Pyoderma Gangrenosum Induced by Levamisole-Adulterated Cocaine: Clinical, Serological, and Histological Findings in a Cohort of Patients

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Levamisole
- Synthetic imidazothiazole derivative
- Early uses: Cancer, RA, IBD
- Mechanism: T lymphocyte proliferation and dose-dependent neutrophil chemotaxis\(^1\)
- Adverse effects: Agranulocytosis (3-10%)
- Current use: Anti-helminthic

Levamisole in Cocaine
- Bulking agent (80% of supply)
- Why a popular additive agent?
  - Physical similarity
  - Nicotinic acetylcholinergic system\(^2\)
  - Indirect serotonin agonist\(^3\)
**Levamisole-Associated Vasculitis / Vasculopathy**

Clinical Presentation

<table>
<thead>
<tr>
<th>Patients</th>
<th>Upper Extremity</th>
<th>Lower Extremity</th>
<th>Trunk</th>
<th>Face</th>
<th>Ears</th>
<th>Nose</th>
<th>Oral</th>
<th>Arthralgias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>34/55</td>
<td>46/55</td>
<td>22/55</td>
<td>26/55</td>
<td>40/55</td>
<td>21/55</td>
<td>4/55</td>
<td>17/55</td>
</tr>
</tbody>
</table>
# Levamisole-Associated Vasculitis / Vasculopathy

## Laboratory Evaluation

<table>
<thead>
<tr>
<th></th>
<th>NPN</th>
<th>Biopsy</th>
<th>Lev</th>
<th>CRP</th>
<th>MPO</th>
<th>PR3</th>
<th>C-ANCA</th>
<th>P-ANCA</th>
<th>ANA</th>
<th>RF</th>
<th>C-IgM</th>
<th>C-IgG</th>
<th>HNE</th>
<th>C3</th>
<th>C4</th>
<th>Cryo</th>
</tr>
</thead>
</table>

## Histopathology:
- **Vasculopathy:**
  - Hyaline thrombi occluding dermal vessels in the absence of vasculitis
- **Vasculitis**
  - Fibrin in vessel walls
  - Leukocytoclasis
  - Erythrocyte extravasation
LEVAMISOLE-ASSOCIATED PYODERMA GANGRENSUM

Only now being reported in the literature
- Multiple isolated case reports\textsuperscript{5-10}
- Incomplete serologic evaluation

Study Cohort
- Cohort: 8 consecutive patients, 22 separate clinical encounters (2011 – 2015)
- Demographics:
  - Age (Mean): 43.6 years
  - Gender: 87.5\% Female
MORPHOLOGY / DISTRIBUTION – VESICULOPUSTULAR (EXTREMITIES)
Morphology / Distribution – Bulous (Dorsal Hands and Phalanges)
Morphology / Distribution - Bullous (Dorsal Hand)
Morphology / Distribution - Bullous / Pustular (Extremity)
Morphology / Distribution - Bullos / Pustular (Extremity)
MORPHOLOGY / DISTRIBUTION - ULcerative (Lower Extremity)
MORPHOLOGY / DISTRIBUTION - ULCERATIVE (LOWER EXTREMITY)
Morphology / Distribution - Cribiform Scarring (Extremity)
Morphology / Distribution - Cribiform Scarring (Extremity)
Morphology / Distribution - Cribiform Scarring (Back)
SIMULTANEOUS PG AND RETIFORM PURPURA (VASCULOPATHIC)
## Lesion Distribution / Morphology

<table>
<thead>
<tr>
<th>Lesion Distribution</th>
<th>Lesion Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Extremity</td>
<td>Vesicopustular</td>
</tr>
<tr>
<td>Dorsal Hand and Fingers</td>
<td>3/8</td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>Bullous</td>
</tr>
<tr>
<td>Trunk / Back</td>
<td>7/8</td>
</tr>
<tr>
<td>Face</td>
<td>Ulcerative</td>
</tr>
<tr>
<td>Ears</td>
<td>8/8</td>
</tr>
<tr>
<td>Nose</td>
<td>Vegetative</td>
</tr>
<tr>
<td>Oral</td>
<td>1/8</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Cribiform Scarring</td>
</tr>
<tr>
<td>6/8</td>
<td>1/8</td>
</tr>
<tr>
<td>75%</td>
<td>12.5%</td>
</tr>
<tr>
<td>50%</td>
<td>12.5%</td>
</tr>
<tr>
<td>100%</td>
<td>37.5%</td>
</tr>
<tr>
<td>37.5%</td>
<td>Retiform Purpura</td>
</tr>
</tbody>
</table>

- Extremity involvement common
- Upper = 75%  | Lower = 100%
- Facial / Aural / Nasal involvement uncommon
- Morphology reflects diversity / clinical evolution of PG lesions
**Serologic Evaluation**

<table>
<thead>
<tr>
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<th>NPN</th>
<th>Biopsy</th>
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<th>ANA</th>
<th>RF</th>
<th>C-IgM</th>
<th>C-IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2/8</td>
<td>8/8</td>
<td>0/8</td>
<td>6/8</td>
<td>7/8</td>
<td>4/8</td>
<td>0/8</td>
<td>7/8</td>
<td>3/8</td>
<td>1/8</td>
<td>5/8</td>
<td>0/8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C-IgG</th>
<th>C3</th>
<th>C4</th>
<th>Cryo</th>
<th>B2GP IgM</th>
<th>B2GP IgA</th>
<th>B2GP IgG</th>
<th>PhosSer IgM</th>
<th>PhosSer IgA</th>
<th>Lupus Anti</th>
<th>Other</th>
</tr>
</thead>
</table>

- Elevations in diverse panel of auto-antibodies
- At least one anti-phospholipid antibody (100%)
- P-ANCA (87.5%)
**OTHER LABS AND HISTOPATHOLOGY**

Cocaine Use: 100% Reported (Confirmed – urine toxicology in every patient at least once)

Histopathology:
- Neutrophil-dominated diffuse dermal infiltrate (All)
- Vasculitis – 5 of 8 patients
- Vasculopathy – 3 patients (setting of dermal infiltrate)
Neutrophilic Dermatosis
Thrombotic Vasculopathy with Neutrophilic Dermatosis
Infectious Workup

- Impetiginization common (6 of 8 patients)
- Variety of pathogens (MRSA, Pseudomonas, Strep Group A and B, Corynebacterium, Proteus, E. Coli)
- All Periodic acid-Schiff, Fite, and other stains negative
Treatment and Recurrence

Treatment: abstinence + optimal wound care
- Systemic steroids in 6 of 8 patients (accelerated recovery, esp. with hand involvement)

Future considerations: Harm-reduction strategy
- Patient noted “suppression with prednisone”. Recurred when prednisone ran out
- Patient self-testing?

Recurrence – 100% driven by cocaine relapse
SUPPORT FOR LEVAMISOLE

❖ Difficult to test for levamisole
  ▪ No internal testing
  ▪ Short half-life

❖ Serology – elevated autoantibodies

❖ No associated disease or precipitating factor for PG

❖ Clinical progression
  ▪ Lesion induction following cocaine use (median 1 week)
  ▪ Improvement / resolution with abstinence
  ▪ Recurrence with relapse
Common end-point – cutaneous ulceration

Clinical Progression

- Levamisole PG: pustule / bulla → ulceration → cribiform scarring
- Levamisole Vasculitis: inflammatory retiform purpura → hemorrhagic bullae → ulceration → atrophic scarring
CONCLUSIONS

- PG is a unique presentation of Levamisole-contaminated cocaine use
- Pustular & bullous subtypes common
- Extremity involvement common
  - Face, ears, and nose involvement less frequent
- Serology – elevated auto-antibody titers
  - P-ANCA
  - Anti-phospholipid antibodies
- Histopathology – diffuse dermal neutrophilic infiltrate
- Treatment - cocaine avoidance / gentle wound care
  - Short courses of steroids on case-by-case basis
  - Super-infection common
  - Harm-reduction strategies


5. Spearman AD. A case of pyoderma gangrenosum associated with cocaine abuse [abstract]. *Journal of Hospital Medicine* 9 Suppl 2: 635


