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Prevalence of pyoderma gangrenosum and Sweet’s syndrome in inflammatory bowel disease at a tertiary healthcare center

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Abstract

Background and aim
Dermatological manifestations are normally found in one third of patients with inflammatory bowel disease. Here, we determined the prevalence, clinical characteristics, intestinal disease activity and treatment response of neutrophilic dermatoses (pyoderma gangrenosum and Sweet’s syndrome) in patients with inflammatory bowel disease.

Methods
We performed a retrospective observational study of patients with inflammatory bowel disease and neutrophilic dermatoses between March 2012 and March 2018.

Results
Of 444 patients analyses, 10 complied with the inclusion criteria: seven had pyoderma gangrenosum and three presented Sweet’s syndrome. One patient developed both pathologies. The prevalence of neutrophilic dermatoses was 2.3% (10/444), comprising 1.6% pyoderma gangrenosum and 0.7% Sweet's syndrome. Six out of seven patients with pyoderma gangrenosum were female and had ulcerative colitis. The most frequent clinical presentation of pyoderma gangrenosum was the ulcerative subtype. Active moderate-to-severe intestinal disease was found in 71.4% of patients. Biological therapy was prescribed
to three patients with partial response to corticosteroids and persistent intestinal disease activity. This therapy was not indicated in any case only for cutaneous manifestations. Three patients with moderate-to-severe Chron’s disease presented classical (n=2) and pustular (n=1) Sweet's syndrome. Complete response was achieved in all Sweet's syndrome cases treated with corticosteroids. Biological therapy was prescribed to control intestinal disease activity.

Conclusions
Pyoderma gangrenosum was the most frequent cutaneous manifestation of neutrophilic dermatoses, predominantly in women with ulcerative colitis and highly associated with intestinal disease activity. Anti-tumor necrosis factor was effective in patients with partial cutaneous and intestinal disease response.

Keywords
Inflammatory bowel disease, pyoderma gangrenosum, Sweet’s syndrome

Abbreviations
IBD: inflammatory bowel disease
EIMs: extraintestinal manifestations
PG: pyoderma gangrenosum
SS: Sweet’s syndrome
CD: Crohn’s disease
UC: ulcerative colitis

INTRODUCTION
Approximately 40% of patients with inflammatory bowel disease (IBD) develop extraintestinal manifestations (EIMs), which may occur after (75%) or before (25%) IBD diagnosis. Skin lesions normally develop in one third of patients with IBD. Neutrophilic dermatoses are reactive EIMs of IBD, which include pyoderma gangrenosum (PG) and Sweet’s syndrome (SS). This heterogenous group of disorders shares the common hystopathological feature of a dense dermal polymorphonuclear neutrophilic infiltrate,
without evidence of vasculitis. Erythema nodosum is the most common cutaneous manifestation in IBD, followed by PG, which is the second most frequent, severe and disabling EIM. Sweet’s syndrome is less common and normally occurs in Crohn’s disease (CD) patients with colonic involvement. The aim of this study was to determine the prevalence, clinical characteristics, relationship with intestinal disease activity and treatment response of neutrophilic dermatoses (PG and SS) in patients with IBD managed at a tertiary care center.

METHODS

We performed a retrospective, observational trial of patients with IBD and neutrophilic dermatoses diagnosed at the Inflammatory Bowel Disease area of the Gastroenterology and Dermatology Services, Hospital General Interzonal de Agudos “General José de San Martín”, La Plata, between March 2012 and March 2018. Patient information was gathered from clinical records. Inclusion criteria were patients > 18 years of age diagnosed with IBD, ulcerative colitis (UC), CD or indeterminate colitis (assessed by clinical, laboratory, endoscopy and histopathological data) and with neutrophilic dermatoses (SS and/or PG) according to the diagnostic criteria for each of the mentioned disorders. Skin lesion were evaluated and then biopsies were performed at the Dermatology Service. All lesions showed histopathological evidence of a neutrophilic infiltrate. Epidemiological data (sex and age), the clinical presentation of dermatological manifestations, the presence of associated EIMs, the relationship with intestinal disease activity and treatment response were also assessed. The Montreal classification was used to categorize IBD in terms of extension and behavior. Clinic disease severity was estimated with the Mayo score for UC and the Harvey-Bradshaw index for CD. Endoscopic disease activity was assessed with the Mayo Endoscopic Score (MES) and the Simple Endoscopic Score for CD, considering the last endoscopic examination within two months before or after development of neutrophilic dermatoses. Treatment response was evaluated six weeks after the start of the treatment. Complete and partial response were defined as the total or partial remission of skin lesions, respectively. Despite time for treatment response is not well-established, most reports set a limit of six weeks. In case of treatment failure after this time, a new therapy was initiated.
All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

RESULTS

We identified 444 patients with IBD. Among these, 307 (69.5%) had UC, 113 (25%) CD and 24 (5.5%) indeterminate colitis. From the total, nine (seven women and 2 men) were diagnosed with neutrophilic dermatoses (mean age, 44 years; range, 22-63 years). Only one patient presented both diseases, i.e., of the ten cases observed, seven corresponded to PG (six women and one man) and three to SS (a man and two women). Two patients had a history of surgery (hemorrhoidectomy and pilonidal cystectomy). Six patients with UC and one with CD were diagnosed with PG. The three SS cases developed in patients with CD (Tables 1 and 2).

The prevalence of neutrophilic dermatoses was 2.3% (10/444), comprising 1.6% PG (7/444) and 0.7% SS (4/444). The prevalence of PG was 1.9% (6/307) in UC and 0.9% (1/113) in CD. The prevalence of SS in CD was 2.6% (3/113). Five patients with neutrophilic dermatoses developed other EIMs of IBD, namely, ocular (n=4, episcleritis, uveitis and keratitis) and articular (n=1, arthralgia) manifestations.

Ulcerative PG was the most frequent clinical presentation; it accounted for 85.7% of cases (n= 6), two of which were post-operative PG. Pustular PG was detected in one patient (14.3%). In all seven cases, pain was the main symptom. Six PG patients presented a single lesion, and only one case showed three simultaneous lesions. Four lesions were located in the lower limbs, one in the vulva and the two post-operative lesions were located in the intergluteal area (Figure 1).

At the time of PG diagnosis, five patients had established IBD and were receiving oral mesalazine (2-4 g/day) for maintenance therapy. Two of them were also receiving immunomodulators (thiopurines). One patient had a history of colectomy resulting from an episode of severe flare refractory to corticosteroid and cyclosporine treatment. The average time between IBD diagnosis and PG development was 13 years (range, 1-39 years). Two patients were concomitantly diagnosed with both IBD and PG.
Intestinal disease activity at the time of PG diagnosis in patients with UC was as follows: clinical and endoscopic remission (n=1) and active disease (n=5, 71.4%) classified into mild (n=1), moderate (n=3) and severe (n=1) by MES. According to the extent of colon involvement, it was classified as extensive colitis (n=3), left-sided colitis (n=1) and proctitis (n=1). The only patient with CD diagnosis had colonic disease with perianal involvement, stricturing behavior and moderate clinical and endoscopic activity (Figure 1).

All patients received systemic corticosteroid treatment (0.5-1 mg/kg/day). Skin response was complete in three patients and partial in another three. One patient failed to follow up. Standard doses of anti-tumor necrosis factor (anti-TNF) for remission induction therapy were prescribed to four patients (three received adalimumab for intestinal and cutaneous disease, and one patient received infliximab for intestinal disease activity), who showed a favorable response (Table 1). None of the patients with complete response to corticosteroids had recurrent lesions.

Among SS patients, two developed the classical and one the pustular lesions of the disease (Figure 2). Two of these patients simultaneously presented subcutaneous lesions (Figure 3). All patients had fever, neutrophilia and ocular manifestations (keratitis and uveitis). The three patients had colonic CD with moderate-to-severe clinical and endoscopic disease activity, and two of them presented perianal lesions. Patients were prescribed 1 mg/kg/day prednisone, obtaining complete response four weeks after drug administration. Biological therapy or immunomodulators was prescribed to all patients with intestinal disease (Table 2). None of them developed recurrent cutaneous lesions.

**DISCUSSION**

In this study, we analysed the prevalence, clinical characteristics, disease activity and treatment response of neutrophilic dermatoses in patients with IBD managed at a tertiary care center. Approximately 50% of patients diagnosed with PG have associated IBD, however, only 1 to 3% of patients with IBD have PG, being more common in ulcerative colitis. 2,3 Concerning SS, data on its prevalence are scarce as a result of its low frequency.1 We found that the prevalence of neutrophilic dermatoses in IBD patients was 2.3%, with PG as the most frequent skin manifestation (1.6%). Classification of patients with neutrophilic dermatoses into IBD subtypes resulted in 1.9% PG in UC, 0.9% PG in CD. Concerning SS, its
prevalence was 0.7% in IBD.

The percentage of other EIMs in IBD patients of our study was 56%. Other reports have described variable EIM prevalence’s, ranging from 6 to 47%. It has also been shown that multiple EIMs may occur concomitantly, and that the occurrence of one becomes a risk factor for the development of other EIMs.³

In general, PG affects females, more than males, in the 20-50 age range.¹ While IBD diagnosis normally precedes PG, PG may occur before or concomitantly with intestinal disease.¹ In our study, 86% of PG patients were women with a mean age of 44 years and only two patients developed PG concomitantly with IBD.

Pyoderma gangrenosum is classified into four clinical subtypes: classical, pustular, bullous and vegetative. Classical PG begins with a sterile pustule or erythematous papule or nodule that rapidly progresses to form a painful ulcer with characteristic erythematous to violaceous, sharply defined, undermined borders, and a necrotic base. These lesions normally heal with cribiform scars and frequently affect the lower limbs, even though they can appear anywhere on the skin as single or multiple lesions.¹ ³ 7-9 The pustular variant is characterized by multiple sterile pustules surrounded by an erythematous halo and by symptoms such as fever and arthralgias. Classical and pustular PG are mostly associated with IBD.² 5,7 In our study, classical PG as a solitary lesion was the most frequent clinical subtype in 85.7% of patients, while only one patient developed pustular PG.

The appearance of lesions in response to skin trauma, known as pathergy, is observed in one third of patients, particularly in peristomal and post-operative PG.⁵ Here, two patients developed PG after hemorrhoidectomy and pilonidal cystectomy (Figure 1).

The correlation of PG with IBD activity is controversial; in general, PG progression is independent of disease activity, although it can improve with IBD treatment.¹ ² According to Marzano et al., the treatment of underlying IBD did not improve skin lesions in 30% of patients.⁶ In another study of 14 patients with UC, the temporal relationship between IBD activity and progression of PG lesions could not be established.¹⁰ On the other hand, Levitt et al. found that 20 out of 34 patients evaluated had active IBD at the moment of PG diagnosis.¹¹ Total colectomy in patients with UC does not ensure PG remission,¹² and recurrences are frequently observed in up to 35% of cases.² Our results showed that 71.4% of patients presented active moderate-to-severe IBD at PG diagnosis, and only one patient developed
PG one year after colectomy.

The management of patients with PG is complex; treatment goals should mainly involve the suppression of inflammatory activity, the healing of local lesions, the control of triggering factors (pathergy), pain control and the treatment of underlying IBD. Corticosteroids are the first line treatment option, administered in 0.5 to 1 mg/kg/day doses.\textsuperscript{2,5} In cases of refractory PG, which is commonly associated with active IBD, anti-TNF drugs (infliximab and adalimumab) are the therapy of choice,\textsuperscript{1,5,13-19} while other immunosuppressants (cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, dapsone, intravenous immunoglobulin) are also valid treatment options.\textsuperscript{1,10,21} In our study, biological therapy was prescribed to the three patients with partial PG response to systemic corticosteroids and persistent intestinal disease activity. This therapy was not used in patients with cutaneous manifestations only.

The manifestation of SS in IBD is exceedingly rare, with only 40 cases reported in the literature to date. This syndrome is mostly associated with CD (70%) and, to a much lesser extent, UC (30%).\textsuperscript{1} It usually presents in women between 30-50 years of age with colonic involvement, and is closely related to IBD disease activity in 67 to 80% of cases.\textsuperscript{2,7} Sweet’s syndrome may appear concurrent with (28%), subsequent to (52%) and prior to (20%) IBD diagnosis.\textsuperscript{2} Our results are in agreement with these data, since we diagnosed three SS cases in CD patients with acute flares, two of which were concurrent with IBD onset. Two SS cases presented the classical lesions, consisting of the sudden onset of painful erythematous and edematous plaques, asymmetrically scattered over the arms, neck and face and accompanied by fever and leukocytosis. Other symptoms include arthralgias, malaise, migraine, myalgia, and ocular pain. Some lesions have the characteristic pseudovesicular aspect resulting from a marked edema of the papillary dermis. The same as with PG, pathergy may be involved, but lesions heal spontaneously without leaving scars.\textsuperscript{2,9} Pustular SS, frequently associated with IBD,\textsuperscript{1} was observed in only one patient. Lesions are characterized by pustules or papules surrounded by an erythematous halo, sometimes indistinguishable from pustular PG. Two patients presented painful erythematous nodular lesions in lower limbs, compatible with subcutaneous SS. Despite these lesions clinically resemble those of erythema nodosum, they histopathological differ by the presence of neutrophilic lobular panniculitis.\textsuperscript{2}
Initial management of SS includes the use of systemic corticosteroid doses (0.5–1mg/kg/day), achieving symptom improvement at six weeks. Thus, it is important to optimize the treatment of intestinal disease. In our SS patients, the response to systemic corticosteroid treatment was complete, and anti-TNF drugs or immunomodulators were needed to control intestinal disease activity.

The main limitation of our study was concerned with the retrospective design, which may lead to loss of information that may affect the validity of results. Taking into account that we investigated a rare inflammatory disease, the number of patients analyzed was significant. Nevertheless, prospective studies are needed to determine the characteristics and behavior of neutrophilic dermatoses in IBD.

**CONCLUSION**

In this study, PG was the most prevalent neutrophilic dermatosis, predominantly in women and UC, and highly associated with intestinal disease activity. On the other hand, SS associated with acute CD flares in all cases. Although corticosteroids were the first line treatment option, anti-TNF were beneficial in cases of cutaneous and intestinal partial response. Multidisciplinary work based on the close monitoring of EIMs in IBD and timely screening and evaluation of intestinal symptoms in patients with neutrophilic dermatoses without known IBD diagnosis could help achieve a right approach to these disorders.

**FUNDING**

This study received no specific financial support.

**REFERENCES**


Table 1. Inflammatory bowel disease and pyoderma gangrenosum.

<table>
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<tr>
<th>Cases</th>
<th>Montreal classification*</th>
<th>Cutaneous manifestation</th>
<th>Clinical disease activity</th>
<th>Endoscopic disease activity</th>
<th>Treatment before IBD</th>
<th>Treatment** **</th>
<th>Progression* **</th>
<th>anti-TNF treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 24-year-old woman</td>
<td>UC A1E3S3</td>
<td>Ulcerative postoperative intergluteal PG</td>
<td>Moderate (Mayo score 2)</td>
<td>Moderate (MES 2)</td>
<td>Mesalazine (4 g/day) + Azathioprine (100 mg/day)</td>
<td>Prednisone (1 mg/kg/day)</td>
<td>Partial response</td>
<td>Adalimumab (intestinal and cutaneous involvement)</td>
</tr>
<tr>
<td>2. 37-year-old woman</td>
<td>UC A2E3S2</td>
<td>Ulcerative lower limbs PG</td>
<td>Remission (Mayo score 0)</td>
<td>Remission (MES 0)</td>
<td>Mesalazine (2 g/day)</td>
<td>Prednisone (1 mg/kg/day)</td>
<td>Complete response</td>
<td>No</td>
</tr>
<tr>
<td>3. 39-year-old woman</td>
<td>UC A2E2S3</td>
<td>Ulcerative vulvar PG</td>
<td>Moderate (Mayo score 2)</td>
<td>Moderate (MES 2)</td>
<td>Mesalazine (4 g/day) + 6-mercaptopurine (150 mg/day)</td>
<td>Prednisone (1 mg/kg/day)</td>
<td>Complete response</td>
<td>Infliximab (intestinal involvement)</td>
</tr>
<tr>
<td>4. 40-year-old woman</td>
<td>UC A2E3S3</td>
<td>Ulcerative lower limbs PG</td>
<td>Moderate (Mayo score 2)</td>
<td>Moderate (MES 2)</td>
<td>Colectomy Mesalazine (4 g/day)</td>
<td>Prednisone (1 mg/kg/day)</td>
<td>Partial response</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>5. 50-year-old woman</td>
<td>CD A2B2pL2</td>
<td>Ulcerative postoperative intergluteal PG + SS</td>
<td>Moderate (Harvey Bradshaw Index 8)</td>
<td>Moderate (SES-CD 11)</td>
<td>---</td>
<td>Prednisone (1 mg/kg/day) + Mesalazine (4 g/day) + Azathioprine (150 mg/day)</td>
<td>Partial response</td>
<td>Adalimumab (intestinal and cutaneous involvement)</td>
</tr>
<tr>
<td>6. 67-year-old woman</td>
<td>UC A3E3S2</td>
<td>Ulcerative lower limbs PG</td>
<td>Severe (Mayo score 3)</td>
<td>Severe (MES 3)</td>
<td>Mesalazine (4 g/day)</td>
<td>Hydrocortisone (1 mg/kg/day)</td>
<td>Lost to follow-up</td>
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</tr>
</tbody>
</table>
7.69-year-old woman

UC A2E3S1

Pustular lower limbs PG

Mild (Mayo score 1)

Mild (MES 1)

---

Prednisone (40 mg/kg/day) + Mesalazine (4 g/day)

Complete response

No

| 7.69-year-old | UC A2E3S1 | Pustular lower limbs PG | Mild (Mayo score 1) | Mild (MES 1) | --- | Prednisone (40 mg/kg/day) + Mesalazine (4 g/day) | Complete response | No |

Table 1. References:
IBD, inflammatory bowel disease; MES, Mayo endoscopic score; UC, ulcerative colitis; CD, Crohn’s disease; PG, pyoderma gangrenosum; SS, Sweet’s syndrome; (SS), SES-CD, simplified endoscopic score for CD.

*Montreal classification for ulcerative colitis: Age (A): A1 (<17 years), A2 (17-40 years), A3 (> 40 years); Extent (E): E1 (proctitis), E2 (left-sided colitis), E3 (extensive colitis); Severity (S): S1 (mild), S2 (moderate), S3 (severe).

*Montreal classification for Crohn’s disease: Age (A): A1 (<17 years), A2 (17-40 years), A3 (> 40 years); Location (L): L1 (ileal), L2 (ileocolonic), L3 (colonic); Behavior (B): B1 (non stricturing, non penetrating), B2 (stricturing), B3 (penetrating); “p” is added to B1-B3 when concomitant perianal disease is present.

**Treatment started after dermatological diagnosis. ***Progression of cutaneous lesion six weeks after treatment.
### Table 2. Inflammatory bowel disease and Sweet’s syndrome.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Montreal classification *</th>
<th>Cutaneous manifestation</th>
<th>Harvey-Bradshaw Index (HBI)</th>
<th>Endoscopic disease activity (SES-CD)</th>
<th>Treatment prior to IBD</th>
<th><strong>Treatment</strong> started after dermatological diagnosis.</th>
<th>***Progression of cutaneous lesion six weeks after treatment.</th>
<th>Anti-TNF treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-year-old woman</td>
<td>CD A2B2pL2</td>
<td>Classical SS + PG</td>
<td>Moderate (8)</td>
<td>Moderate (11)</td>
<td>-</td>
<td>Prednisone (1mg/kg/day)</td>
<td>Complete response</td>
<td>Adalimumab (intestinal involvement)</td>
</tr>
<tr>
<td>33-year-old man</td>
<td>CD A2B2pL2</td>
<td>Pustular and subcutaneous SS</td>
<td>Severe (13)</td>
<td>Severe (16)</td>
<td>Mesalazine (4 g/day) + azathioprine (150 mg/day)</td>
<td>Hydrocortisone (1mg/kg/day)</td>
<td>Complete response</td>
<td>Infliximab (intestinal involvement)</td>
</tr>
<tr>
<td>37-year-old woman</td>
<td>CE A2B1L2</td>
<td>Classical and subcutaneous SS</td>
<td>Severe (13)</td>
<td>Severe (16)</td>
<td>-</td>
<td>Hydrocortisone (1mg/kg/day)</td>
<td>Complete response</td>
<td>Azathioprine (intestinal involvement)</td>
</tr>
</tbody>
</table>

Table 2. References:
CD, Crohn’s disease; PD, pyoderma gangrenosum; HBI, Harvey-Bradshaw Index; SS, Sweet’s syndrome; syndrome de Sweet (SS), SES-CD, simplified endoscopic score for CD.

*Montreal classification for Crohn’s disease: Age (A): A1 (<17 years), A2 (17-40 years), A3 (> 40 years; location (L): L1 (ileal), L2 (ileocolonic), L3 (colonic); behavior (B): B1 (non stricturing, non penetrating), B2 (stricturing), B3 (penetrating); “p” is added to B1-B3 when concomitant perianal disease is present.

**Treatment started after dermatological diagnosis. ***Progression of cutaneous lesion six weeks after treatment.
Figure 1. Intergluteal pyoderma gangrenosum and Crohn’s disease.

Figure 2. Crohn’s disease and classical Sweet’s syndrome.
Patient with CD and SS diagnosis. A- Upper back erythematous and edematous lesions. B- Erythematous lesions with pustules on the forearms. C- Endoscopic image of the sigmoid colon, showing loss of vascular pattern, narrowing and deep, longitudinal ulcers affecting the whole circumference (SES-CD 16).
Figure 3. Crohn’s disease and classical and subcutaneous Sweet’s syndrome.

Patient with CD and SS. A- Classical SS: erythematous, pseudovesicular plaques on the left forearm and arm. B- Subcutaneous SS: subcutaneous nodules covered by erythematous skin on the right leg. C- Endoscopic image of the proximal sigmoid colon showing loss of vascular pattern and deep, longitudinal ulcers with a cobblestone appearance and friability.