**Comparison of Clinical Features between Pyoderma Gangrenosum Concomitant by Inflammatory Bowel Disease and Idiopathic Pyoderma Gangrenosum**

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**Abstract**

**Background:** Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that is highly associated with inflammatory bowel disease (IBD). Certain PG patients with no systemic disorders have been diagnosed with idiopathic PG. This study sought to clarify the difference between PG with IBD and idiopathic PG based on clinical features, laboratory tests, and medications.

**Methods:** Twelve patients with PG and IBD and 24 patients with idiopathic PG, who were hospitalized in Peking Union Medical College Hospital from 2000 to 2017, were retrospectively categorized into the IBD group and control group, respectively. Data of clinical features, laboratory tests, and medications were collected and compared between the two groups.

**Results:** Both groups were similar with respect to their clinical features. However, the IBD group had an increased occurrence of arthralgia or arthritis (58.3% vs. 12.5%, \( P = 0.007 \)), anemia (83.3% and 29.2%, \( P = 0.004 \)), and an increased percentage of antineutrophilic cytoplasmic antibody (ANCA)-positive patients (85.7% and 0.0%, \( P < 0.001 \)), compared to the control group.

**Conclusion:** PG patients with IBD had increased occurrence rates of arthralgia or arthritis, anemia, and ANCA-positive status compared to idiopathic PG patients.

**Key words:** Crohn Disease; Idiopathic; Pyoderma Gangrenosum; Ulcerative Colitis

**INTRODUCTION**

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that generally presents with painful, tender and erythematous papules, sterile pustules, vesicles, or fluctuant nodules that can rapidly progress to expanding ulcers characterized by a violaceous undermined border and necrotic base.¹ The ulcers may enlarge or spontaneously heal with a characteristic cribriform scar.² PG commonly occurs in adults 20–50 years of age, with a female predominance.³ Approximately 50% of PG patients have underlying diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis, and hematological disorders,⁴ and patients without underlying diseases are categorized as having idiopathic PG. IBD, comprising of Crohn’s disease (CD) and ulcerative colitis (UC), is an idiopathic and inflammatory disease of the intestinal tract.⁵ The incidence of PG in IBD patients has been reported to be approximately 0.5–1.2%.⁶

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The relationship between PG and IBD is complex, and the pathogenesis of the co-occurrence of both diseases in certain patients is poorly understood. Both diseases involve an aberrant immune system, with increased levels of inflammatory mediators, tumor necrosis factor alpha (TNF-α), interleukin 17 (IL-17), and IL-23. Immunosuppressive therapy is the major treatment strategy for both diseases. Moreover, adalimumab and infliximab (monoclonal antibodies that act downstream in the IL-17 pathway by blocking TNF-α) are highly effective therapies for both diseases. Furthermore, an abnormal immune response with crossover autoantibodies that have the same target antigens in the bowel and skin and crossover genetic factors also partially contribute to the association between PG and IBD.

To the best of our knowledge, no study has focused on the differences between the clinical characteristics of and medications used for PG patients with IBD and idiopathic PG patients; although, several studies with low numbers of PG patients with IBD have been published. Therefore, in this study, we retrospectively recruited these two patient groups, seeking to clarify their differences based on clinical features, laboratory tests, and medications.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Peking Union Medical College Hospital.

Data source

Seventy-four patients, who were diagnosed with PG and hospitalized in Peking Union Medical College Hospital from January 1, 2000, to January 31, 2017, were retrospectively identified by searching the registration system of our hospital for the International Classification of Diseases (ICD) codes (10th revision), including L88. Concurrent diseases were also recorded, particularly for IBD patients. The ICD codes for UC include K510, K511, K512, K513, K518, and K519, and the ICD codes for CD include K500, K501, K508, and K509. A total of 1943 patients with IBD were hospitalized during the study.

Identification of the cases and controls

Chart records of all 74 PG patients were critically and simultaneously reviewed by one dermatologist and one gastroenterologist. The diagnosis of PG was based on the patient’s medical history and confirmation of the typical clinical lesions. IBD patients were diagnosed based on the diagnostic criteria reported in previous studies. Finally, 12 PG patients with IBD were categorized into the IBD group, and 24 PG patients with no systemic diseases were categorized into the control group. In the IBD group, one patient was associated with hepatitis B virus infection, and one patient with obliterative bronchiolitis.

Outcome measurements

Data were obtained through chart reviews and included demographics (age and gender), family history, disease duration, disease phenotype (PG subtype), the presence of arthralgia or arthritis, laboratory test results, histopathologic features, and medications. The PG subtypes were classified as follows based on different clinical appearance: (1) classical, (2) superficial granulomatous, (3) pustular, (4) bullous, and (5) unknown. The targeted lesion size was recorded by the dermatologist based on the maximal longitudinal length and maximum perpendicular length and then converted into the area using a formula (length × width × 0.785), which approximates an ellipse. The laboratory tests included hemoglobin (Hb), serum albumin, erythrocyte sedimentation rate (ESR), and antineutrophilic cytoplasmic antibodies (ANCAs). Complete blood cell count tests indicated anemia for Hb of <110 g/L in women and <120 g/L in men. Only data from the initial hospitalization were primarily collected for the statistical analysis if the patient was hospitalized multiple times during the study period.

Statistical analysis

Continuous variables, which were normally distributed, were presented as the mean ± standard deviation (SD). Continuous variables, which were not normally distributed, were presented as median (Q1, Q3). Between group differences were statistically examined using the Student’s t-test or the Mann-Whitney U-test for continuous variables. Categorical variables from the two groups were compared using Fisher’s exact test. P values were two-tailed, and the significance level was set at P < 0.05. All analyses were performed with SPSS statistical software version 22.0 (IBM, Armonk, NY, USA).

Results

Clinical characteristics of all pyoderma gangrenosum patients

Among 74 PG patients, 12 (16.2%) PG patients with concurrent IBD, including 11 (14.9%) UC patients and one (1.4%) CD patient, were included in the IBD group; and 24 (32.4%) patients with idiopathic PG were included in the control group. The clinical characteristics of all patients are summarized in Table 1. Among 36 PG patients included in this study, 18 (50.0%) patients were male, 7 (19.4%) patients were current smokers; the mean onset age of the first episode of PG was 34.3 ± 13.1 years and 24 (66.7%) PG patients were of the classical subtype [Figure 1]. Of these 36 PG patients, 25 (69.4%) patients had only one episode of PG, 4 (11.1%) patients had two to three episodes and 7 (19.4%) had more than three episodes. Eleven patients (30.6%) developed only one lesion, 10 patients (27.8%) presented two to three lesions, and 15 (41.7%) presented more than three lesions. The location of the PG lesions was variable, with the most common sites being the lower extremity (86.1%). A peristomal lesion was reported in 86.1% of patients. Skin biopsies were obtained from 20 patients with idiopathic PG and 9 patients with PG and...
The histopathologic findings revealed edema, mixed inflammatory cell infiltrate, predominantly neutrophilic infiltrate and vasculitis, follicular-based pustules, necrosis, and hemorrhage. Twelve (41.4%) of 29 skin biopsies showed signs of vasculitis [Figure 3].

**Comparison of clinical features and medications between the inflammatory bowel disease and control groups**

No significant differences in gender, smoking status, or the onset age of PG were observed between the IBD and control groups [Table 1]. The IBD and control groups had similar PG features, including the proportion of the predominant classical type (66.7% vs. 66.7%), high frequency of lower extremity involvement (91.7% vs. 83.3%), median area of the target lesions (19.6 cm² [12.0, 90.3 cm²] vs. 37.7 cm² [8.2, 108.3 cm²]), and incidence of frequent recurrence (16.7% vs. 20.8%). However, arthralgia and arthritis were more common in the IBD group (58.3% vs. 12.5%, \(P = 0.007\)). Compared with the control group, the IBD group consistently had a lower Hb level (118.4 ± 28.8 g/L vs. 94.4 ± 26.7 g/L, \(P = 0.021\)) and a higher incidence of anemia (29.2% vs. 83.3%, \(P = 0.004\)). The ANCA test was performed in 14 patients with idiopathic PG and 7 patients with PG and IBD; 6/7 (85.7%) patients in the IBD group were ANCA positive, whereas no patient (0/14) in the control group was ANCA positive.

![Figure 1: The clinical appearance of pyoderma gangrenosum. Several ulcers on the lower limbs had characteristic violaceous undermined edges and a necrotic base.](image-url)

| Characteristics                  | Total (n = 36) | Control group (n = 24) | IBD group (n = 12) | Statistical value | \(P\)  |
|----------------------------------|----------------|------------------------|-------------------|-------------------|------|
| Gender, n (%)                    |                |                        |                   |                   |      |
| Male                             | 18 (50.0)      | 10 (41.7)              | 8 (66.7)          |                   | 0.289*|
| Female                           | 18 (50.0)      | 14 (58.3)              | 4 (33.3)          |                   |      |
| Smoking status, n (%)            |                |                        |                   |                   |      |
| Male                             | 7 (19.4)       | 6 (25.0)               | 1 (8.3)           |                   | 0.384*|
| Onset age (years), mean ± SD (range) | 34.3 ± 13.1 (10–64) | 33.1 ± 13.8 (10–64) | 36.7 ± 11.8 (21–58) | -0.770* | 0.447 |
| Subtype of PG, n (%)             |                |                        |                   |                   |      |
| Classical                        | 24 (66.7)      | 16 (66.7)              | 8 (66.7)          |                   | 0.455*|
| Superficial granulomatous        | 3 (8.3)        | 1 (4.2)                | 2 (16.7)          |                   |      |
| Pustular                         | 3 (8.3)        | 3 (12.5)               | 0 (0.0)           |                   |      |
| Bullous                          | 0 (0.0)        | 0 (0.0)                | 0 (0.0)           |                   |      |
| Unknown                          | 6 (16.7)       | 4 (16.7)               | 2 (16.7)          |                   |      |
| Area of target lesion (cm²), median (Q1, Q3) | 37.7 (9.5, 94.2) | 37.7 (8.2, 108.3) | 19.6 (12.0, 90.3) | 198.0i | 0.822 |
| Episodes of PG, n (%)            |                |                        |                   |                   | 1.000*|
| 1                                | 25 (69.4)      | 16 (66.7)              | 9 (75.0)          |                   |      |
| 2–3                             | 4 (11.1)       | 3 (12.5)               | 1 (8.3)           |                   |      |
| >3                              | 7 (19.4)       | 5 (20.8)               | 2 (16.7)          |                   |      |
| Number of lesions, n (%)         |                |                        |                   |                   | 0.144*|
| 1                                | 11 (30.6)      | 8 (33.3)               | 3 (25.0)          |                   |      |
| 2–3                             | 10 (27.8)      | 4 (16.7)               | 6 (50.0)          |                   |      |
| >3                              | 15 (41.7)      | 12 (50.0)              | 3 (25.0)          |                   |      |
| Location of lesions, n (%)       |                |                        |                   |                   |      |
| Upper limb                       | 12 (33.3)      | 10 (41.7)              | 2 (16.7)          |                   | 0.260*|
| Lower limb                       | 31 (86.1)      | 20 (83.3)              | 11 (91.7)         |                   | 0.646*|
| Other                            | 13 (36.1)      | 8 (33.3)               | 5 (41.7)          |                   | 0.720*|
| Vasculitis (histopathologic findings), n/N (%) | 12/29 (41.4)  | 7/20 (35.0)            | 5/9 (55.6)        |                   | 0.422*|

*Fisher’s exact test; †Student’s t-test; ‡Mann-Whitney U-test. SD: Standard deviation; IBD: Inflammatory bowel disease; PG: Pyoderma gangrenosum.
had ANCA (P < 0.001). No significant differences were found in the levels of serum albumin and ESR between two groups [Table 2].

Systemic corticosteroids were prescribed in 66.7% of patients in the IBD group and 83.3% of patients in the control group. Compared with the control group, the IBD group was prone to receive biologic agents and was prescribed fewer immunosuppressive agents. However, the differences were not statistical significance. Minocycline, a systemic tetracycline antibiotic, was used in 37.5% of patients in the control group, but only in 8.3% of patients in the IBD group [P = 0.115, Table 2]. All patients in the IBD and 95.8% of patients in control groups demonstrated an improved disease status at the time of discharge.

**DISCUSSION**

PG, as an inflammatory skin disorder, is usually accompanied by other systemic disorders, including IBD, hematological disorders, and rheumatoid diseases. However, approximately 20–30% of cases are idiopathic.[16] Due to the rarity of PG, only a few studies in Caucasian-dominant groups have been published while even fewer reports have addressed Asian populations.[12,13] To date, no evidence has shown that the efficacy of PG treatment differs between IBD patients and non-IBD patients. Furthermore, no study has revealed the differences in PG manifestations between IBD patients and non-IBD patients. In this retrospective cohort study, we showed that 16.2% of PG patients had IBD. Compared with the control group, the IBD group had a higher incidence of arthralgia or arthritis, lower Hb levels and a higher rate of ANCA-positive status. However, no significant differences between two groups were observed in the demographics, PG type and medications.

This study confirmed the previous finding that PG patients commonly exhibit various comorbidities (50–70%),[17] particularly IBD. However, the proportion of IBD patients among PG-assumed patients in this study was slightly

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**Table 2: Clinical characteristics and treatment of the patients in the IBD and control groups**

| Characteristics                  | Control group (n = 24) | IBD group (n = 12) | Statistical value | P     |
|----------------------------------|------------------------|--------------------|-------------------|-------|
| Clinical manifestations, n (%)   |                        |                    |                   |       |
| Oral ulcers                      | 1 (4.2)                | 2 (16.7)           | 0.253*            |       |
| Arthropathy                      | 3 (12.5)               | 7 (58.3)           | 0.007*            |       |
| Laboratory results               |                        |                    |                   |       |
| Hemoglobin (g/L), mean ± SD      | 118.4 ± 28.8           | 94.4 ± 26.7        | 2.414†            | 0.021 |
| Anemia, n (%)                    | 7 (29.2)               | 10 (83.3)          | 0.004*            |       |
| Albumin (g/L), median (Q1, Q3)   | 34.0 (26.5, 37.0)      | 33.5 (23.8, 35.0)  | 214.0†            | 0.788 |
| ESR (mm/h), median (Q1, Q3)      | 25.5 (5.3, 71.5)       | 31.5 (14.5, 84.0)  | 214.5†            | 0.416 |
| ANCA, n/N (%)                    | 0/14 (0.0)             | 6/7 (85.7)         | <0.001*           |       |
| Medication use, n (%)            |                        |                    |                   |       |
| Systemic corticosteroids         | 20 (83.3)              | 8 (66.7)           | 0.397*            |       |
| Immunosuppressive agents§        | 10 (41.7)              | 3 (25.0)           | 0.468*            |       |
| Anti-TNF agents§                 | 1 (4.2)                | 2 (16.7)           | 0.253*            |       |
| Antibiotics (minocycline)        | 9 (37.5)               | 1 (8.3)            | 0.115*            |       |
| Others¶                          | 5 (20.8)               | 0 (0.0)            | 0.146*            |       |

*Fisher’s exact test; †Student’s t-test; ‡Mann-Whitney U-test; §Immunosuppressive agents included cyclosporine, azathioprine, cyclophosphamide, Tripterygium wilfordii; ‖Anti-TNF agents: Infliximab; Others included thalidomide, compound glycyrrhizin tablets, colchicines. SD: Standard deviation; IBD: Inflammatory bowel disease; PG: Pyoderma gangrenosum; ESR: Erythrocyte sedimentation rate; ANCA: Anti-neutrophilic cytoplasmic antibodies.
lower than the findings of previous studies of Western populations (16.2% and 34.0%, respectively), partly due to the low incidence of IBD in China. Less than 1% of IBD patients suffered from PG, a finding that aligned with the findings of previously published studies. Controversies exist regarding whether the incidence of PG with UC is higher than the incidence of PG with CD. Al Ghazal et al. reported that 6.6% of patients had UC and 2.7% had CD among 259 PG patients. However, PG with CD was more prevalent than PG with UC in other studies. The data of this study also supported the higher incidence of PG with UC than PG with CD. Differences in genomics, lifestyle habits, environmental factors, economic statuses, the incidence rates of CD and UC and affordable medical service would influence the case determinations.

Previous studies have shown that PG classically presented with one or more painful ulcers with violaceous, undermined borders on the lower legs. Less commonly, PG can present with tender nodules or pustules on other sites of the body. PG lesions can be single or multiple, unilateral or bilateral, and can range in size from several centimeters to the surface of an entire limb. Biopsy of a PG lesion rarely yields characteristic features of the disease, and tissue pathology should not be used to exclude a PG diagnosis. The study findings showed no significant differences in the onset of PG, gender, major subtype of PG (classical type), most commonly involved site (lower extremities), and even the proportion of vasculitis between IBD and control groups. However, the occurrence of arthralgia or arthritis was significantly more common in the IBD group than the control group in this study. Powell et al. reported that arthritis occurred in up to 37% of patients with PG and that arthritis and PG could occur simultaneously as extraintestinal manifestations (EIMs) of IBD. Bhagat and Das observed an autoimmune reaction toward an isoform of tropomyosin (tropomyosin-related peptide), which was expressed in the eye (nonpigmented ciliary epithelium), skin (keratinocytes), joints (chondrocytes), biliary epithelium, and gut. This type of autoimmune reaction might partially reveal the pathogenesis of the concurrent EIMs. However, this study did not identify a considerable proportion of patients with oral ulcers or eye lesions.

Previous studies have reported that anemia was a significant comorbidity of PG, leading to the hypothesis that anemia could be a possible co-factor in the pathogenesis of PG. Similarly, we detected anemia in 29.2% and 83.3% of patients in the control and IBD groups, respectively. IBD patients with an active disease status usually suffered from iron-deficiency anemia, chronic disease anemia or mixed anemia, which could have contributed to our findings.

ANCAs are auto-antibodies directed against azurophilic proteins within neutrophils, including perinuclear ANCAs (p-ANCAs) and cytoplasmic ANCAs. A typical p-ANCA is often detected in 40–80% of UC patients, which favors the diagnosis of UC and is closely associated with disease activity. Although few reports have described the positive detection of ANCAs in PG patients or a neutrophilic dermatosis with features of PG, the exact prevalence of ANCAs in the context of PG is still unclear. Von Den Driesch et al. tested 12 of 44 PG patients for ANCAs, and all were negative. The results of the present study also confirmed the rarity of ANCA-positive status in idiopathic PG patients and provided some indication that ANCA-positive PG patients might present with gastrointestinal symptoms later, finally resulting in a diagnosis of IBD.

In terms of medications, some investigators have suggested the first-line use of systemic corticosteroids, with or without an immunosuppressive agent, for patients with idiopathic PG. The medications for IBD can improve the healing of PG in PG patients with IBD. Recently, anti-TNF-α agents have been used to treat PG patients with IBD. In this study, systemic use of corticosteroids was indeed found to be the primary systemic therapy for patients in both groups. Meanwhile, PG patients with IBD tended to more commonly use infliximab but use fewer immunosuppressive agents and antibiotics, although the differences were not statistically significant. Remarkably, minocycline, a systemic tetracycline antibiotic, was used by 37.5% of patients in the control group. Systemic antibiotics, including tetracyclines, in addition to their role in inhibiting secondary bacterial infection, may also modulate the course of PG through anti-inflammatory mechanisms. However, no specific consensus exists on the different medications for these two groups.

The study was noteworthy because it innovatively focused on the differences in the clinical features and medications between patients with PG and IBD and those with idiopathic PG. This study had some limitations. First, a sample size of this study was small because of the rarity of the disease, as well as the retrospective nature of the data. These two factors increased the difficulty of obtaining meaningful statistical data. Second, this study was performed in a tertiary medical center, and thus, a greater proportion of the patients enrolled in this study had an active disease status. Moreover, the idiopathic PG group might have included cases that later developed into IBD. Finally, this study did not obtain long-term data of prognosis to collect recurrence information. Such information would undoubtedly be useful. A prospective multi-center cohort study is required to clearly elucidate the differences in clinical characteristics and long-term prognosis between PG patients with IBD and idiopathic PG patients.

In conclusion, PG is a rare EIM of IBD, and PG patients with concurrent IBD had a higher incidence of arthralgia or arthritis, lower Hb levels and a higher rate of ANCA-positive status than idiopathic PG patients.

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Conflicts of interest
There are no conflicts of interest.

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