Therapeutic Efficacy of the Combination Therapy of Corticosteroids and 5-Aminosalicylic Acid for Treatment of Pyoderma Gangrenosum with Ulcerative Colitis

Wei Chen, Lijuan Xiang1, Li Li

Abstract

Background: Pyoderma gangrenosum (PG) in inflammatory bowel disease (IBD) is a rare cutaneous condition and its treatment remains controversial due to limited data. Aims and Objectives: The purpose of this study was to investigate the characteristics and treatment response to specific therapies of IBD-associated PG. Methods: In this retrospective study, we reviewed a series of cases of IBD-associated PG patients who presented at our institution, and collected clinical data, such as demographics, characteristics, subtype, and disease activity of IBD and specific therapies used and their treatment response. Results: In total, 42 cases were identified: 69% female and 92.9% with ulcerative colitis (UC). At PG diagnosis, 93% had active and 7% inactive IBD. PG ulcers occurred predominantly on the legs (33.3%); 14.3% had multiple lesions. In total, 20/39 UC patients received the combination therapy of systemic corticosteroids and 5-aminosalicylic acid (5-ASA) with a good response in 19 patients (95%). Seven patients received the monotherapy of 5-ASA with a response rate of 43%. Five patients were successfully treated with systemic corticosteroids alone. Other patients were treated with intravenous immunoglobulin, infliximab, or cyclophosphamide alone or in combination with corticosteroids and all showed a good response. Conclusion: Our study indicates the therapeutic efficacy of corticosteroids in combination with 5-ASA, which may be considered as the first-line therapy for UC-associated PG.

Key Words: Inflammatory bowel disease, pyoderma gangrenosum, therapy

Introduction

Pyoderma gangrenosum (PG), an uncommon neutrophilic dermatosis, presents as an inflammatory papule or pustule and progresses rapidly to form a painful ulcer with violaceous undermined borders. PG can be either idiopathic or associated with underlying systemic conditions, particularly inflammatory bowel disease (IBD), such as Crohn’s disease and ulcerative colitis (UC). The pathogenesis of the lesion is not fully understood, but it is thought be a multifactorial combination with neutrophil dysfunction, cytokines dysregulation, and specific genetic mutation.[1]

PG is a challenging cutaneous condition due to the lack of validated diagnostic criteria and evidence-based therapies.[4] As the incidence of PG is low, treatment options are mainly based on expert opinion, anecdotal data from case reports, retrospective cohort studies. A review of the literature based on >350 PG patients demonstrated therapeutic efficacy of systemic corticosteroids or cyclosporine alone or together and recommended that they should be considered as the first-line therapy.[5] Patients without response to standard treatment procedures should be administrated with other drugs, including intravenous immunoglobulins (IVIGs), dapsone, cyclophosphamide, azathioprine, tacrolimus, mycophenolate mofetil, and anti-TNFα therapy. Topical treatment may be sufficient for localized PG. However, another systematic review of IBD-associated PG,[4] based on 60 cases, reported a low response rate for systemic corticosteroids (22%) and recommended anti-TNFα agents with the highest response rate (92%) as the first-line therapy.

The standard and effective therapy for IBD-associated PG is still controversial due to the paucity of case reports and RCTs. In this retrospective study, we reviewed a
series of cases with the aim to provide evidence-based data on disease characteristics and treatment response in patients of PG concurrent with IBD.

Methods
We retrospectively reviewed medical records of 42 IBD-associated PG patients who presented at our institution during the period from January 2007 to May 2018, and collected detailed clinical data, such as demographics, PG characteristics, subtype, and disease activity of IBD and specific therapies used and their treatment response. These data were obtained from chart review and recorded on a standard data collection sheet. Given the small sample size, descriptive statistics were mainly used and analyses were exploratory in nature.

Results
Demographic characteristics of patients
The baseline and demographic characteristics of these 42 patients were summarized in Table 1. The majority were women (29) and 39 had UC (92.9%). Almost 23.8% of the sample were smokers at the time of inclusion. The ulcerative subtype of PG was observed in 32 cases, pustular subtype in 5 cases, peristomal subtype in 4 cases, and vegetative subtype in 1 case. Stoma were present in three patients with Crohn’s disease and one patient with UC and only 14.3% were on IBD therapy at new PG onset (5-aminosalicylic acid and corticosteroids were the most frequently reported treatments). Other cutaneous manifestations were infrequently observed in patients, whereas joint involvement was more common affecting 19% of the sample.

PG characteristics
PG ulcers were most frequently located on the legs and only a single ulcer or two were present in over half of those cases [Table 2]. PG was confirmed by biopsy in 31 cases and diagnosed with clinical manifestation without biopsy in 11 cases. In total, 39 patients had active IBD with clinical symptoms with or without blood test. Active IBD was confirmed by endoscopy in 29/39 patients with the activity classed as moderate in most cases. Three cases were in remission at the time of presentation of PG based on the absence of clinical manifestation with normal blood tests without endoscopy.

PG response to specific therapies
In this study, we concentrated on therapeutic efficacy only in patients with UC-associated PG, not in those with other IBD subtypes due to a very limited case numbers. The initial therapy for new onset PG was defined as “first-line” therapy. When first-line treatment failed to induce remission or complete healing, the subsequent therapy was defined as “second-line” therapy. The good response to a specific therapy was defined as clinical improvements of both skin lesions and luminal symptoms, in other words, a decrease >50% in lesion size, in addition to a decrease/cease in mucopurulent

### Table 1: Baseline and demographic characteristics of the patients included

| Variable                             | (n=42) |
|--------------------------------------|--------|
| Age (year)                           | 40.5±14.6 |
| Sex                                  |        |
| Female                               | 29 (69.0%) |
| Male                                 | 13 (31.0%) |
| Smoker                               | 10 (23.8%) |
| Type of IBD                          |        |
| Ulcerative colitis                   | 39 (92.9%) |
| Crohn’s disease                      | 3 (7.1%) |
| Disease duration (year)              | 5.6±3.4 |
| Presence of stoma                    | 4 (9.5%) |
| Patients on IBD therapy at PG onset  | 6 (14.3%) |
| Patients on no IBD therapy at PG onset| 14 (33.3%) |
| IBD therapy at PG onset was unspecified| 22 (52.4%) |
| Other cutaneous manifestations of IBD| 4 (9.5%) |
| Joint involvement                    | 8 (19.0%) |

IBD: Inflammatory bowel disease, PG: Pyoderma gangrenosum. †Mean±SD.

### Table 2: Characteristics of pyoderma gangrenosum

| Variable                             | (n=42) |
|--------------------------------------|--------|
| Site                                 |        |
| Legs                                 | 14 (33.3%) |
| Feet                                 | 9 (21.4%) |
| Abdomen                              | 5 (11.9%) |
| Multiple sites                       | 6 (14.3%) |
| Arm                                  | 4 (9.5%) |
| Genitals                             | 2 (4.8%) |
| Peristomal                           | 2 (4.8%) |
| Lesion size (cm)                     | 6.9±4.4 |
| Lesion number                        |        |
| One ulcer                            | 16 (38.1%) |
| Two ulcers                           | 15 (35.7%) |
| Three ulcers                         | 5 (11.9%) |
| More than three ulcers               | 6 (14.3%) |
| Diagnosis of PG                      |        |
| By biopsy                            | 31 (73.8%) |
| By clinical manifestation without biopsy| 11 (26.2%) |
| Time between onset of IBD and presentation of PG (year) | 4.3±3.0 |
| IBD status at time of presentation of PG |        |
| Remission                            | 3 (10.3%) |
| Mildly active                        | 6 (20.7%) |
| Moderately active                    | 12 (41.4%) |
| Severely active                      | 8 (27.6%) |

IBD: Inflammatory bowel disease, PG: Pyoderma gangrenosum. †Mean±SD. †n=32 (data unavailable for remaining patients). ‡n=35 (data unavailable for remaining patients). ¶N=29 (data unavailable for remaining patients)
bloody stool. All first-line therapies used; response rates and need for second-line therapies were summarized in Table 3.

The combination of corticosteroids and 5-aminosalicylic acid (5-ASA) was the most frequently used therapy in patients with 17 receiving it as first line and three as second line. Encouragingly, a good response to the combination therapy was reported in 19/20 patients, with corticosteroid-dependent response in one case. The patient, who died with a severe complication of cerebral venous sinus thrombosis, was the only one that did not respond to the combination therapy. It is worthwhile to note a case where a 26-week pregnant woman healed with the combination therapy and gave birth to a healthy baby without any drug-associated side effects.

Seven patients received monotherapy with 5-ASA and three had a good response. Of them, four cases did not respond and received second-line therapy with the addition of corticosteroids or cyclophosphamide alone or in combination for healing. Besides, five cases were healed with corticosteroids alone as first-line therapy.

IVIG was given to two patients as monotherapy and other two as combination therapy with all having a good response. Of the latter two patients, one was treated with IVIG + 5-ASA and the other with IVIG + 5-ASA + corticosteroids.

Infliximab together with other agents as combination therapy was given to three patients. One was administrated with 5-ASA and the other two with corticosteroids and 5-ASA in addition to infliximab. They were all successfully treated with no adverse effects.

Cyclophosphamide was usually used as adjuvant treatment and combined with corticosteroids and 5-ASA for severe or corticosteroid-dependent cases. Such combination therapy was adopted in three patients with a good response.

### Table 3: Summary of all first-line therapies used, response rates, and need for second-line therapies in 39 ulcerative colitis associated pyoderma gangrenosum

| First-line therapies used | Number | Response | Second-line required |
|--------------------------|--------|----------|----------------------|
| Corticosteroids+5-ASA    | 17     | 16       | 1                    |
| 5-ASA alone              | 7      | 3        | 4                    |
| corticosteroids alone    | 5      | 5        | 0                    |
| IVIG (alone or in combination) | 4     | 4        | 0                    |
| Infliximab (in combination) | 3     | 3        | 0                    |
| Cyclophosphamide (in combination) | 3   | 3        | 0                    |

5-ASA: 5-aminosalicylic acid, IVIG: Intravenous immunoglobulin

#### Discussion

In this study, we retrospectively reviewed a large case series of IBD-associated PG in Chinese population. Some points to note include that the occurrence of PG was more common in females than in males. Interestingly, in our study, 39 cases (92.9%) had UC, although previous studies reported controversial results about the association between a particular IBD subtype and PG. A previous systematic review of 60 cases reported a similar PG occurrence in UC and Crohn’s disease. However, in a large population-based Manitoba cohort, PG was more prevalent in patients with Crohn’s disease. The correlation between PG and a specific IBD subtype seems to be affected by demographic characteristics, especially races. Traditionally, it was thought that PG onset and IBD activity followed independent courses. However, PG frequently occurred in patients with an established diagnosis of IBD and was concomitant with active luminal disease in this study. This result was consistent with the findings of a previous study, which revealed that 75% of patients with PG onset had active IBD disease. These findings indicate that the correlation between luminal disease activity and PG is stronger than previously reported.

Of all the therapies reported, the combination therapy of systemic corticosteroids and 5-ASA was the most commonly used one (n = 20) and appeared to be significantly effective in UC patients (95% response rate). This therapy was reported only in three cases in the literature and all showed a complete resolution. The efficacy of the combination therapy can be explained in two aspects. On the one hand, systemic corticosteroids was therapeutically effective and strongly recommended as first-line therapy for both PG and UC. In this study, good response to corticosteroids as first-line monotherapy was reported in 5/5 patients. On the other hand, 5-ASA was strongly recommended as first-line treatment in mild-to-moderate UC in clinical practice guidelines. The successful use of 5-ASA was observed in 3/7 UC patients in this study and 2/2 in the literature, suggesting that it is possible that 5-ASA may play a direct role in remission of PG. Oka reported that 5-ASA could treat UC-associated PG via downregulation of IL-8 production from fibroblasts in the skin lesions. Another study reported that topical 5-ASA cream successfully treated PG via suppression of leukocyte motility and cytotoxicity. We cannot exclude the possibility that the improvement of PG is secondary to the improvement of UC and it is beneficial to control underlining UC activity for PG management. It appears that corticosteroids with therapeutic efficacy to both PG and UC might be a stone that can be used to kill two birds, and 5-ASA might have a similar dual effect. Thus, the combination of these two drugs is promising in the management of UC-associated PG and should be considered as the first-line therapy.
With respect to this complicated condition of PG patients with active UC, treatment regimen is directed to both PG and UC. Corticosteroids is a good choice due to its known therapeutic efficacy to both PG and UC separately. Five-ASA is also administered due to digestive symptoms and its known association of PG with UC. That is why this combination therapy is most frequently used in our center, but it is hard to specify which treatment is more effective for which component of the association. When patients were separately administrated with corticosteroids or 5-ASA in our study, it seemed that corticosteroids were more effective than 5-ASA (5/5 vs. 3/7). More studies are required to investigate this issue.

We noted that first-line therapies with IVIG, infliximab, or cyclophosphamide were administered in a very limited number of UC-associated PG cases, most of which were treated in combination with corticosteroids and/or 5-ASA in our center. It is hard to determine to which therapy these patients responded, given the therapeutic efficacy of corticosteroids and 5-ASA in other cases. In this study, we provided little therapeutic evidence of IVIG, infliximab or cyclophosphamide in the management of UC-associated PG. Several studies had reported controversial results of first-line therapy with anti-TNF-α agents. Studies comparing first-line therapy of anti-TNF-α agents with corticosteroids are needed to provide more solid evidence for clinical recommendation. Furthermore, cost may be a limiting factor for the option of anti-TNF-α or IVIG therapy in a developing country, such as China, and these treatments may be considered as second-line therapies.

There are several limitations of this study. First, the collection of standard information was not available due to the retrospective nature of this study. Second, the case number is unsurprisingly so limited, but given the rarity of this entity, we believe that it still provides valuable data of disease characteristics and treatment outcomes of PG complicating IBD. More studies are needed to further investigate the clinical characteristics and treatment strategies of this rare cutaneous condition. Third, recurrence data were unavailable, although such information would undoubtedly be useful.

**Conclusion**

PG appears to be more prevalent in females and patients with UC in Chinese population. New PG occurrence is predominantly associated with active UC-related inflammatory activity and a re-evaluation of intestinal activity is needed. From the data reviewed here, corticosteroids in combination with 5-ASA may be considered as first-line therapy for UC-associated PG.

**Financial support and sponsorship**

This study was supported by 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University and Natural Science Foundation of China (No. 81673084).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): An updated review. J Am Acad Dermatol 2015;73:691-8.
2. Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma gangrenosum: An update on pathophysiology, diagnosis and treatment. J Am Acad Dermatol 2017;18:355-72.
3. Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: An evidence-based review of the literature based on more than 350 patients. J Am Acad Dermatol 2005;53:273-83.
4. Agarwal A, Andrews JM. Systematic review: IBD-associated pyoderma gangrenosum in the biologic era, the response to therapy. Aliment Pharmacol Ther 2013;38:563-72.
5. Polcz M, Gu J, Florin T. Pyoderma gangrenosum in inflammatory bowel disease: The experience at Mater Health Services' Adult Hospital 1998-2009. J Crohns Colitis 2011;5:148-51.
6. Yüksel I, Başar O, Ataseven H, Ertuğrul I, Aşan M, İbiş M, et al. Mucocutaneous manifestations in inflammatory bowel disease. Inflamm Bowel Dis 2009;15:546-50.
7. Tan WC, Ong CK, Lo KS, Leong KN. Pyoderma gangrenosum. Med J Malaysia 2007;62:251-3.
8. Akay N, Boyvat A, Heper AO, Soykan I, Arica IE, Bektas M, et al. Behçet's disease-like presentation of bullous pyoderma gangrenosum associated with Crohn's disease. Clin Exp Dermatol 2006;31:384-6.
9. Lee JI, Park HJ, Lee JY, Cho BK. A case of pyoderma gangrenosum with ulcerative colitis treated with mesalazine. Ann Dermatol 2010;22:422-5.
10. Hambin TJ. Pyoderma gangrenosum. Lancet 1998;351:1134.
11. Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: The Toronto consensus. Gastroenterology 2015;148:1035-58.e3.
12. Oka M. Pyoderma gangrenosum and interleukin 8. Br J Dermatol 2007;157:1279-81.
13. Sanders CJ, Hulsmans RF. Successful treatment of pyoderma gangrenosum with topical 5-aminosalicylic acid. Cutis 1993;51:262-4.
14. Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: An updated review. J Eur Acad Dermatol Venereol 2009;23:1008-17.
15. Brooklyn TN, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, et al. Infliximab for the treatment of pyoderma gangrenosum: A randomised, double blind, placebo controlled trial. Gut 2006;55:505-9.