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A confounding clinically aggressive case of necrotizing granulomatous and suppurative dermatitis

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Abstract

Superficial granulomatous pyoderma gangrenosum is a rare, superficial, vegetating form of pyoderma gangrenosum that tends to occur as a single lesion, most commonly on the trunk. Herein, we report a clinically confounding case of disseminated superficial granulomatous pyoderma gangrenosum in a patient with a 5-year history of painful and chronic ulcerations of the bilateral upper extremities and face in a sun exposed distribution. This was a diagnostically challenging case due to the treatment-refractory nature of our patient's skin lesions and the atypical clinical and histologic presentations encountered. We review our clinical decision process and acknowledge other entities that were considered during the clinical course of this case. Additionally, we discuss the lack of responsiveness to various treatment options with eventual successful clearance of this patient's active skin disease with initiation of adalimumab.

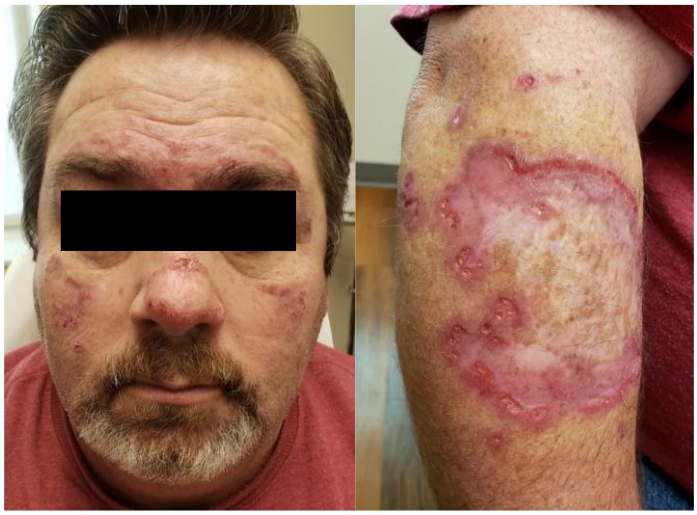
Keywords: granulomatous dermatitis, pyoderma gangrenosum, superficial, suppurative

Introduction

Superficial granulomatous pyoderma gangrenosum (SGPG) is a rarely encountered variant of pyoderma gangrenosum (PG) that typically presents as a single lesion, most commonly on the trunk [1,2]. In contrast to classic PG, histologic examination of SGPD demonstrates a superficial granulomatous inflammatory infiltrate, which may lead to diagnostic confusion for those unacquainted with this entity. We would like to call attention to SGPD through the discussion of a patient with an atypical presentation, and outline his treatment course and ultimate successful clearance of disease with initiation of adalimumab.

Case Synopsis

A 58-year-old man presented with a 5-year history of recurrent, chronic, painful ulcerative plaques on sun-exposed areas of his arms, face, and ears that were not responsive to medium strength topical corticosteroids (**Figure 1**). Initial histology revealed necrotizing granulomatous and suppurative dermatitis and a perilesional direct immunofluorescence study was non-diagnostic. Two additional biopsies were obtained, one of which



Figures *1*. *Cutaneous examination at time of initial visit. The patient presented with ulcerative, vegetative, erythematous plaques on the bilateral forearms, ears, and face.*

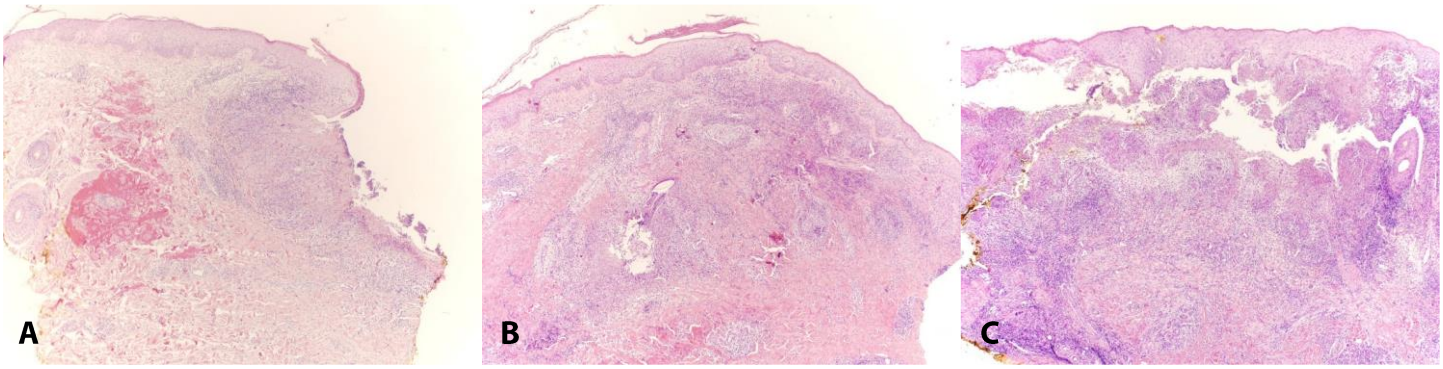


Figure 2. ***A)*** *Initial histology revealed necrotizing granulomatous and suppurative dermatitis. A perilesional direct immunofluorescence study was also performed at this time and was non diagnostic.* ***B)*** *A second histology sample revealed folliculitis with an adjacent neutrophilic abscess and Gram-positive cocci.* ***C)*** *A third histology sample demonstrated mixed dermal inflammation with an increase in dermal neutrophils.*

revealed folliculitis with an adjacent neutrophilic abscess and Gram-positive cocci, and the second demonstrated mixed dermal inflammation with an increase in dermal neutrophils (**Figure 2**). Tissue culture grew oxacillin-sensitive *Staphylococcus aureus* and an appropriate antibiotic course was completed without resolution of ulcerations. Tissue PCR testing was negative for fungal and mycobacterial DNA.

At that time, in the presence of varied histologic findings, the differential diagnosis included an infectious etiology and non-infectious conditions such as perforating granuloma annulare, palisading and neutrophilic granulomatous dermatitis (PNGD), and pyoderma gangrenosum. Dapsone and a high-dose prednisone taper were initiated, which resulted in significant improvement in the patient's skin lesions and pain. However, dapsone had to be discontinued due to a severe episode of methemoglobinemia requiring temporary supplemental oxygen.

Unfortunately, reappearance of inflamed, crusted papules and plaques at the periphery of previous ulcerations occurred 1.5 months after completion of the corticosteroid taper and did not improve with increased dosing of dapsone. Mycophenolate mofetil was trialed, but due to intolerable GI side effects, this was discontinued. Azathioprine and colchicine provided minimal response over the next several months, but a second high dose prednisone taper again offered significant benefit and was needed for symptom control. Over the next several months, the patient continued to experience intermittent superinfections of his skin lesions requiring antibiotic therapy. During the course of his illness, given mild erythrocytosis noted in a complete blood count, multiple studies were performed to exclude an underlying hematologic malignancy, all of which were negative.

A trial of oral tofacitinib was considered but the patient's medical insurer denied coverage due to lack of an FDA-approved indication. Given the patient's refractory symptoms and difficulty with insurance coverage, the patient was referred to the Veteran's Affairs Hospital. Upon presentation, the patient complained of severe, intolerable pain associated with his ulcerations and endorsed suicidal ideation related to his skin disease. At this time a high-dose, long-term prednisone taper was re-initiated and the patient was started on adalimumab, as well as doxycycline, given concern for superinfection. Repeated tissue PCR were also performed and were again negative for fungal and mycobacterial DNA. Given the patient's history of service in Afghanistan, leishmaniasis PCR was included and was negative. The patient significantly improved and presented with only one active lesion at his two month follow up visit at which time he was down to 10mg of prednisone per day. His related pain resolved and his mental health returned to baseline. Adalimumab was continued (40mg every two weeks) and doxycycline was stopped. Currently, 10 months after initial presentation to Veteran's Affairs Hospital, the patient is without evidence of

active disease and he is completing the prednisone taper (current dose of 1mg per day), with plans to taper completely over the next month (**Figure 3**).

Case Discussion

Herein, we report the case of a man with chronic, refractory, bilateral upper extremity and facial granulomatous dermatitis. We report this patient's cutaneous findings as a diagnostically challenging, clinically and histologically atypical case of disseminated SGPG, that responded well to adalimumab and prednisone. We present this confounding case due to the evolving diagnosis based on the varied histologic findings, clinical presentation, and refractory responses to trials of systemic therapies including antibiotics, dapsone, mycophenolate mofetil, colchicine, and azathioprine.

Early in the course of his disease, the differential diagnosis was broad. The presence of necrotizing granulomatous and suppurative dermatitis in conjunction with cultured *Staphylococcus aureus* was highly suspicious for infection, though lesions failed to resolve with appropriate courses of antibiotics.

Noninfectious causes were then considered after treatment of the secondary infection, with perforating granuloma annulare and PNGD considered to be possible etiologies. Clinical findings, common therapies utilized, and typical histological findings of these conditions are summarized in **Table 1**. As perforating granuloma annulare and PNGD were considered, dapsone was trialed with some improvement, although a prednisone taper initiated around the same time was likely providing most of this clinical benefit. Mycophenolate mofetil, azathioprine, and colchicine were also trialed with little success. The patient's clinical findings and persistence of symptoms despite the above therapies led us to reconsider perforating granuloma annulare or PNGD as possible causes.

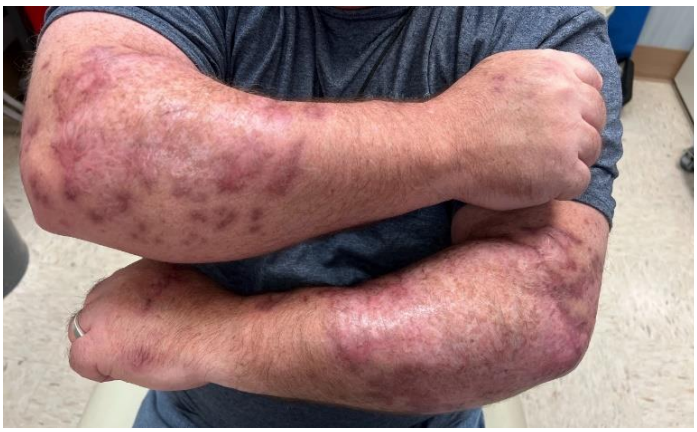


Figure 3. *Cutaneous examination after initiation of adalimumab. Patient remains clear of active disease as he tapers off prednisone (currently 1mg/day) and continues treatment with adalimumab. Areas of post inflammatory hyperpigmentation and scarring remain.*

Owing to treatment failures, with the exception of systemic corticosteroids, and an additional histologic sample revealing dermal inflammation with increased dermal neutrophils, we further considered neutrophilic dermatoses such as Sweet syndrome, superficial PG, or a Sweet-like drug eruption. In both Sweet syndrome and Sweet-like drug eruption, edematous papules and plaques can develop, which sometimes result in ulcerations, especially in the vesiculobullous variant of Sweet syndrome (**Table 1**). Histopathology for these conditions show dense dermal neutrophilic inflammation and edema, but lack a granulomatous component as was seen in our patient's initial biopsy. Additionally, Sweet syndrome is typically a self-limiting condition, resolving in 2-6 weeks with oral prednisone; Sweet-like drug eruption typically resolves after discontinuation of an offending agent (**Table 1**). Although superficial PG was also considered, our patient's presentation and clinical findings were not typical of those reported in previous cases. However, when considering our patient's disease course retrospectively, his skin lesions did respond well to prednisone, as would be expected in cases of pyoderma gangrenosum. Histologically, the three separate specimens, though with varied findings, all had features that are possible to see in different stages and forms of PG. This case is an important reminder for dermatopathologists that there are variants of PG that have a granulomatous component, and that "folliculitis," in the appropriate setting, may represent an incipient lesion of PG.

Review of superficial pyoderma gangrenosum

In 1988, Wilson Jones and Winkelmann introduced the concept of a localized, superficial, vegetative

form of pyoderma gangrenosum that displayed a granulomatous histopathology [4]. They used the designation "superficial granulomatous pyoderma" to refer to this clinical entity. However, this rare superficial granulomatous variant of pyoderma gangrenosum has been referred to as superficial granulomatous pyoderma gangrenosum (SGPG) in the more recent literature. The classic histopathology of SGPG includes a three-layered granuloma in the superficial dermis not typically observed in other PG variants. The layers include a central superficial abscess surrounded by giant cells and histiocytes enveloped by an outermost layer comprised of lymphocytes, eosinophils, and plasma cells [4,14].

Based on observations in 25 patients, Wilson-Jones and Winkelmann described this clinical entity as typically presenting with solitary, verrucous, ulcerative, cribriform skin lesions most commonly occurring on the trunk or lower extremities. Only one of these 25 patients had involvement of the facial skin [4]. At the time of the initial observations, these patients had disease courses ranging from 6 months to 12 years. Only three of these 25 patients had underlying medical disorders. The skin lesions in these patients typically responded well to first line therapy including topical corticosteroids and oral antibiotics.

More recent reports have described SGPG lesions involving the face [15,16]. Most such patients have had solitary SGPG lesions involving the malar areas of the face. Others have had lesions below the neck as well. Patients having multiple widespread lesions have been reported as having a disseminated form of SGPG [17]. Disseminated SGPG patients with facial lesions have been reported to be more resistant to first line treatments, typically requiring systemic immunosuppressive therapy for control.

We are not aware of other reported cases of disseminated SGPG with skin lesions in a sun-exposed, symmetric distribution on the arms, malar areas of face, external ears, and nasal tip. These clinical features along with the treatment-refractory nature of our patient's skin lesions suggest that this is a rather unique clinical presentation of disseminated SGPG. Per review of the literature, there are rare reports of SGPG, and even more rare are reports of this condition with facial involvement [14,15].

Conclusion

Although our patient's widespread cutaneous presentation with facial involvement and treatment-refractory nature are uncommonly seen in superficial PG, we believe this patient's findings are best categorized as an atypical or rare variant of this condition. Initially, these anomalous findings distracted us from narrowing our diagnosis to a granulomatous variant of superficial PG, therefore delaying the diagnosis and initiation of adalimumab. In conclusion, we present this case to bring recognition to the difficulties associated with diagnosing SGPG due to the clinically and histologically diverse presentations of this disease process, as well as the successful treatment of this condition with adalimumab.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Differential diagnostic considerations based on case histologic and clinical findings.*

Clinical Diagnosis	Morphology	Anatomic distribution	Commonly utilized therapies	Pathology
Our patient	Initially presented as blistering skin eruption Secondary lesions were ulcerative, vegetative papules and plaques	Symmetric sun exposed areas of arms, ears, nose, and face	Poor response to medium strength topical corticosteroids, azathioprine, colchicine, dapsone, and mycophenolate mofetil Overwhelming response to oral prednisone and adalimumab	1) Necrotizing granulomatous and suppurative dermatitis 2) Mixed dermal inflammation with an increase in dermal neutrophils 3) Suppurative folliculitis with Gram positive cocci
Superficial pyoderma gangrenosum	Ulcerating or vegetative lesions, commonly with granulation tissue at bases [3]	Commonly a single lesion [2] of the trunk > extremities> face > groin > scalp [1]	Intralesional corticosteroids, antimicrobial therapy including tetracyclines, minocycline, sulfa drugs, and oral corticosteroids with some success [4,5] Some reports of improvement with cyclosporine [6,7], infliximab [8], or immunoglobulin [9]	Granulomatous inflammation that is often "layered". Central neutrophil-dense zone with cellular debris, a surrounding layer of histiocytes, and an outer zone of plasma cells and eosinophils [10]
Palisaded and neutrophilic granulomatous dermatitis	Papules that often exhibit central umbilication, sometimes exhibiting ulceration [11]	Symmetric distribution favoring upper extremity extensor surfaces [11]	Topical and intralesional steroids, hydroxychloroquine, and dapsone [11]	Varied findings depending on age of lesion. Early lesions demonstrate neutrophil dense dermal inflammation with leukocytoclastic vasculitis, older lesions show palisaded granulomas with collagen trapping and leukocytoclasis
Sweet's syndrome	Painful, edematous papules and plaques that can become bullous Ulcerative lesions can be seen in the vesiculobullous variant of Sweet syndrome [3]	Symmetric distribution favoring upper extremities, head, and neck [3]	May resolve spontaneously Treatment of choice is oral prednisone Other therapeutic options include dapsone, colchicine, and potassium iodide [3]	Neutrophil dense dermal inflammation that may involve the subcutis. Dermal edema is often prominent, as is leukocytoclasis
Blastomycosis-like pyoderma gangrenosum	Vegetive and ulcerative papules and plaques, nodules, draining sinuses, and crypts [12]	Sun exposed areas, most commonly forearm and upper arm Other areas affected include hand, chest, thigh, neck and scalp Typically presents with one solitary lesion [12]	Systemic antibiotics Oral retinoids, curettage, topical antibiotics, systemic or intralesional steroids, and CO_2 laser [13]	Verrucous epidermis with varying degrees of pseudoepitheliomatous hyperplasia. Often with cystic spaces containing neutrophilic collections that connect to the epidermis. Gram stain may reveal bacteria
Perforating granuloma annulare	Centrally umbilicated papules that may exhibit ulceration [11]	Commonly found on the dorsal surfaces of the fingers and hands [11]	No treatment necessary if asymptomatic and localized	Palisaded granulomas which involve the papillary dermis and surround degenerated collagen, often with

			Topical or intralesional steroids, topical tacrolimus, and cryosurgery Phototherapy, niacinamide, and antimalarials may be trialed in cases with significant disease burden [11]	mucin. The overlying epidermis is acanthotic with a visible channel through which the degenerated collagen is extruded