BRIEF REPORT

Purpura, Cutaneous Necrosis, and Antineutrophil Cytoplasmic Antibodies Associated With Levamisole-Adulterated Cocaine

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Objective. To describe the clinical and serologic abnormalities in 6 patients who presented with retiform purpura and extensive cutaneous necrosis after exposure to levamisole-adulterated cocaine.

Methods. All patients were evaluated at San Francisco General Hospital or the University of California San Francisco Medical Center. Each underwent standard screening for substances of abuse and had urine tested for the presence of levamisole by liquid chromatography tandem mass spectrometry. Routine laboratory, autoantibody, and antiphospholipid antibody testing was performed in the hospitals’ clinical or reference laboratories. Testing for atypical antineutrophil cytoplasmic antibodies (ANCAs) was performed separately using commercially available enzyme-linked immunosorbent assay kits.

Results. The patients were women ages 39–50 years who presented with retiform purpura and cutaneous necrosis. Skin biopsies revealed a predominantly small-vessel thrombotic vasculopathy with varying degrees of vasculitis. Four patients were neutropenic. All tested positive for lupus anticoagulant, had IgM antibodies to cardiolipin, and tested strongly positive for ANCAs in a perinuclear pattern by immunofluorescence. Each patient had antibodies to multiple components of neutrophil granules, including neutrophil elastase, lactoferrin, cathepsin G, proteinase 3, and myeloperoxidase.

Conclusion. Rheumatologists should be aware of this distinctive form of necrotic purpura, its associated autoantibodies, and its link to levamisole-adulterated cocaine.

Levamisole was previously used as an immunomodulatory agent for the treatment of colon cancer, rheumatoid arthritis, and relapsing pediatric nephrotic syndrome, but toxicity led to its withdrawal from the market (1,2). Now available as a veterinary anthelmintic medication, levamisole has emerged as a prevalent adulterant of illicit cocaine in the US. Recent reports link the use of levamisole-laced cocaine to life-threatening agranulocytosis (3–5) and to a distinctive form of necrotic purpura previously reported in children treated with levamisole for nephrotic syndrome (6). Herein we describe 6 cases of necrotic purpura that developed in users of cocaine adulterated with levamisole. This syndrome manifests clinically as retiform purpura and cutaneous necrosis involving the extremities, face, and ears. The predominant histopathology is a small-vessel thrombotic vasculopathy rather than vasculitis. All patients have lupus anticoagulant (LAC), IgM antibodies to cardiolipin, and antineutrophil cytoplasmic antibodies (ANCAs) with specificities for elastase and other components of neutrophil granules.

PATIENTS AND METHODS

All patients were seen at either San Francisco General Hospital or the University of California San Francisco (UCSF) Medical Center and provided written consent for the review of their medical history and for the collection of serum and urine samples in accordance with a protocol approved by the UCSF Committee on Human Research. We tested for levamisole in urine using a qualitative liquid chromatography tandem mass spectrometry method. Briefly, samples were spiked with an internal standard and tested along with calibrators and controls using a levamisole standard (Sigma-Aldrich). The presence of levamisole was monitored using an ion transition specific to levamisole. When the ion transition was present at the correct chromatographic retention time, mass spectra were

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acquired and matched to the mass spectra of a levamisole standard for positive identification.

ANCA immunofluorescence assays and testing for antibodies to myeloperoxidase (MPO) and proteinase 3 (PR3) were performed by the clinical and reference laboratories of UCSF or San Francisco General Hospital. The ANCA pattern was determined using slides containing ethanol-fixed neutrophils, and perinuclear ANCA (pANCA) positivity was confirmed using formalin-fixed slides. Antibodies to MPO and PR3 were determined using multianalyte fluorescence detection and reported in arbitrary units (AU) per milliliter as negative (≤19 AU/ml), equivocal (20–25 AU/ml), or positive (≥26 AU/ml). Antibodies to neutrophil lactoferrin, cathepsin G, lysozyme, and elastase were detected by enzyme-linked immunosorbent assays (ELISAs) using a commercial kit according to the recommendations of the manufacturer (Orgentec) and quantified in AU per milliliter using known concentrations of positive antibody controls provided by the manufacturer; results were considered negative (≤10 AU/ml), equivocal (11–20 AU/ml), or positive (≥21 AU/ml). All other laboratory studies were performed by the clinical and reference laboratories of the hospitals.

**RESULTS**

All patients were women between the ages of 39 and 50 years (Table 1). Five patients reported smoking “crack” cocaine, and one inhaled cocaine in powder form. Each presented with purpura that progressed to necrosis and ulceration of the skin (Figures 1A–D). The lesions affected the arms, legs, face (particularly the skin overlying the zygomatic arch), and ears, with relative sparing of the trunk and back. In several cases, extensive lower extremity lesions required debridement and skin grafting. In all cases, biopsies of the skin at the edge of the purpuric lesions demonstrated diffuse small-vessel thrombosis (Figures 1E and F). In 4 cases, skin biopsy specimens showed varying degrees of vascular and perivascular inflammation (Figures 1E and F); there was no evidence of associated vasculitis in the remaining 2 cases.

All patients tested positive by urine toxicology for recent exposure to cocaine and to levamisole, as measured by liquid chromatography tandem mass spectrometry (results are available from the author upon request). Four patients were neutropenic, and 2 had

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**Table 1.** Demographic characteristics, histopathology, and autoantibodies in the 6 patients exposed to levamisole-adulterated cocaine*

<table>
<thead>
<tr>
<th>Patient/age/sex</th>
<th>Pathology</th>
<th>ANA, titer (pattern)</th>
<th>LAC</th>
<th>IgM aCL</th>
<th>IgG aCL</th>
<th>IgM anti-β₂GPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/48/F</td>
<td>Small-vessel thrombosis, small-vessel vasculitis</td>
<td>1:160 (speckled)</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>2/43/F</td>
<td>Small-vessel thrombosis</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3/46/F</td>
<td>Small-vessel thrombosis</td>
<td>1:640 (diffuse)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>4/50/F</td>
<td>Small-vessel thrombosis, vasculitis</td>
<td>1:80 (speckled)</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>5/39/F</td>
<td>Small-vessel thrombosis, vasculitis</td>
<td>1:640 (diffuse)</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>6/40/F</td>
<td>Small-vessel thrombosis, vasculitis</td>
<td>1:640 (diffuse)</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* ANA = antinuclear antibody; LAC = lupus anticoagulant; IgM aCL = IgM anticardiolipin antibody; IgM anti-β₂GPI = IgM anti–β₂-glycoprotein I antibody.

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* Figure 1. **A–D,** Images of patients with necrotic, retiform purpura involving the legs and ear. **E and F,** Biopsy specimens of the skin from the arm of a patient with levamisole-associated vasculopathy, showing microvascular thromboses with surrounding inflammation (**E**) and occasional vasculitis (**F**).
absolute neutrophil counts at the lower limit of the normal range (range for all 6 patients 200–2,200 neutrophils/µl). Erythrocyte sedimentation rates determined by the Westergren method were 27–105 mm/hour in the 5 patients tested, serum C-reactive protein levels were elevated in all 5 patients tested (range 14.9–104.4 mg/liter), and 3 patients had antibodies to hepatitis C (none with detectable cryoglobulins), while none of the patients had hepatitis B surface antigenemia (data not shown).

Antinuclear antibodies were detected by immunofluorescence in all but one patient, with varying patterns and titers ranging from 1:80 to 1:640 (Table 1). All patients had LAC and moderate to high titers of IgM anticardiolipin antibodies; 3 patients also had IgM antibodies to β2-glycoprotein I (Table 1). None had detectable IgG antibodies to cardiolipin or to β2-glycoprotein I (Table 1). All patients had pANCA in titers ranging from 1:640 to ≥1:20,480 (Table 2). ELISA revealed antibodies to neutrophil elastase, lactoferrin, cathepsin G, PR3, and MPO (Table 2). There were no detectable antibodies to lysozyme.

**DISCUSSION**

Use of levamisole-adulterated cocaine is associated with a distinctive clinical syndrome that is characterized by purpura and cutaneous necrosis, thrombosis of small cutaneous vessels, and autoantibodies, including LAC, IgM antibodies to cardiolipin, and high-titer ANCA-specificities for neutrophil elastase, lactoferrin, cathepsin G, PR3, and MPO. This pattern of strong pANCA positivity as determined by immunofluorescence together with targeting of multiple neutrophil antigens is similar to that seen in vasculitis induced by propylthiouracil, hydralazine, and other drugs (7). Apart from neutropenia, the syndrome appears limited to the skin, without evidence of the involvement of other organ systems.

Although the combination of purpura and pANCA positivity suggests a diagnosis of microscopic polyangiitis (MPA), several features clearly distinguish this syndrome from MPA. The purpura is retiform and has a distribution (over the ears and zygomatic arch) that is different from the palpable purpura seen in ANCA-associated vasculitis and other small-vessel vasculitides. In contrast to patients with MPA, these patients often are neutropenic. The magnitude of the pANCA positivity as assessed by immunofluorescence is unusually high for MPA and is discordant with the relatively low levels of antibodies to MPO detected by ELISA. Finally, despite the presence of ANCA, the predominant histopathologic finding is small-vessel thrombosis rather than classic leukocytoclastic vasculitis, and all patients have antibodies associated with increased thrombotic risk, including LAC and IgM antibodies to cardiolipin.

Neutropenia is a well-recognized toxicity of levamisole. The other findings we describe herein closely resemble those described in previous reports of purpura and autoimmunity linked to levamisole when used as therapy for pediatric nephrotic syndrome (8–14). Purpura in the pediatric cases had a predilection for the ears and cheeks, an unusual distribution that was also seen in our cases (13). Skin biopsies revealed thrombotic vasculopathy with varying degrees of vasculitis. Autoantibodies in those cases, as in ours, included LAC, IgM antibodies to phospholipid, and ANCA. Discontinuation of levamisole in the pediatric cases led to complete resolution of skin findings within 2–3 weeks and to the disappearance of autoantibodies over a time course that ranged from 2 to 14 months (13). Therefore, exposure to levamisole in the absence of cocaine and other adulterants can induce the purpura, histologic abnormalities, and autoantibodies that were found in our patients.

The US Drug Enforcement Agency first detected levamisole in cocaine in April 2005 (15). The prevalence

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**Table 2.** ANCA specificities in the 6 patients exposed to levamisole-adulterated cocaine*

<table>
<thead>
<tr>
<th>Patient</th>
<th>ANCA IIF</th>
<th>PR3</th>
<th>MPO</th>
<th>Elastase</th>
<th>Cathepsin G</th>
<th>Lactoferrin</th>
<th>Lysozyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:20,480</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>1:2,560</td>
<td>Negative</td>
<td>Equivocal</td>
<td>Positive</td>
<td>Equivocal</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>1:20,480</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>1:640</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Equivocal</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>1:20,480</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>1:5,120</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* Positive, negative, and equivocal results are defined in Patients and Methods. For all patients, a perinuclear staining pattern was detected by antineutrophil cytoplasmic antibody (ANCA) indirect immunofluorescence (IIF). PR3 = proteinase 3; MPO = myeloperoxidase.
of this adulterant in cocaine bricks remained low (<5% throughout 2006 and <10% throughout 2007) until October 2008 (30%) and then increased substantially, reaching 70% in October 2009 (15). Children treated with levamisole developed necrotic purpura only after therapy with the drug for 16 months or longer (mean 24 months), suggesting that prolonged exposure to levamisole may be necessary to induce this syndrome (13). Our first patient presented in July 2009. A recent report from Rochester, New York described 2 patients with the same constellation of findings as ours; toxicology screening was positive for cocaine in each case, but the patients were not tested for levamisole (16). Another report described 2 Canadian patients who tested positive for levamisole exposure, developed similar skin manifestations, and had pANCA directed against “atypical” antigens (6).

Necrotic purpura was an uncommon complication of prolonged levamisole therapy for pediatric nephrotic syndrome, developing in <3% of treated children. Thus, it is likely that only a small fraction of those exposed to levamisole-adulterated cocaine will develop this syndrome. The number at risk, however, is large, given the current prevalence of levamisole as an adulterant in cocaine and the number of active users of cocaine in the US (estimated to be 1.9 million in the 2008 National Survey on Drug Use and Health) (17). Physicians should be aware of this distinctive form of necrotic purpura, its associated autoantibodies, and its link to levamisole-adulterated cocaine.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Graf had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Graf, Lynch, Yeh, Kral, Dominy, Imboden.

Acquisition of data. Graf, Lynch, Yeh, Tarter, Richman, Nguyen, Dominy, Imboden.

Analysis and interpretation of data. Graf, Lynch, Yeh, Nguyen, Kral, Dominy, Imboden.

REFERENCES

17. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2008 NSDUH: national findings. URL: http://oas.samhsa.gov/NSDUH/2k8 NSDUH/2k8results.cfm#Ch2.