Hidradenitis Suppurativa and Concomitant Pyoderma Gangrenosum

A Case Series and Literature Review

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Background: Hidradenitis suppurativa (HS) and pyoderma gangrenosum (PG) are both rare inflammatory skin conditions that are associated with systemic inflammatory diseases. We performed a retrospective medical chart review of patients with an overlap of HS and PG.

Observations: We identified 11 cases of PG lesions presenting in patients with HS. Ten of the patients were women, and 9 were obese. All the patients developed HS lesions first, a median of 2.5 years (range, 0-15 years) preceding the appearance of PG lesions. All patients required multiple therapeutic agents because their diseases were often poorly responsive to standard therapies. Two patients received tumor necrosis factor inhibitors; 1 responded to treatment. One patient was treated with anakinra (interleukin-1 receptor antagonist) and had a 75% improvement of her lesions.

Conclusions: We have identified a group of patients who have an overlap of PG and HS. Pyoderma gangrenosum can appear at any point after the development of HS and often has a severe, refractory course. We propose that PG and HS may represent variant manifestations of cytokine dysregulation by the innate immune system with common etiology. New therapeutic agents are eagerly sought, and further investigation with regard to interleukin 1 blockade is warranted.

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Pyoderma gangrenosum (PG) is a rare inflammatory skin condition with lesions most commonly appearing on the lower extremities but which may occur anywhere else on the body.1 The classic ulcerative PG lesion presents as a painful nodule or pustule that breaks down and evolves into an enlarging ulcer with a raised, undermined border.2 Approximately 50% of patients with PG have associated systemic diseases, including inflammatory bowel disease (IBD), myeloproliferative disorders, and inflammatory arthritis.3-4 Biopsy specimens from the edge of the ulcers typically show neutrophilic inflammation, and lesions further evolve to demonstrate a suppurative granulomatous dermatitis.2

Hidradenitis suppurativa (HS) typically presents in the axillae, perineum, and inframammary sites and is characterized by the presence of multiple abscesses, fibrosis, and sinus tracts.5 It is associated with acne, Crohn disease, dissecting cellulitis of the scalp, obesity, pilonidal disease, and smoking, and, like PG, HS has nonspecific histologic findings.5,6 The appearance of HS and PG lesions in the same patient has been rarely reported. We defined patients to include in this series as those having clinical diagnoses of HS and either PG lesions in HS sites or PG lesions in other body sites. Patients meeting inclusion criteria were identified by clinicians at University of California, San Francisco, and Yale University, New Haven, Connecticut. This was a retrospective medical chart review and literature review.

REPORT OF CASES

We identified 11 patients who met our criteria for having an overlapping presentation of HS and PG. Patients were included if they presented with morphologic characteristics consistent with HS (eg, with multiple aseptic abscesses, sinus tracts, and scarring in intertriginous sites) and in addition had ulcerations and histologic findings (where available) consistent with PG either in the same anatomical location as their HS lesions or in a distant location, such as the legs. We identified an ulcer as PG based on the clinical presentation of a rapidly expanding painful ulcer with undermined edges. The characteristics of these patients are summarized in the Table. The median age of HS onset was
Table. Summary of Clinical Presentations in the Current Series and in a Literature Review of Patients With Pyoderma Gangrenosum (PG) and Hidradenitis Suppurativa (HS)

<table>
<thead>
<tr>
<th>Source</th>
<th>No.²/Sex/ Age, y</th>
<th>Location of Lesions</th>
<th>Age at Onset of Lesions, y (Duration of PG Lesions)</th>
<th>Comorbidity</th>
<th>Treatment(s) Attempted, Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>1/F/23</td>
<td>HS: axillae, breasts, groin; PG: breasts, groin; concomitant: breasts, groin</td>
<td>HS: age 21; PG: age 23 (&gt;6 mo)</td>
<td>Pilonidal cyst, asthma, anxiety, AN, obesity</td>
<td>Tacrolimus ointment, topical and systemic clindamycin (NR); IL-triamcinolone acetone, clofetastol, cefadroxil (PR)</td>
</tr>
<tr>
<td>This study</td>
<td>2/F/23</td>
<td>HS: left axilla, right breast, right groin; PG: left axilla, right breast, right groin, face; concomitant: axilla, breast, groin</td>
<td>HS/PG: age 23 (&gt;20 mo)</td>
<td>Colitis, depression, AN, obesity</td>
<td>Amoxicillin, cipiroxacin, metronidazole, tetracycline, cephalin, fluoronazole, clindamycin, tacrolimus ointment, 0.1%, cyclosporine discontinued after 1 mo owing to headache (NR); doxycycline, prednisone, 40-60 mg/d, IL-triamcinolone, etanercept, methotrexate, and infliximab (PR)</td>
</tr>
<tr>
<td>This study</td>
<td>3/F/33</td>
<td>HS: axillae, groin; PG: groin, infra-abdominal pannus; concomitant: groin</td>
<td>HS: age 25; PG: age 26 (&gt;7 y)</td>
<td>Cystic acne, pilonidal cyst, hemorrhoids, back and knee pain, AN, obesity</td>
<td>Tetracycline, norethindrone/ethyl estradiol, spironolactone, minocycline, metronidazole gel, 0.75% (NR); fluoronazole, cefadroxil, dapsone, ethinyl estradiol, IL-triamcinolone monthly, spironolactone (PR)</td>
</tr>
<tr>
<td>This study</td>
<td>4/M/20</td>
<td>HS-like: buttocks, groin; PG: buttocks, groin; concomitant: buttocks and groin</td>
<td>HS: age 17; PG: age 20 (&gt;1.5 y)</td>
<td>Acne, iron-deficiency anemia, pyogenic granuloma affecting umbilicus and buttock</td>
<td>Infliximab, 3 doses, 6-mercaptopurine, mesalazine, dapsone cream, adalimumab (NR); anakinra (PR)</td>
</tr>
<tr>
<td>This study</td>
<td>5/F/27</td>
<td>HS: axillae, groin, inframammary; PG: bilateral breasts; concomitant: breasts</td>
<td>HS: age 20; PG: age 27 (1 mo)</td>
<td>Borderline DM type 2, hypertension, hemorrhoids, obesity</td>
<td>IL-triamcinolone and doxycycline (R)</td>
</tr>
<tr>
<td>This study</td>
<td>6/F/50</td>
<td>HS: axillae, inframammary, groin, perianal, inner thighs, abdominal wall; PG: groin; concomitant: groin</td>
<td>HS: age 32; PG: unknown, diagnosed at age 50</td>
<td>DM type 2; coronary artery disease, chronic colitis, depression, chronic anemia, obesity</td>
<td>NS</td>
</tr>
<tr>
<td>This study</td>
<td>7/F/30</td>
<td>HS: axillae; PG: left breast</td>
<td>NS</td>
<td>Mild anemia</td>
<td>NS</td>
</tr>
<tr>
<td>This study</td>
<td>8/F/48</td>
<td>HS: axillae, inguinal sites; PG: bilateral lower legs</td>
<td>HS: age 15; PG: age 30 (&gt;18 y)</td>
<td>Pilonidal sinus, SLE vs rheumatoid arthritis, DM type 2, hypertension, depression, obesity</td>
<td>Dapsone and prednisone, 40 mg/d (PR)</td>
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<tr>
<td>This study</td>
<td>9/F/14</td>
<td>HS: axillae, inframammary, gluteal cleft, inguinal folds, posterior neck, back folds, lower abdomen, medial thighs; PG: bilateral anterior lower legs</td>
<td>HS: age 14; PG: age 16 (&gt;10 mo)</td>
<td>DM type 2, depression, arthritis, gastritis, chronic anemia, AN, obesity</td>
<td>Minocycline, cyclosporine, tacrolimus ointment, 0.1%, clofetastol ointment, pulsed high-dose solumedrol, prednisone (NR); anakinra (PR); rifampin and clindamycin (PR)</td>
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<tr>
<td>This study</td>
<td>10/F/48</td>
<td>HS: axillae, perineum, groin, thighs, abdominal pannus; PG: anterior legs</td>
<td>HS: age 20; PG: age 23 (15 mo)</td>
<td>Cystic acne, depression, DM type 2, hypertension, asthma, obesity</td>
<td>Thalidomide and prednisone, 20-80 mg/d (NR); tacrolimus ointment, 0.3%, and minocycline (R)</td>
</tr>
<tr>
<td>This study</td>
<td>11/F/33</td>
<td>HS: axillae, groin, inframammary, posterior neck, lower abdomen; PG: legs, axillae, groin; concomitant: axillae, groin</td>
<td>HS: age 21; PG: unknown</td>
<td>Hypothyroidism, anemia, back pain, obesity</td>
<td>NS</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>1/F/45</td>
<td>HS: axillae; PG: groin and axillae; concomitant: axillae</td>
<td>HS: age 32; PG: age 57 (1 mo)</td>
<td>Iron-deficiency anemia</td>
<td>Predisolone, 30 mg (R)</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>2/F/45</td>
<td>HS: chest and axillae</td>
<td>HS: age 23; PG: age 45 (2 y)</td>
<td>SLE, glomerulonephritis</td>
<td>Predisolone, 40 mg, azathioprine, 150 mg (NR); IVIG 2 mg/kg/mo, IV cyclophosphamide, 500 mg, 3 × wk (R)</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>3/M/51</td>
<td>PG: back of hands</td>
<td>HS: age 21; PG: age 51 (1 wk)</td>
<td>Acne, psoriasis, parainfluenza</td>
<td>Prednisolone, 12.5 mg (NR); cyclosporine, 4.5 mg/kg (R)</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>4/F/35</td>
<td>PG: lower legs</td>
<td>HS: age 17; PG: age 35 (3 y)</td>
<td>None</td>
<td>Prednisolone, 200 mg, dapsone, 100 mg (NR); cyclosporine A, 4 mg/kg (R)</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>5/M/42</td>
<td>PG: back of thigh, lower abdomen</td>
<td>HS: age 22; PG: age 42 (6 y)</td>
<td>Acne</td>
<td>Cyclosporine, 5 mg/kg (NR); trimethoprim, 200 mg</td>
</tr>
<tr>
<td>Ah-Weng et al⁷</td>
<td>6/M/44</td>
<td>PG: lower legs</td>
<td>HS: age 24; PG: age 44 (4 mo)</td>
<td>Acne</td>
<td>Minocycline, 200 mg, dapsone, 100 mg (NR); cyclosporine A, 4 mg/kg (R)</td>
</tr>
<tr>
<td>Moschella⁶</td>
<td>7/F/36</td>
<td>HS: axillae, right groin; PG: left leg</td>
<td>HS: age 24; PG: age 32 (4 y)</td>
<td>Acne, Crohn disease</td>
<td>Azathioprine, oral prednisone (NR); infliximab, 5 mg/kg × 7 infusions (R)</td>
</tr>
</tbody>
</table>

20.5 years (range, 14-32 years), and the median age of PG onset was 23 years (range, 16 to ≥32 years). Hidradenitis suppurativa lesions were mostly found in the typical interfingrous sites, with 1 patient (case 9) having all of her skin folds affected, including folds on her back and posterior neck (Figure 1). With the exception of 1 patient (case 4), all of the patients were women. Nine of the 10 women in the case series were obese. Other co-
morbidities included type 2 diabetes mellitus (5 patients), coronary artery disease (1 patient), acanthosis nigricans (4), acne (3), hypertension (3), anemia (5), asthma (2), colitis (2), gastritis (1), arthritis (1), depression (5), and anxiety (1). Three patients had a history of pilonidal cyst/sinus (cases 1, 3, and 8). Two distinct groups were identified: patients with PG in sites where the patient had HS lesions (n=6 patients) and those with PG in sites distinct from HS lesions (n=5 patients).

**CASES WITH PG IN HS CONCOMITANT SITES**

Slightly more than half of patients (cases 1-6) had PG lesions develop in the same sites affected by their HS disease (Figure 2). For these patients, PG lesions developed a median of 2 years (range, 0-7 years) after HS had been present and affected the breasts, groin, axillae, and buttocks. One patient (case 2) had HS and PG lesions that presented around the same time, so the onset of PG lesions was counted as occurring 0 years after HS onset; in every other case HS preceded PG lesions by at least 1 year. The PG lesions of 1 patient resolved after a month; another patient had resolution of her PG lesions after 15 months. Two other patients still have active lesions to date; 1 patient has had PG lesions for over 10 years, and another has had PG lesions for over 12 years.

**CASES WITH PG IN HS DISTINCT SITES**

Four of these patients (cases 8-11) had classic PG lesions on their legs, and 1 patient (case 7) had a PG lesion on her breast. One patient (case 9) developed ulcerations in a linear pattern in areas of old HS scarring, and it was unclear if these ulcerations were predominantly PG or if they were chronic HS ulcerations. Patient 9 also had classic PG lesions on her legs (Figure 1). Of these 5 patients, PG developed a median of 3 years (range, 2-15 years) after HS onset. One patient had resolution of her PG lesions after 15 months. Two other patients still have active lesions to date; 1 patient has had PG for over 10 months, and another has had PG lesions for over 18 years.

**HISTOPATHOLOGIC CHARACTERISTICS**

Seven patients had biopsy specimens taken of their PG lesions. All biopsy specimens demonstrated a mixed inflammatory infiltrate, including neutrophils. Findings from special stains and tissue cultures when performed were negative for infection. The histologic findings were consistent with the diagnosis of PG.

**LABORATORY MARKERS OF INFLAMMATION**

Four patients had leukocytosis, and 3 of them had an elevated absolute neutrophil count. The C-reactive protein was measured in 4 patients; 2 had elevated levels: 8.1 mg/L and 15.9 mg/L (reference range, 0-6.3 mg/L). The erythrocyte sedimentation rate (ESR) was increased in 4 patients; 2 had elevated levels: 8.1 mg/L and 15.9 mg/L (reference range, 0-6.3 mg/L). Four patients had a history of pilonidal cyst/sinus (cases 1, 3, and 8). Two distinct groups were identified: patients with PG in sites where the patient had HS lesions (n=6 patients) and those with PG in sites distinct from HS lesions (n=5 patients).
creased in 3 patients of the 4 in whom it was measured: 62 mm/h, 63 mm/h, and 130 mm/h (reference range, 0-15 mm/h).

TREATMENTS

The patients with PG in HS concomitant sites were as follows: 1 patient (case 5) had lesions that resolved 1 month after treatment with doxycycline and intrale- sional triamcinolone acetonide. To date, 4 patients still have active lesions. Two patients were treated with tumor necrosis factor (TNF) inhibitors; 1 patient (case 2) had a partial response while receiving treatment with etanercept, was switched to infliximab, but showed no further improvement, and the other (case 4) failed treatment with infliximab and then with adalimumab. The lesions of the latter patient (case 4) showed minimal improvement during treatment with anakinra, an interleukin 1 (IL-1) antagonist, after 1 month and substantial improvement when treated with cyclosporine. All of these patients were treated with intralesional triamcinolone at some point during their course, with at least partial success in each case.

The patients with PG in HS distinct sites were as follows: the PG lesions in 1 patient (case 10) responded to tacrolimus ointment and minocycline after failing treatment with thalidomide and prednisone, 20 to 80 mg/d, and another patient (case 8) had a partial response to dapsone cream and prednisone, 40 mg/d, thus far. One patient (case 9) had a very refractory course of disease, failing treatment with minocycline, cyclosporine, topical tacrolimus, and topical and systemic steroids. She had a 75% improvement in size and depth of her PG ulcers after 3 weeks of treatment with anakinra, 100 mg/d subcutaneously (Figure 1). Six weeks later when she was not receiving therapy, her ulcers enlarged again, and they showed a partial response to rifampin and clindamycin hydrochloride. Follow-up information on response to treatments was not available for 3 patients (cases 6, 7, and 11).

COMMENT

We found 20 cases of concomitant PG and HS from a search of the English-language, peer-reviewed literature. The characteristics of these patients are summarized in the Table. Seven of the patients were women, and 8 were men. The median age at HS onset was 24 years (range, 17-40 years), and the median age at PG onset was...
43 years (range, 32-57 years). Pyoderma gangrenosum developed a median of 19 years after HS onset (range, 5 months to 30 years). The HS lesions were mostly in the axillae, groin, and buttocks. One patient was described as having PG and HS in the same site, and 12 had PG lesions in sites distinct from their HS affected sites, such as on the lower extremities (10 cases). Comorbidities included acne (7 cases), arthritis (3 cases); Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) syndrome (3 cases); iron-deficiency anemia (1); lupus (1); glomerulonephritis (1); psoriasis (1); Crohn disease (1); and Behcet disease (1). The PG lesions lasted a median of 1 year (range, 1 week to 6 weeks).

Our case series is different from prior case reports in that in our patients, PG developed in a much shorter time period (median period, 3 years) after HS had been present compared with prior case reports (median period, 2 decades). We also saw a predominance of women, which may just reflect that HS is a more common disease in women. We also saw a predominance of women, which may just reflect that HS is a more common disease in women. To our knowledge, the epidemiology of PG has not been reported in the literature, so it is unclear if there is sex disequilibrium. In addition, we were surprised by the low prevalence of IBD in both our patients and prior cases given its association with HS and with PG; of our 11 patients (18%) had nonspecific colitis, and only 1 patient in the 20 prior cases (5%) was reported to have any bowel disease (Crohn disease). Finally, most of our patients were obese, a characteristic which had not been commented on in the previous case reports, and which may just be reflective of typical patients with HS.

The pathogenesis for both HS and PG is incompletely understood. Hypothesized etiologic factors for HS include follicular plugging, leading to rupture of the pilosebaceous unit and a resulting inflammatory response, abnormal apocrine gland secretion, and endocrinologic factors, such as hyperandrognism; bacteria are thought to likely play a secondary role in exacerbating the disease. The pathogenesis of PG is also unknown, although neutrophil defects in chemotaxis or hyperreactivity have been suggested as possible etiologic factors. Both diseases are characterized by an intense inflammatory response that is mediated by neutrophils, and both diseases are commonly seen with other inflammatory processes such as IBD. Crohn disease is thought to be a member of the class of autoinflammatory diseases, or diseases characterized by systemic inflammation from dysregulated innate immune signaling pathways in the absence of autoantibodies or antigen-specific T cells. In addition, PG and HS are features of the Pyoderma gangrenosum, Acne, and Pyogenic Arthritis (PAPA) syndrome, a recognized autoinflammatory disease resulting from overexpression of IL-1B. Other autoinflammatory conditions, such as Behcet disease, are associated with PG and SAPHO is associated with HS.

Our patients demonstrated evidence of systemic inflammation with elevated acute phase reactants and multiple comorbidities also associated with proinflammatory phenotypes, such as obesity, type 2 diabetes mellitus, and coronary artery disease. We suggest that PG and HS may be in part due to dysregulation of the innate immune system, and that these diseases may be considered to be within the spectrum of the cutaneous disorders seen with the recently described autoinflammatory syndromes. Our hypothesis could tie into some of the current ideas regarding the etiologies of HS and PG. For example, perhaps in patients with HS, the original trigger was follicular plugging causing rupture of the pilosebaceous unit; however, it is the exaggerated and uncontrolled inflammatory response of these individuals to this stimuli that causes HS lesions to develop. In patients with PG, neutrophil dysfunction could be a part of the dysregulated innate immune system of these individuals, who have also been found to have high levels of the inflammatory cytokine IL-8 in their skin ulcers.

Tumor necrosis factor inhibitors have been found to be effective in treating both PG or HS with or without underlying inflammatory bowel disease. Pyoderma gangrenosum lesions have been reported to improve in a patient with PAPA syndrome after treatment with anakinra, and 1 of our patients (case 9), who did not have a known PAPA (CD2BP1) gene mutation, had a 75% improvement in her refractory PG lesions after 3 weeks of treatment with anakinra, suggesting that IL-1 may also be involved in the pathogenesis of PG not associated with PAPA syndrome.

The consistent temporal relationship of PG occurring after HS in all reported cases thus far may suggest that PG may be a late-onset cutaneous manifestation of the same underlying inflammatory process that triggered the preceding HS. This inflammatory process is most commonly local, with coexistent PG and HS lesions. These overlap cases are not frequently reported. Distant PG lesions may occur in the patient with HS in the setting of systemic inflammation from the HS, analogous to PG occurring on the skin in a patient with IBD of the gut. It is conceivable that in overlap cases, HS with chronic ulcerations might resemble PG, and because PG and HS cannot be distinguished by histologic examination given that it is rare to see differentiating features on a biopsy specimen, such as sinus tracts in HS, this confers diagnostic uncertainty. We identified an ulcer as PG based on presentation of a rapidly expanding painful ulcer with dusky undermined borders, which clinically behaved more like PG than HS, a disease characterized by abscesses, fibrosis, and sinus tracts.

Individually, both HS and PG are frequently conditions that are difficult to effectively treat. Our experience and that of others treating patients with comorbid HS and PG has similarly been challenging. Systemic corticosteroids are still first-line treatment for PG, although they are not frequently used in HS owing to the chronic nature of HS and the adverse effect profile of long-term use of these agents. Corticosteroids have profound anti-inflammatory properties and likely exert their effects on multiple cellular pathways. Traditional anti-neutrophilic agents, such as dapsone and colchicine, have largely been ineffective treatments for HS and PG. Although 1 patient with concomitant HS, PG, and Behcet disease had PG lesions that initially resolved with colchicine treatment, 2 weeks later his PG relapsed, and treatment with prednisone, 60 mg/d, resulted in gradual improvement. Cyclosporine resulted in remissions in some patients, perhaps owing to its antineutrophilic properties. Antibiotics, particularly the tetracycline class, have
been helpful in a minority of cases as adjunctive therapy and may reflect their anti-inflammatory effects with regard to the innate immune system. Anti-TNF therapies and now anti–IL-1 therapy are promising modalities, which are likely to be increasingly used in the future.

Last, we draw attention to the 7 patients in our case series with PG lesions in an HS distribution because of the possibly severe consequences of misdiagnosis. In 1 study of 44 patients with PG, lesions were enlarged in 8 patients by unsuccessful local surgical treatments before they were correctly diagnosed as PG. Given the lack of specific serologic or histopathologic studies to unequivocally distinguish between PG and HS in patients who have an overlap of the 2 diseases, we recommend medical treatment of these PG lesions if possible because surgical excision may worsen the patient’s condition.

In summary, we describe 11 patients presenting with HS and concomitant PG lesions. We found that PG can occur in the same sites affected by HS or in distinct sites. Pyoderma gangrenosum in these patients is often refractory to the standard anti-inflammatory and antibiotic therapies, and TNF or IL-1 blockade may be helpful. We believe that there is a link between PG and HS and note that both share features with the class of autoinflammatory diseases. A better understanding of the underlying pathogenesis of PG and HS is needed to optimize treatment for these patients. This might include examining tissue and serum TNF and IL-1 levels and conducting further clinical trials with cytokine-blocking therapies.

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REFERENCES