, nearly 100 cases of neutropenia associated with levamisole-adulterated cocaine have been reported in medical literature in North America and Europe. These patients, variably testing positive for cocaine and/or levamisole, have presented with symptoms including fever, generalized lymphadenopathy, oral ulcers, opportunistic infections, retiform purpura and, in at least one case, death.<sup>1-3,5-8</sup> Exposure to levamisole can be tested by urinary gas chromatography, but this assay is not widely available and is of limited utility given the short urinary half-life of levamisole (5-6 hours).<sup>1,2</sup> While the exact mechanism of levamisole-induced neutropenia remains unknown, reports of HLA-B27, lupus anticoagulant and **anti-neutrophil cytoplasmic antibody (ANCA)** positivity among neutropenic patients exposed to levamisole suggest a potential autoimmune pathophysiology.<sup>1,8,9</sup> G-CSF has been proposed as a treatment to shorten the duration of levamisole-induced neutropenia and minimize associated complications, but its relative efficacy for this purpose has not been firmly established.<sup>1</sup>

### CASE

A 64-year old man with a history of alcohol and cocaine abuse presented with three days of cervical lymphadenopathy, painful oral ulcers, sore throat and anorexia. He reported nasal and oral use of approximately 5g of cocaine in the previous month, but denied any other constitutional symptoms, exposures, past medical history, or medications.

Vital signs were within normal limits. Pertinent physical exam findings included oral candidiasis, tender nasopharyngeal ulcerations, sub-

mandibular and anterior cervical lymphadenopathy, normal cardiopulmonary exam, absence of hepatosplenomegaly or rash, and normal neurologic exam. Laboratory findings showed severe neutropenia (ANC 200), but normal hemoglobin, platelets, serum chemistries, LFTs, urinalysis and CXR. Urine toxicology was positive for cocaine.

The patient was admitted for workup of his neutropenia and lymphadenopathy, and management of the nasopharyngeal lesions and candidiasis. He was treated with fluconazole and empiric broad-spectrum antibiotics and given supportive care. Infectious workup was negative for Gonorrhea and Chlamydia, HIV, HCV, CMV, VZV and B19 Parvovirus, but revealed equivocal EBV and HBV titers (negative on follow-up). Chest and abdominal CT scans were negative for malignancy. Rheumatologic workup demonstrated positive c-ANCA, proteinase-3 and lupus anticoagulant antibody, but negative p-ANCA, ANA and RF. The patient exhibited neither signs nor symptoms of Wegener's granulomatosis and denied history of thrombosis. His positive c-ANCA and proteinase-3 serologies were attributed to cocaine-induced midline nasal disease, and the positive lupus anticoagulant antibody was ascribed to levamisole exposure—associations reported previously in the literature.<sup>1,10</sup> Given his history and otherwise negative workup, it was concluded that, despite negative urinary levamisole gas chromatography, his isolated severe neutropenia was likely due to use of levamisole-adulterated cocaine. Over his two-week hospital course, his ANC slowly resolved to 1800 on discharge without G-CSF treatment, with improvement of the candidiasis and lymphadenopathy.

### DISCUSSION

Approximately 2.39% and 4.11% of the US and RI adult populations, respectively, reported cocaine use within the past year in 2006 and 2007. RI ranks second only to the District of Columbia.<sup>11</sup> Given the high rate of cocaine use within RI and pervasive contamination of the cocaine supply with levamisole,

Results of urinary toxicology tests	Cocaine positive (half-life = 3-4 days)	Cocaine negative
Levamisole positive (half-life = 5-6 hours)	-Almost certain	-Possible, but confusing
Levamisole negative	-Probable (this case) -Lupus anticoagulant Ab?	-Possible (with history), but less likely

**Table 1:** Is this *otherwise unexplained* neutropenia due to levamisole-adulterated cocaine? Results from urinary toxicology tests for cocaine and levamisole can aid clinicians in diagnosing neutropenia induced by levamisole-adulterated cocaine (based on W110-UMC system for standardized case causality assessment)<sup>12</sup>

health care workers in RI should maintain a high index of suspicion for levamisole exposure among patients.

This case of probable levamisole-induced neutropenia illustrates several important considerations. When encountering patients with neutropenia of unknown etiology and/or a history of cocaine use, clinicians should take a thorough history. That history should include questions about recent cocaine or crack use. If a patient's history or physical exam suggests cocaine exposure, a urinary toxicology screen and levamisole gas chromatography should be ordered quickly, given the short half-lives of both cocaine and levamisole (3-4 days and 5-6 hours, respectively).<sup>2</sup> This case corroborates prior evidence that lupus anticoagulant antibody can play a role in confirming levamisole exposure in urinary levamisole-negative patients,<sup>1</sup> but further studies are needed to establish the positive predictive value, specificity, and clinical implications of the antibody in this clinical context.

Notably, a positive history of cocaine use does not definitively indicate levamisole ingestion because not all cocaine is contaminated, and there appears to be regional variation in the prevalence of levamisole-tainted cocaine.<sup>3</sup> Similarly, confirmed ingestion of levamisole does not exclude the presence of other more common causes of neutropenia. As evidenced by this case, given the short urinary half-lives of cocaine and levamisole, patients with negative urinary levamisole and/or cocaine levels could conceivably have levamisole-associated neutropenia if the exposure were outside of the urine toxicology screen window. Levamisole-induced neutropenia should remain a diagnosis of exclusion, reserved for cases in which other causes of neutropenia have been ruled out and clinical suspicion, in conjunction with laboratory data, is particularly suggestive. Table 1 depicts how cocaine, levamisole and lupus anticoagulant antibody test results can inform clinical suspicion of levamisole-associated neutropenia.

G-CSF has been identified as a potential treatment for levamisole-induced neutropenia, but is generally not begun until other causes of neutropenia have been excluded.<sup>1</sup> This case underscores the clinical challenge in making this diagnosis, and subsequently, the decision to initiate treatment. Waiting for laboratory results to return can delay treatment, leading to lower neutrophil counts, longer hospital stays, additional morbidity and mortality, and ultimately higher health care costs. In patients presenting with neutropenia of unknown etiology, more widespread and timely screening for cocaine, levamisole and lupus anticoagulant antibody could expedite treatment with G-CSF, if appropriate.

Further studies are needed to identify: 1) the prevalence of levamisole in the cocaine supply; 2) the incidence of levamisole-induced neutropenia from cocaine use; 3) the sensitivity and specificity of urinary levamisole and lupus anticoagulant antibody as diagnostic tests; 4) the therapeutic efficacy of G-CSF in treating patients with neutropenia in the setting of cocaine use, after other common etiologies are excluded; and 5) the natural history and associated morbidity and mortality of confirmed levamisole-associated neutropenia.

The US Government's **Substance Abuse and Mental Health Services Administration (SAMHSA)** has issued a nationwide public health alert regarding levamisole-adulterated cocaine, and encourages clinicians to report suspected and confirmed cases to state health departments or local Poison Con-

rol Centers.<sup>3</sup> We encourage hospitals and health centers to educate physicians and staff, who should in turn inform at-risk patients, their communities, and the popular media regarding yet another dangerous complication of cocaine use.

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## Disclosure of Financial Interests:

The authors and/or significant others have no financial interests to disclose.

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