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Neutrophilic Dermatoses Overlap Syndrome with Temporal Relationship to Cocaine Usage: A Case Report

✉ Marisa Tandy¹, ✉ Trisha Khanna², ✉ Madeline Gleave Parson³, ✉ Michael Noparstak¹

¹Acadia Dermatology, Maine, USA

²Orlando Dermatology Residency Program, Florida, USA

³Phoenix Dermatology Residency Program, Arizona, USA

ABSTRACT

Neutrophilic dermatoses (ND) are conditions historically attributed to an undetected bacterial infection. Three of the more common ND are pyoderma gangrenosum (PG), Sweet's syndrome (SS) and neutrophilic dermatosis of the dorsal hands (NDDH), which have many points of clinical overlap. We herein report a rare presentation of recurring cocaine-induced ND overlap syndrome including PG, SS, and NDDH in an adult Caucasian female with a longstanding history of cocaine use. The patient presented with a generalized eruption of juicy, eroded, erythematous papules and nodules. Biopsies obtained revealed marked papillary dermal edema with a robust infiltrate of neutrophils and her labs revealed elevated inflammatory markers and elevated perinuclear anti-neutrophil cytoplasmic antibodies. The rash resolved after cocaine cessation and a prednisone taper. This case highlights a unique temporal relationship between cocaine use and recurrence of ND.

Keywords: Neutrophilic dermatoses, pyoderma gangrenosum, Sweet's syndrome, neutrophilic dermatosis of the dorsal hands, leukocytoclastic vasculitis

Introduction

Historically, neutrophilic dermatoses (ND) were attributed to an undetected bacterial infection; however, current theories include a clonal response to antigenic stimuli, neutrophilic dyscrasia, neutrophil dysfunction, and genetic influences [1,2,3,4]. Three of the more common ND are pyoderma gangrenosum (PG), Sweet's syndrome (SS), and neutrophilic dermatosis of the dorsal hands (NDDH). These diseases have many points of clinical overlap.

PG is a form of ND with an incidence of 3-10 cases per million people each year. It is most common in women 40 to 60 years old and may be associated with medical conditions such as inflammatory bowel disease (IBD), rheumatoid arthritis, and hematologic malignancies. Clinical subtypes of PG include ulcerative (most common), bullous, vegetative, pustular, and peristomal. Classic PG is a painful,

ulcerative lesion with a cribriform pattern, violaceous border, and an undermined epidermal edge [5].

SS, otherwise known as acute febrile neutrophilic dermatosis, is another example of ND. It generally presents in females 47 to 57 years old with fever, leukocytosis, painful plaques, and neutrophils on pathology without infection. There are three types, including classic, malignancy-associated, and drug-induced. Common triggers for classic SS include prior infection, vaccination, inflammatory disorder, and pregnancy [5].

NDDH is debated as a separate disease from SS; however, it is clearly a neutrophilic dermatosis as it exhibits a neutrophilic infiltrate without an active infection [6]. NDDH is most common in women and presents as a sudden onset of fever, leukocytosis, and painful plaques on the dorsal hand(s). Unlike in SS, bullae are common and may ulcerate. NDDH also is more often associated with vasculitis,



Address for Correspondence: Marisa Tandy Asst. MD, Acadia Dermatology, Maine, USA

Phone: +1 207 222 3112 **E-mail:** acadia dermatology@gmail.com **ORCID ID:** orcid.org/0000-0001-6886-7477

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where SS is not. The connection to an underlying malignancy warrants cancer screening in these patients [7].

Levamisole is an anti-helminthic drug used primarily in veterinary medicine. Previously, the FDA-approved its use in colon cancer post-resection, [8] however it was removed from the market in 2000 due to adverse reactions including neutropenia, agranulocytosis, and vasculitis [9,10,11]. Due to its similar appearance, cheaper cost, and ability to increase and prolong the euphoria from cocaine, it is a common bulking agent in cocaine sold in the United States. Cocaine inhibits monoamine transporters for serotonin (SERT), norepinephrine (NET) and dopamine (DAT). Aminorex is a levamisole metabolite that also inhibits NET and DAT, and causes efflux of SERT; which explains its ability to produce similar amphetamine-like properties and prolong the associated euphoria [8]. It has been found to increase the half-life of cocaine from 1 hour to 5.5-6 hours [12]. The United States Drug Enforcement Administration reports that the amount of seized cocaine containing levamisole rose from <10% in 2008 to 87% in 2016, before declining to 40% in 2017 [13,14,15].

We present a case of cocaine-induced ND overlap syndrome, including PG, Sweet's syndrome, and ND of the dorsal hands. Based upon cocaine's common contamination with levamisole, it is reasonable to think that this drug may play a contributory role in this patient's findings.

Case Report

A 47-year-old Caucasian female with an extensive history of cocaine use was seen in the hospital with a recurrent, painful, and non-

pruritic rash. She presented with a generalized eruption of juicy, eroded, erythematous papules and nodules. Evidence of the juicy lesions were visible on her buttock (Figure 1) her dorsal hallux at the interphalangeal joint (Figure 2), and an erythematous ulcer with central necrosis and violaceous borders was present on her left thigh (Figure 3). She was seen multiple times prior to our consultation for recurrence of the same rash.

Biopsies obtained from her buttock lesions exhibited marked papillary dermal edema with a robust infiltrate of neutrophils (Figure 4) and tissue culture was negative for bacteria, fungi, and mycobacteria. The patient has no known underlying disease process associated with a neutrophilic dermatosis, such as IBD, leukemia, multiple myeloma, or rheumatoid arthritis. Her labs were unremarkable except for elevated inflammatory markers and an elevated perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). Her erythrocyte sedimentation rate and C-reactive protein were elevated at 65 and 62.1, respectively. During her admission, she was treated with a 6-week 1 mg/kg prednisone taper along with cocaine cessation, and her rash resolved completely.

Of note, she was readmitted to the hospital several months later with the same rash, which occurred 2 weeks after she had relapsed on cocaine. The rash recurrence exemplifies the temporal relationship between cocaine use and her rash. Moreover, her rash completely resolved again after cocaine cessation and a prednisone taper.

Blood cultures have been negative over the course of her hospital admissions and she has not had any response to antibiotics. She has had multiple debridements over the course of her disease due



Figure 1. Numerous juicy eroded erythematous papules and nodules scattered on the buttocks



Figure 2. A juicy erythematous nodule with a central erosion on the interphalangeal joint of the right dorsal thumb

to presumed infection resulting in considerable scarring, most notably on her lower extremities. The patient has a cocaine-induced neutrophilic dermatoses overlap syndrome with concurrent PG, Sweet’s syndrome, and NDDH.

Discussion

Cocaine has been associated with ND [16], including 8 cases of PG with cocaine use reported by Jeong et al. [17]. These cases of PG have had +p-ANCA, + human neutrophilic elastase antibody titers (the most specific marker for levamisole-associated vasculitis), and even histopathologic findings of vasculitis in common with levamisole associated leukocytoclastic vasculitis [18]. Table 1 further



Figure 3. An erythematous to violaceous ulceration with some necrosis on the left thigh adjacent to a cribriform scar from prior PG that had been debrided

PG: Pyoderma gangrenosum

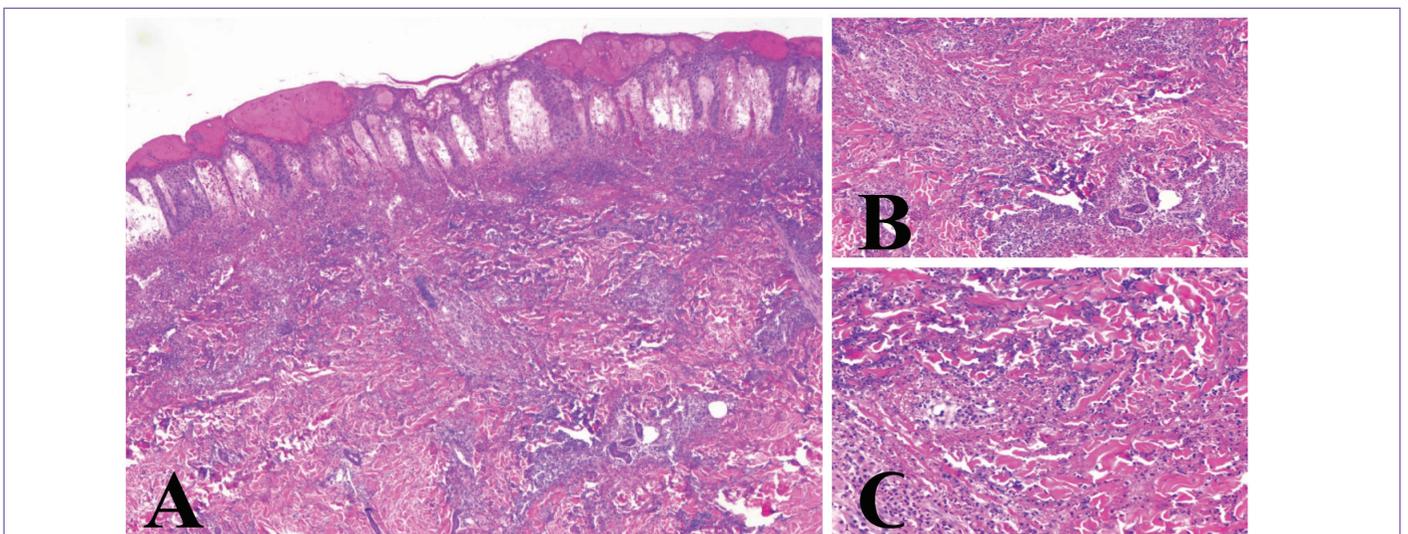


Figure 4. A biopsy taken from a nodule located on patient’s buttock. A) 40X reveals marked dermal edema with a robust neutrophilic infiltrate consistent with sweets. B) 100X C) On 200X marked dermal neutrophilic infiltrate without signs of infection or vasculitis

	Pyoderma gangrenosum	Sweet syndrome	Neutrophilic dermatosis of the dorsal hands	Levamisole vasculitis
Clinical presentation	Painful, well-demarcated ulcer with undermined, violaceous border	Tender, erythematous papules and nodules coalesce to plaques	Tender, erythematous papules and nodules coalesce to plaques +/- ulceration	Painful, palpable purpura, +/- bullae that may ulcerate
Lesion location	Lower legs Atypically: hands or elsewhere	Face, arms, neck	Dorsal hands	Lower legs Higher specificity: Helix and zygomatic arch
p-ANCA	+/-	+	+/-	+
Associated co-morbidities	Malignancy, IBD, systemic disease, vasculitis	Fever and leukocytosis, pregnancy, malignancy, drug-induced, post-vaccination, infection	Fever and leukocytosis, malignancy	Cocaine use
Pathergy	Yes	Yes	Yes	Yes
Treatment*	Topical or systemic corticosteroids, dapson, potassium iodide, cyclosporine, TNF-Alpha inhibitors	Topical or systemic corticosteroids, dapson, potassium iodide colchicine if corticosteroids are contraindicated	Topical or systemic corticosteroids, dapson, potassium iodide colchicine if corticosteroids are contraindicated	Systemic corticosteroids cyclophosphamide, rituximab, methotrexate, thalidomide, cocaine cessation
*In all cases, stopping the offending agent, such as cocaine, is paramount in stopping the disease progression p-ANCA: Perinuclear anti-neutrophilic cytoplasmic antibodies, IBD: Inflammatory bowel disease, TNF: Tumor necrosis factor alpha				

distinguishes PG, SS, NDDH, and levamisole vasculitis clinical findings and treatment options [6,19]. Most notably, PG generally lacks the fever and leukocytosis common to both SS and NDDH. NDDH diagnosis is distinguished from SS based upon the location of the lesions. A leukocytoclastic vasculitis may be present in any of the diseases; however, levamisole vasculitis has specific clinical and laboratory findings, including +c-ANCA and palpable purpura, commonly on lower extremities and helices.

Among her widespread lesions, the juicy generalized nodules on her buttock (Figure 1) are suggestive of SS. The lesions on her dorsal hands (Figure 2) coincide with the location of NDDH. The ulcerations most prominent on her thigh (Figure 3) particularly calls to mind PG. Unfortunately, she has had multiple debridements over the course of her disease. Some ND, including PG, exhibit pathergy. Otherwise insignificant trauma to the skin, may lead to ulcers that are resistant to healing [5]. This phenomenon in the presence of debriding these lesions led to substantial scarring that could have been avoided with earlier diagnosis and treatment.

Ethics

Informed Consent: Written consent obtained from patient for the case presentation.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.N., Concept: M.N., Desing: M.N., M.T., M.G.P., Data Collection or Processing: M.N., Analysis or Interpretation: M.N., T.K., M.G.P., Literature Search: M.N., M.T., M.G.P., Writing: M.T., T.K., M.G.P., M.N.

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