

Pyoderma Gangrenosum Presenting with Inflammatory Bowel Disease Involving Different Sites and Treatment of Infliximab

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Abstract

Pyoderma gangrenosum (PG) is an uncommon neutrophilic dermatosis characterized by inflammatory and ulcerative conditions of the skin. Typically, PG begins as a violet-colored inflammatory papule or pustule with a well-defined, purulent erythematous base that evolves into a painful ulcer. Additionally, PG may manifest as bullous, vegetative, peristomal, and extracutaneous lesions. Over half of the individuals with PG have the condition in conjunction with an underlying systemic disease, most commonly inflammatory bowel disease, hematologic disorders, or rheumatoid arthritis. Diagnosing PG requires identifying consistent clinical and histological features while ruling out other inflammatory or ulcerative skin disorders, as there are no unique clinical or histological signs definitive for PG. With an incidence rate estimated at 3–10 cases per million annually, PG predominantly affects young to middle-aged adults, typically between 40 and 60 years of age, and is more frequently diagnosed in women. At Uludağ University's Gastroenterology Department, we have reviewed five cases with varying sites of involvement, comparing them against the existing body of literature.

Keywords: Crohn's disease, pyoderma gangrenosum, ulcerative colitis

INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon neutrophilic dermatosis manifesting as an inflammatory and ulcerative condition of the skin.¹ The typical presentation of PG is a violet-colored inflammatory papule or pustule that evolves from a circumscribed, purulent erythematous base into a painful ulcer. Additionally, PG may present as bullous, vegetative, peristomal, and extracutaneous lesions.¹ Over half of the cases of PG are associated with an underlying systemic disease, with the most prevalent comorbidities being inflammatory bowel disease, hematologic disorders, and rheumatoid arthritis. The diagnosis of PG relies on identifying consistent clinical and histological features and ruling out other inflammatory or ulcerative skin disorders.² PG lacks specific clinical or histological markers. It is a rare condition, with an estimated incidence of 3–10 cases per million people annually, and typically emerges in adults aged 40–60 years, affecting women more frequently than men.³

At the Gastroenterology Department of Uludağ University, we reviewed five cases with various sites of involvement against the backdrop of a literature review. Tables 1 and 2 detail the cases, and the accompanying figures illustrate their condition before and after treatment. All cases were previously diagnosed with either ulcerative colitis or Crohn's disease and were receiving standard treatment regimens, with the exception of infliximab, which was administered at the prescribed doses. Biopsies and endoscopic evaluations were repeated during episodes of skin activity. Infliximab treatment was provided at 5 mg/kg weekly, with efficacy evaluations conducted at the six-week mark. Skin assessments were performed at the initial visit and again at six weeks, as documented in photographs. Disease activity assessments at week six utilized physical examination and laboratory evaluations, employing the Crohn's Disease Activity Index (CDAI) for Crohn's disease and the Truelove-Witts scale for ulcerative colitis. Clinical and biological improvements were noted in parallel with treatment. During this period, no repeat endoscopic evaluations were conducted.

PYODERMA GANGRENOSUM PATHOGENESIS

PG is associated with increased expression of various interleukins (IL) and tumor necrosis factor (TNF-alpha) in the affected skin areas. Specifically, there is upregulation of IL-1-beta, IL-1-alpha, IL-8, IL-12, IL-15, IL-17, IL-23, IL-36, and TNF-alpha. This elevation of cytokines results in proinflammatory activation, characterized by enhanced inflammasome activity, dysregulation of the innate immune system, chemotaxis, and neutrophil activation. Additionally, PG tissue shows increased expression of pattern recognition receptors (PRRs), JAK2, and STAT1, which points to dysfunctions in both adaptive and innate immune responses. The complement pathway, particularly involving C5a, plays a significant role in neutrophil activation, chemotaxis, and inflammatory signaling.

Mutations in autoinflammatory genes such as MEFV, NLRP3, NLRP12, NOD2, and LPIN2 have been identified in PG, as well as in acne and hidradenitis suppurativa (PASH) syndrome and other inflammatory conditions. Advancements in understanding the molecular pathways involved in PG have led to the development of more targeted therapies, including inhibitors of TNF-alpha, IL-1, IL-17, IL-23, and IL-6.⁴⁻⁶

The clinical manifestations of PG are diverse, encompassing four primary subtypes:

1. Ulcerative (classic) PG: This is the most common variant of PG.
2. Bullous (atypical) PG.
3. Pustular PG.
4. Vegetative PG.

All subtypes of PG are marked by a clinical course that typically begins with the emergence of a destructive inflammatory papule, pustule, vesicle, or nodule. These lesions often expand rapidly into erosions or ulcers. Except in the case of vegetative PG, the progression of the lesion is usually swift, and the associated pain is disproportionately intense compared to the lesion's appearance. Fever may or may not be present along with these symptoms.⁷

Detailed descriptions of these main PG variants are as follows:

Ulcerative (classical) PG: Representing the majority of PG cases, the ulcerative form typically begins as a tender, inflamed papule, pustule, or vesicle that appears on normal skin or at a site of trauma. Most commonly, lesions occur on the lower extremities and trunk, but they can also develop in other areas.^{8,9}

The initial inflammatory lesion in PG typically expands peripherally while degenerating centrally, resulting in ulcer formation. The ulcer's edge is often characterized by a bluish or purplish hue. Irregular growth of the affected tissue can lead to a serpiginous configuration. The ulcer's base is generally purulent and necrotic, with its depth often extending into the subcutaneous adipose tissue and, in some cases, reaching the fascia.

Patients with PG may present with either a single lesion or multiple lesions at various stages of development. The ulcers typically heal with atrophic cribriform scars.

Bullous (atypical) PG: This less common, superficial variant of PG is most prevalent in patients with hematologic diseases. Contrary to ulcerative PG, the arms and face are the usual sites of involvement. Patients with bullous PG often exhibit rapid development of blue-grey inflammatory bullae, which quickly erode into superficial ulcers. Given the strong association of bullous PG with hematologic diseases, patients without a known hematologic disorder should be closely monitored for the potential emergence of such conditions.¹⁰

Pustular PG: Typically associated with inflammatory bowel disease, pustular PG often flares up during acute exacerbations of the bowel condition. Affected patients usually present with the rapid development of painful pustules surrounded by erythema, often accompanied by fever and joint pain. Pyostomatitis vegetans, marked by numerous small pustules and erosions in the oral mucosa, may be considered a variant of pustular PG.

Vegetative PG: Vegetative Pyoderma gangrenosum (also known as superficial granulomatous pyoderma) is typically a localized, solitary, and superficial form of PG, presenting as a slow-growing, mildly painful nodule, plaque, or ulcer. Characterized by a verrucous quality, it differs from ulcerative PG in that it does not have defined borders or a purulent base. The head, neck, and trunk are the most frequent sites of occurrence for vegetative PG.

Special regions: Beyond the morphological subtypes previously discussed, PG can also present in specific regions, leading to variants such as peristomal PG, genital PG, and extracutaneous PG.

Peristomal Pyoderma Gangrenosum: This rare variant of PG is marked by the development of ulcerative PG-like lesions near a stoma. Commonly found in patients with ulcerative colitis or Crohn's disease, it can occur months or even years after stoma formation. Trauma from the stoma or irritation caused by stoma secretions may contribute to the development of peristomal PG.¹¹

Genital PG: Involving areas like the vulva, penis, or scrotum, genital PG manifests with lesions similar to ulcerative PG and is an exceptionally rare form of the condition.

Extracutaneous PG: PG can occasionally affect extracutaneous sites, leading to sterile neutrophilic infiltration in organs such as the lungs, intestines, cornea, liver, spleen, heart, bones, muscles, and the central nervous system.

Postoperative PG: This form of PG emerges at surgical sites, typically within two weeks post-surgery. Initial symptoms include erythema at the surgical site and severe pain disproportionate to the physical findings, followed by wound dehiscence or the development of small ulcerations that evolve into larger ulcers. Postoperative PG appears more frequently in women and commonly affects areas such as the breasts and abdomen.¹¹

Related Diseases

In over 50% of patients diagnosed with PG, there is an association with a systemic disease. The most commonly related conditions include inflammatory bowel disease, rheumatoid arthritis, and hematologic diseases or malignancies. The occurrence of PG can either precede or follow the diagnosis of these associated diseases. Furthermore, the clinical course of PG may or may not mirror that of the associated systemic condition.^{12,13}

DIAGNOSIS

Clinical, histopathologic, and laboratory findings of PG are not specific, making its diagnosis contingent on the exclusion of other possible conditions. A comprehensive clinical history, physical examination, and skin biopsy should be conducted for all patients. The development of ulcers in patients with diseases known to be associated with PG should prompt consideration of this diagnosis. Additionally, once PG is diagnosed, it is important to assess patients for any underlying associated diseases.^{14,15}

Diagnostic Criteria: The newer diagnostic criteria for ulcerative PG, established through Delphi consensus, are highly beneficial for diagnosis. These criteria include one major criterion and eight minor criteria, encompassing histologic findings, patient history, clinical examination, and treatment responses:¹⁷

- Major Criterion:

- Biopsy of an ulcer showing neutrophilic infiltrate

- Minor Criteria:

- o Exclusion of infection
- o Positive pathergy test
- o Presence of inflammatory bowel disease or inflammatory arthritis
- o Rapid development of ulcerating papules, pustules, or vesicles

- o Peripheral erythema, limitation, and tenderness at the ulceration site
- o Presence of multiple ulcerations, with at least one on the anterior lower leg
- o Presence of white or “crumpled paper” scars at healed ulcer sites
- o Reduction in ulcer size within one month of starting immunosuppressive medication

For a diagnosis, at least one major criterion and four minor criteria are required.

The PARACELSUS score, another diagnostic approach, uses a point system with slightly different major and minor criteria.¹⁸ This system is specifically designed to differentiate venous leg ulcers from PG.

Pathology: Early PG lesions exhibit perifollicular inflammation and intradermal abscess formation. As lesions progress to ulceration, findings typically include epidermal and superficial dermal necrosis with underlying mixed inflammatory cell infiltrate and abscess formation. Giant cells may be observed, and vascular changes suggestive of lymphocytic vasculitis may be present at the tissue edges of the lesion. Leukocytoclastic vasculitis may also be evident.

Laboratory Studies: Similar to tissue biopsies, there are no laboratory tests that definitively diagnose PG. Non-specific findings like leukocytosis, elevated erythrocyte sedimentation rate, and raised C-reactive protein levels may be observed.¹⁹

TREATMENT

Due to limited data on PG interventions, definitive treatment guidelines are not established. The management approach for PG is primarily informed by small, uncontrolled studies and clinical experience. Generally, patients receive a combination of topical and/or systemic therapies aimed at suppressing inflammation, alongside wound care measures that create a conducive environment for healing. Although initial signs of healing may appear within days of starting treatment, complete healing of the ulcer often requires weeks or even months.

Laboratory tests play a supportive role in differential diagnosis and in identifying associated PG-related diseases.²⁰ A crucial first step in managing lesions resembling PG is the thorough exclusion of other disorders that may cause cutaneous ulceration

Wound Care: The goal of wound care in PG is to foster optimal conditions for ulcer healing.

Local Care: Wounds should be gently cleaned with warm sterile saline or a mild antiseptic prior to dressing application. Dressings that maintain a moist wound environment and do not adhere to the ulcer base are often preferred to aid healing.

The selection of a specific type of wound dressing is contingent upon the nature of the lesion and the preferences of the patient and clinician. For instance, highly exuding ulcers may benefit from more absorbent dressings, such as alginates, to prevent tissue maceration.

Pathergy, a phenomenon where lesions exacerbate at sites of trauma, can occur in PG. Thus, it is important to avoid unnecessary traumatic damage to the ulcerated area, such as using wet-to-dry dressings or applying caustic substances like silver nitrate.

Care for the surrounding skin is also vital. Barrier creams, such as zinc oxide paste or petroleum jelly, or ointments can help protect the skin around the wound’s edge from deterioration.

Surgery: The role of surgery in the management of PG wounds is contentious due to the potential for pathergy, a phenomenon where trauma exacerbates the condition. Surgical interventions are generally reserved for specific circumstances, such as when there is an accumulation of necrotic tissue that increases the risk of infection, or when vital structures like tendons or ligaments are exposed in the ulcer bed. Despite reports of numerous PG cases worsening following surgery, certain procedures—such as gentle debridement, skin flaps or grafts, partial thickness grafts with negative pressure wound therapy, and the application of bioengineered keratinocyte autografts or allogeneic cultured dermal substitutes—have shown benefits. To minimize pathergy, surgical procedures should ideally be performed when the patient is in good overall health, disease activity is in remission, and the patient is receiving concurrent systemic therapy.

Limited Disease: For patients with mild, localized PG (for example, a few superficial ulcers or vegetative PG), local interventions can be considered as initial therapy.

Local Corticosteroids: Topical corticosteroids are commonly prescribed as both primary and adjunctive treatments for PG, but the evidence supporting their effectiveness is largely drawn from a limited number of retrospective studies and case reports. High-potency topical corticosteroids, such as clobetasol propionate, are typically applied once or twice daily.

Local Calcineurin Inhibitors: Topical tacrolimus, available in concentrations ranging from 0.03% to 0.3%, has demonstrated effectiveness in treating PG through numerous case reports, several prospective case series, and uncontrolled studies.

Topical Tacrolimus: This medication is commercially available as ointments in 0.03% and 0.1% concentrations. Typically, patients are advised to apply the 0.1% ointment once or twice daily. Signs of recovery may be observable from the first few days to weeks of treatment. However, complete healing of an ulcer can take several weeks to several months. Treatment is generally well-tolerated, though some patients may experience a slight burning sensation at the application site.

Systemic or Rapidly Progressive Disease: Most PG patients require more than local treatment. Systemic therapy is considered a first-line intervention for PG that is not confined to a few superficial ulcers or a single vegetative PG plaque. Systemic agents are also recommended for patients with mild PG who do not respond to local treatments.²⁰

In patients with mild PG (a few superficial ulcers or vegetative PG), the local administration of corticosteroids or a calcineurin inhibitor may be sufficient for treatment. In contrast, systemic therapy is typically required in patients with more extensive PG. Glucocorticoids are the most prescribed systemic drugs because a rapid response is often observed, and the drugs are relatively low cost and easily administered. Systemic cyclosporine is an alternative first-line treatment for patients who cannot tolerate systemic glucocorticoid therapy.

A wide range of other systemic immunomodulatory drugs can be used as alternative or adjunctive therapies for PG that does not respond ad-

Table 1. Cases

CASE NAME-SURNAME	AGE AND SEX	COMORBIDITY	ADDITIONAL MEDICINES USED	DERMATOLOGICAL FINDINGS	HISTOPATHOLOGY	UNDERLYING DISEASE PATHOLOGY	ENDOSCOPIC FINDINGS	TREATMENT
1. N.S.	56 years old, Female	TYPE 2 DM (10 years)	Metformin 1000 2 × 1	Vagen labium majus, hard-based ulcer with 1 cm erythematous edges near the anus.	Ruptured suppurative folliculitis and surrounding granulomatous inflammation with central abscessing Multiple fibroepithelial polyps with chronic inflammatory infiltration sub-epithelial scar tissue, ulceration suppurative neutrophilic inflammatory granulation tissue.	Crohn's disease, Montreal A3L2B1P Pathology; Superficial ulceration and chronic active inflammatory infiltration; sigmoid colon, and rectum,	Ulcerated 4-5 cm lesion in the perianal region; proctitis and aphthous ulcerations in the sigmoid colon.	Prednisolone, Azathioprine, Mesalazine, Infliximab
2. F.U.	62 years old, Female	Type 2 DM, HT, Dyslipidemia	Dapagliflozin 10 mg 1 × 1, Insulin glargine 1 × 14 U Rosuvastatin 10mg 1 × 1, Losartan 100 mg 1 × 1	On the left breast, 2-3cm dark purplish, erythematous, two hard ulcers with a painful base, one of which is eroded in the middle.	Epidermal cystic lesion with surrounding suppurative inflammatory granulation tissue; left breast.	Crohn's disease, Montreal A3L2B1P; Chronic inflammatory infiltration; transverse colon. Chronic inflammatory infiltration; descending colon. Chronic inflammatory infiltration; sigmoid colon. Chronic inflammatory infiltration; rectum.	Anal inspection revealed two fistula orifices in the left gluteal region and between the anus and vulva. The colonoscope was advanced to 80 cm. The mucosa and lumen of the rectum were normal. Ulcerations in the sigmoid colon starting at 20 cm from the anal verge and continuing along the descending colon, and transverse colon, with normal mucosal areas in between, sometimes linear, causing a paving stone appearance.	Azathioprine, Mesalazine, Infliximab
3. I.S.	36 years old, Male	Ulcerative colitis for 13 years	He is not taking any medication except for the treatment of ulcerative colitis.	Ulcerations on bilateral cruris with regularly circumscribed epithelialized islets ranging 7-10 cm in size.	Ulceration and inflammatory granulation tissue covered with fibrinous exudate.	Ulcerative colitis findings compatible with inflammatory bowel disease (ulcerative colitis); colon, biopsy	2018: Ulcerative colitis with mild activity (extended involvement) 2022: Ulcerative colitis with mild activity (extended involvement).	Azathioprine, Mesalazine, Infliximab

Table 2. Cases

CASE NAME-SURNAME	AGE AND SEX	COMORBIDITY	ADDITIONAL MEDICINES USED	DERMATOLOGICAL FINDINGS	HISTOPATHOLOGY	UNDERLYING DISEASE PATHOLOGY	ENDOSCOPIC FINDINGS	TREATMENT
4. AE	33 years old, Female	Ulcerative colitis for 7 years	No medication except for treatment of Ulcerative Colitis	10 cm ulceration on the anterior side of the left tibia with erythematous margins and black hard base in the center.	Perivascular inflammation with superficial and deep eosinophils and septal panniculitis. Pyoderma gangrenosum cannot be ruled out.	Ulcerative colitis. Chronic active inflammatory infiltration; rectum.	The mucosa was severely hyperemic, edematous, and granular in the rectum at the distal sigmoid colon. Pseudopolyps were observed. No vascular pattern could be seen in the mucosa. Surrounding ulcers and exudate were observed. Spontaneous bleeding foci were present.	Mesalazine 800 3 × 1, Infliximab
5. Z. Ç.	42 years old, Female	Allergic asthma + AS	Sulfasalazine	A 3cm hard-based ulcer with erythematous margins on the inner side of the left thigh in the perineal vagina vulva neighborhood.	Ulceration and necrotizing suppurative chronic inflammation. Perivascular lymphocyte infiltration (consistent with Pyoderma gangrenosum.)	Crohn's disease, Ulceration, nonspecific inflammatory granulation tissue, regenerative changes in intact epithelium, chronic active inflammatory infiltration; colon.	In the segment between 15–45 cm from the rectum to the anal verge; the vascular pattern was not discernible. Deeper than 2 cm ulcers were present.	Mesalazine 3 × 1 Prednisolone Infliximab

equately to first-line treatments. Examples include biologics, conventional immunosuppressives, dapsone, and minocycline.

Infliximab has shown efficacy for PG, and its simultaneous use in inflammatory bowel disease supports the use of this drug in patients with both diseases. In patients with mild PG, who are refractory to local therapy, dapsone or minocycline, which are usually well tolerated, may be used. Intravenous immune globulin (IVIg) and alkylating agents are treatment options typically reserved for patients with severe refractory diseases.

PG commonly occurs alongside other diseases, such as inflammatory bowel disease, hematologic malignancy, and arthritis. While the progression of PG doesn't always mirror that of these associated conditions, treatment of the underlying disorder can sometimes lead to improvement in PG symptoms. There is growing evidence supporting the effectiveness of anti-TNF (tumor necrosis factor) biologic agents in treating PG. Though medications like mycophenolate mofetil, azathioprine, and methotrexate are typically not sufficient as standalone treatments, they may prove beneficial when used in combination with systemic glucocorticoids or other systemic therapies.

Infliximab: The utilization of infliximab, a chimeric antibody targeting TNF-alpha, is on the rise for treating PG, particularly in cases involving inflammatory bowel disease. It is often used alongside other topical or systemic therapies, primarily oral prednisolone. Various studies have reported clinical signs of recovery with infliximab treatment, noting improvement rates of up to 49% usually by the second week of treatment and 69% by the sixth week.^{21,22}

Other Biologic TNF-alpha Inhibitors: Beyond infliximab, additional biologic TNF-alpha inhibitors have shown potential effectiveness in treating PG. Adalimumab, administered in dosages such as 40 mg weekly or 40 mg bi-monthly, has been linked to ulcer healing in various case reports. The majority of these reported cases involve patients with concurrent inflammatory bowel disease or rheumatoid arthritis. Although the bulk of research and literature on PG has been explored in the field of dermatology, the contributions from gastroenterology are predominantly in the form of case series. This underscores the need for further studies investigating the efficacy of TNF-alpha inhibitors in PG treatment.²¹

DISCUSSION

PG is a relatively rare condition, with an estimated incidence of 3–10 cases per million people annually. It predominantly affects young and middle-aged adults, typically presenting between the ages of 40 and 60, with a higher prevalence observed in women. At the Gastroenterology Department of Uludağ University, we conducted an analysis of five cases with varied sites of involvement, referencing existing literature. The details of these cases are presented in Tables 1 and 2, and their statuses before and after treatment are depicted in the accompanying figures. Each case had been previously diagnosed with either ulcerative colitis or Crohn's disease and was undergoing standard treatments, with the exception of infliximab, which was administered as per the prescribed dosages. Biopsies and endoscopic evaluations were repeated during periods of skin activation for all cases. Patients with a definitive diagnosis received weekly infliximab treatment at a dose of 5 mg/kg, with efficacy assessments conducted at the six-week mark. Skin evaluations were performed at the beginning and at six weeks, and these assessments were visually documented. Disease activity assessments at week six involved physical examinations and laboratory evaluations, employing the CDAI for Crohn's disease and the Truelove-Witts scale

for ulcerative colitis. The findings indicated a parallel improvement in both clinical and biological aspects following the treatment. During this time, no further endoscopic evaluations were undertaken.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K.K.; Supervision – F.E.; Critical Review – F.E., M.E.D.

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