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

Authors:
Florencia Giraudo, Eugenia Miraglia, María Laura Garbi, Martín Yantorno, María Roxana Maradeo, Gustavo Javier Correa, Francisco Tufare

DOI: 10.17235/reed.2020.7431/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Prevalence of pyoderma gangrenosum and Sweet’s syndrome in inflammatory bowel disease at a tertiary healthcare center

Florence Giraudo1, Eugenia Miraglia2, María Laura Garbi1, Martín Yantorno1, María Roxana Maradeo2, Gustavo Javier Correa1, Francisco Tufare1

1 Gastroenterology and 2 Dermatology Departments. Hospital Interzonal General de Agudos (HIGA) “General San Martín”. La Plata, Argentina

Received: 29/07/2020
Accepted: 21/10/2020

Correspondence: Florence Giraudo. Servicio de Gastroenterología. HIGA “General San Martín”. Calle 2, número 627, piso 13, departamento C. 1900 La Plata, Buenos Aires. Argentina
e-mail: giraudoflorencia@hotmail.com

Conflicts of interest: none to declare.
Funding: this study received no specific financial support.

ABSTRACT

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

Methods: a retrospective, observational study was performed in patients with inflammatory bowel disease and neutrophilic dermatoses between March 2012 and March 2018.
Results: of 444 patients analyzed, 10 complied with the inclusion criteria. Seven had pyoderma gangrenosum and three presented Sweet's syndrome; and one patient developed both pathologies. The prevalence of neutrophilic dermatoses was 2.3% (10/444), comprising 1.6% with pyoderma gangrenosum and 0.7% with 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 for cutaneous manifestations only. Three patients with moderate-to-severe Crohn’s disease presented classical (n = 2) and pustular (n = 1) Sweet’s syndrome. A 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 females 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.

INTRODUCTION
Approximately 40% of patients with inflammatory bowel disease (IBD) develop extraintestinal manifestations (EIMs), which may occur before (25%) or after (75%) IBD diagnosis (1,2). Skin lesions normally develop in one third of patients with IBD (1,3). Neutrophilic dermatoses are reactive EIMs of IBD, which include pyoderma gangrenosum (PG) and Sweet’s syndrome (SS). This heterogeneous group of disorders shares the common histopathological feature of a dense dermal polymorphonuclear
neutrophilic infiltrate, without evidence of vasculitis (1,2,4). Erythema nodosum is the most common cutaneous manifestation in IBD, followed by PG, which is the most severe and disabling EIM. Sweet’s syndrome is less common and normally occurs in Crohn’s disease (CD) patients with colonic involvement (1,2).

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**

A retrospective, observational trial was performed in 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 collected from clinical records. Inclusion criteria were patients > 18 years of age, diagnosed with IBD, either 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 of each of the above-mentioned disorders. Skin lesions were evaluated and 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. Clinical disease severity was estimated using 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 the development of the neutrophilic dermatoses.

Treatment response was evaluated six weeks after the start of the treatment. Complete and partial responses were defined as the total or partial remission of skin lesions, respectively. Despite the fact that the time to treatment response is not well-
established, most reports set a limit of six weeks. A new therapy was initiated in case of treatment failure after this time (5,6).

All procedures in this study were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its subsequent amendments. An 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, 9 (7 females and 2 males) 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 females and one male) and three to SS (one male and two females). Two patients had a history of surgery (hemorrhoidectomy and pilonidal cystectomy). Six patients with UC and one with CD were also 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 % for PG (7/444) and 0.7 % for 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 and accounted for 85.7 % of cases (n = 6), two of which were post-operative PG. Pustular PG was detected in one patient (14.3 %). Pain was the main symptom in all seven cases. 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 (Fig. 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 were also receiving immunomodulators (thiopurines). One patient had a history of colectomy resulting from an episode of a severe flare refractory to corticosteroid and cyclosporine treatment. The average time between IBD diagnosis and PG development was 13 years.
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, this was classified as extensive colitis (n = 3), left-sided colitis (n = 1) and proctitis (n = 1). The only patient with a CD diagnosis had colonic disease with perianal involvement, stricturing behavior, and moderate clinical and endoscopic activity (Fig. 1).

All patients received systemic corticosteroid treatment (0.5-1 mg/kg/day). The skin response was complete in three patients and partial in another three. One patient was not followed up. Standard doses of anti-tumor necrosis factor (anti-TNF) for remission induction therapy were prescribed in 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 a complete response to corticosteroids had recurrent lesions.

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

DISCUSSION

This study analyzed 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 had associated IBD. However, only 1 to 3 % of patients with IBD have PG, which is more common in
ulcerative colitis (2,3). With regard to SS, data on its prevalence are scarce due to its low frequency (1). We found that the prevalence of neutrophilic dermatoses in IBD patients was 2.3 %, and PG was the most frequent skin manifestation (1.6 %). The classification of patients with neutrophilic dermatoses into IBD subtypes resulted in 1.9 % for PG in UC and 0.9 % for PG in CD. With regard to SS, its prevalence was 0.7 % in IBD.

The percentage of other EIMs in IBD patients in our study was 56 %. Other reports have described a variable EIM prevalence, 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 age range of 20-50 years (1). While an IBD diagnosis normally precedes PG, PG may occur before or concomitantly with intestinal disease (1). In our study, 86 % of PG patients were females 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 cribriform 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, was observed in one third of patients, particularly in peristomal and post-operative PG (5). Here, two patients developed PG after hemorrhoidectomy and pilonidal cystectomy (Fig. 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 (1). Another study of 14 patients with UC showed that the temporal relationship between IBD activity and the progression of PG lesions could not be established (10). On the other hand, Levitt et al. found that 20 of 34 patients evaluated had active IBD at the time 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 as 0.5 to 1 mg/kg/day doses (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 (1,5,13-19), whereas other immunosuppressants (cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, dapsone, intravenous immunoglobulin) are also valid treatment options (1,20,21). In our study, biological therapy was prescribed to the three patients with a 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 with UC (30%) (1). It usually presents in females between 30-50 years of age with colonic involvement, and is closely related to IBD disease activity in 67 to 80% of cases (2,7). Sweet’s syndrome may appear concurrent with (28%), subsequent to (52%), and prior to (20%) an IBD diagnosis (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. Pathergy may also be involved, as with PG, but lesions heal spontaneously without leaving scars (2,9).

Pustular SS, frequently associated with IBD (1), was observed in only one patient. Lesions are characterized by pustules or papules surrounded by an erythematous halo and are sometimes indistinguishable from pustular PG. Two patients presented painful erythematous nodular lesions in the lower limbs, compatible with subcutaneous SS. Despite the fact that these lesions clinically resemble those of erythema nodosum, they differ at the histopathological level by the presence of neutrophilic lobular panniculitis (2).

The initial management of SS includes the use of systemic corticosteroid doses (0.5-1 mg/kg/day), achieving symptom improvement at six weeks. Thus, it is important to optimize the treatment of intestinal disease (1). 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 due to 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 females and UC, and was highly associated with intestinal disease activity. On the other hand, SS was associated with acute CD flares in all cases. Although corticosteroids were the first-line treatment option, anti-TNFs were beneficial in cases of cutaneous and intestinal partial response. Multidisciplinary studies based on the close monitoring of EIMs in IBD, timely screening, and the evaluation of intestinal symptoms in patients with neutrophilic dermatoses without a known IBD diagnosis could help to achieve the correct approach to these disorders.
REFERENCES


<table>
<thead>
<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.</td>
<td>24-year-old female</td>
<td>UC A1E3S3</td>
<td>Ulcerative postoperative intergluteal PG</td>
<td>Moderate (Mayo score, 2)</td>
<td>Mesalazine g/day + azathioprine mg/day</td>
<td>Prednisone mg/kg/day</td>
<td>Partial response</td>
<td>Adalimumab (intestinal and cutaneous involvement)</td>
</tr>
<tr>
<td>2.</td>
<td>37-year-old female</td>
<td>UC A2E3S2</td>
<td>Ulcerative lower-limb PG</td>
<td>Remission (Mayo score, 0)</td>
<td>Mesalazine g/day</td>
<td>Prednisone mg/kg/day</td>
<td>Complete response</td>
<td>No</td>
</tr>
<tr>
<td>3.</td>
<td>39-year-old female</td>
<td>UC A2E2S3</td>
<td>Ulcerative vulvar PG</td>
<td>Moderate (Mayo score, 2)</td>
<td>Mesalazine g/day + 6-mercaptopurine (150 mg/day)</td>
<td>Prednisone mg/kg/day</td>
<td>Complete response</td>
<td>Infliximab (intestinal involvement)</td>
</tr>
<tr>
<td>4.</td>
<td>40-year-old female</td>
<td>UC A2E3S3</td>
<td>Ulcerative lower-limb PG</td>
<td>Moderate (Mayo score, 2)</td>
<td>Colectomy</td>
<td>Mesalazine g/day</td>
<td>Partial response</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>5.</td>
<td>50-year-old female</td>
<td>CD A2B2pL2</td>
<td>Ulcerative postoperative or intergluteal</td>
<td>Moderate (Harvey-Bradshaw Index, 8)</td>
<td>---</td>
<td>Prednisone mg/kg/day + mesalazine g/day</td>
<td>Partial response</td>
<td>Adalimumab (intestinal and cutaneous involvement)</td>
</tr>
<tr>
<td>PG + SS</td>
<td>azathioprine (150 mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Gender</td>
<td>IBD</td>
<td>Extent</td>
<td>Location</td>
<td>Behavior</td>
<td>Ulcerative postoperative or intergluteal PG + SS</td>
<td>Severity</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>--------</td>
<td>-----</td>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>-----------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>6.</td>
<td>67-year-old female</td>
<td>UC A3E3S2</td>
<td>Ulcerative lower-limb 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>
</tr>
<tr>
<td>7.</td>
<td>69-year-old female</td>
<td>UC A2E3S1</td>
<td>Pustular lower-limb PG</td>
<td>Mild (Mayo score, 1)</td>
<td>Mild (MES 1)</td>
<td>---</td>
<td>Prednisone (40 mg/kg/day) + mesalazine (4 g/day)</td>
<td>Complete response</td>
</tr>
</tbody>
</table>

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: 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); 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>†Treatment</th>
<th>‡Progression</th>
<th>Anti-TNF treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-year-old female CD A2B2pL2 Classical SS + PG Moderate (8) Moderate (11) - Prednisone (1 mg/kg/day) Complete response Adalimumab (intestinal involvement)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33-year-old male CD A2B2pL2 Pustular and subcutaneous SS Severe (13) Severe (16) Mesalazine (4 g/day) + azathioprine (150 mg/day) Hydrocortisone (1 mg/kg/day) Complete response Infliximab (intestinal involvement)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-year-old female CE A2B1L2 Classical and subcutaneous SS Severe (13) Severe (16) - Hydrocortisone (1 mg/kg/day) Complete response Azathioprine (intestinal involvement)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CD: Crohn’s disease; PD: pyoderma gangrenosum; HBI: Harvey-Bradshaw Index; SS: Sweet’s syndrome; 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.
Fig. 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 the vascular pattern, narrowing and deep, longitudinal ulcers affecting the whole circumference (SES-CD 16).
Fig. 3. Crohn’s disease and classical, 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 the vascular pattern and deep, longitudinal ulcers with a cobblestone appearance and friability.