

Pyoderma Gangrenosum: A Commonly Overlooked Ulcerative Condition

Daniel Zunsheng Tay¹, Ki-Wei Tan², Yong-Kwang Tay^{1,2}

¹Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, ²Department of Dermatology, Changi General Hospital Singapore, Singapore 529889

ABSTRACT

Background: Pyoderma gangrenosum (PG) is a rare, inflammatory, destructive neutrophilic dermatosis, which mimics other ulcerative conditions. **Materials and Methods:** In a retrospective study based on patients diagnosed with PG over a 3-year period (2010–2013), we evaluated demographics, anatomical sites, number of lesions, subtypes, histopathology, associated conditions, treatment regimens, healing time, and recurrence. **Results:** Of our five patients, there were three males and two females, age ranging between 19 and 58 years (mean age 38 years). Four had single lesions localized to the lower limbs while one had multiple lesions (more than five) over bilateral hands and legs. Ulcerative subtype was observed in all the patients. One exhibited pathergy. Skin biopsies were done in four patients, revealing dense neutrophilic infiltrates in three cases and leukocytoclastic vasculitis in one. Associated systemic diseases were observed in all patients, four having inflammatory bowel disease and one having both systemic lupus erythematosus and anti-phospholipid syndrome. The patients were all treated with systemic corticosteroids either alone or in combination with immunosuppressants (e.g., azathioprine, mycophenolate mofetil, tacrolimus), and wound dressing. Split-thickness skin graft was done in one patient. Complete healing was achieved in all patients, ranging from one to 3 months after diagnosis. No recurrence was reported. **Conclusions:** Systemic corticosteroids, either alone or in combination with steroid-sparing agents are the mainstay of treatment. Should family physicians encounter a rapidly progressing ulcer that has poor response to usual wound management, timely referral to dermatology should be made.

Keywords: Bluish edge, painful, pyoderma gangrenosum, rapid progression, ulcer

Introduction

Pyoderma gangrenosum (PG) is a rare, often destructive, painful inflammatory dermatosis, presenting as a tender nodule or pustule. This erodes to form a progressively enlarging ulcer with a raised, undermined, violaceous border.^[1,2] Lesions may be single or multiple, and heal with an atrophic cribriform scar.^[3]

Despite its aggressive appearance that can be mistaken for necrotizing fasciitis, a life-threatening infective condition, PG is noninfectious.^[4,5] It is included in the spectrum of neutrophilic dermatoses and comprises of 4 subtypes – ulcerative, pustular, bullous, and vegetating or superficial granulomatous.^[6]

Pyoderma gangrenosum can be idiopathic but is often associated with systemic disease in 50–70% of cases.^[7] The

list of associations is many and includes inflammatory bowel disease, arthritic conditions (e.g., rheumatoid arthritis), lymphoproliferative disorders, malignancy, hepatitis, human immunodeficiency virus infection, sarcoidosis, and hereditary hypogammaglobulinemia.^[7-9]

Pyoderma gangrenosum occurs most commonly on the lower limbs^[9] but may occur at other areas such as the head and neck, hand, penis, scrotum, breast, and vulva.^[10-13]

Materials and Methods

This was a retrospective study conducted at the Department of Dermatology, Changi General Hospital Singapore, and was approved by the Institutional Review Board (ref: 2014/266/E). We evaluated inpatients that were diagnosed with PG between January 2010 and December 2013.

The demographics (age, gender, preceding trauma, specialties admitted), anatomical site, number of lesions, subtypes,

Address for correspondence: Dr. Yong-Kwang Tay, Department of Dermatology, Changi General Hospital Singapore, 2 Simei Street 3, Singapore 529889. E-mail: yong_kwang_tay@cgh.com.sg

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/2249-4863.148113

histopathologic reports, associated conditions, treatment regimens, healing time, and recurrence were reviewed.

Results

There were three males and two females, aged between 19 and 58 years, with a mean age of 38 years [Table 1].

The majority were admitted to the orthopedic surgery department (three cases); one was admitted under general medicine and one under gastroenterology. Of the five patients, one exhibited the pathergy phenomenon.^[2] Patient 1 was admitted to orthopedics for debridement of an abscess at the left anterolateral leg and later developed PG at the same location.

Lesions were single for four patients; all localized on the lower limb while one case was reported to have multiple lesions (more than five) over bilateral upper and lower limbs. The lesions for all cases were of the ulcerative subtype [Figure 1].

A skin biopsy was performed on four patients that revealed dense neutrophilic infiltrate in three cases and leukocytoclastic vasculitis in one [Figure 2].

All patients had preexisting systemic conditions. Four had inflammatory bowel disease, and one had both systemic lupus erythematosus (SLE) and anti-phospholipid syndrome (APS). Of the four having inflammatory bowel disease, three had ulcerative colitis (UC), and one had Crohn's disease (CD). One of the cases diagnosed with UC also had concomitant hepatitis



Figure 1: A view of the ulcerative subtype of PG in patient 1

Table 1: Results of the five patients

Age/sex	Associated disease	Interval between primary diagnosis and development of PG (months)	Anatomical site (number of lesions)	Duration of ulcer	Histopathologic report	Pathergy	Treatment	Healing time (months)	Recurrence
21/male	UC	9	Lower limb (1)	1-day	Dense neutrophilic infiltrate	Yes	IV cloxacillin, IV penicillin, PO augmentin, PO prednisolone 35 mg OM, PO tacrolimus 1 mg OM, PO mycophenolate mofetil 500 mg OM	3	No
19/male	CD	49	Lower limb (1)	3 days	Leukocytoclastic vasculitis	No	PO cefalexin, PO metronidazole, tetracycline HCl 3% ointment, PO prednisolone 40 mg OM	1	No
46/female	SLE, APS	32	Lower limb (1)	1-month	Dense neutrophilic infiltrate	No	PO cloxacillin, PO augmentin, PO prednisolone 50 mg OM, PO anarex	2	No
46/male	UC, hepatitis C	9	Bilateral upper and lower limbs (>5)	2 weeks	Dense neutrophilic infiltrate	No	IV cloxacillin, IV penicillin, PO ciprofloxacin, betamethasone dipropionate ointment 0.05%, IV hydrocortisone 100 mg QDS, PO prednisolone 40 mg OM, PO mesalazine 2 g BD, PO azathioprine 75 mg OM, debridement	2	No
58/female	UC	130	Lower limb (1)	3 months	No biopsy done	No	IV cloxacillin, IV penicillin, PO ciprofloxacin PO penicillin, PO tramadol, PO paracetamol, PO sulfasalazine 1500 mg BD, betamethasone dipropionate cream, debridement twice, split-thickness skin graft	3	No

PG: Pyoderma gangrenosum; UC: Ulcerative colitis; CD: Crohn's disease; SLE: Systemic lupus erythematosus; APS: Antiphospholipid syndrome; OM: Once daily in the morning; BD: Twice daily; QDS: Four times daily; IV: Intravenous. In all our patients, PG developed after the onset of the primary condition

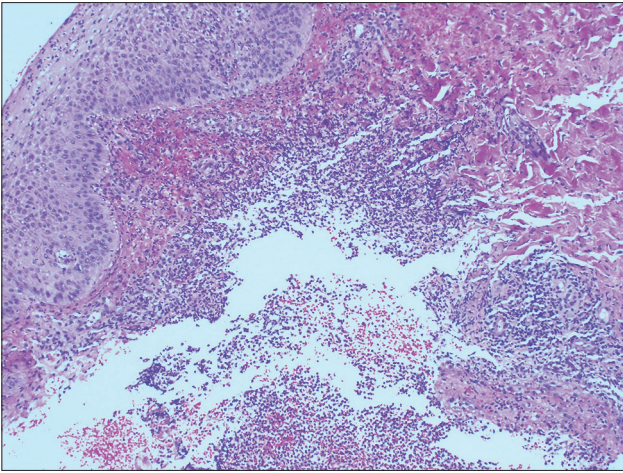


Figure 2: A dense neutrophilic infiltrate showing a nodular dermatitis with a predominance of neutrophils. There is evidence of ulceration, acanthosis, neutrophilic exocytosis, epidermal spongiosis, abscess formation, and hemorrhage (H and E, $\times 20$)

C infection. The case with CD was noted to have had a previous episode of PG of the scrotum in 2008 that was treated at a different center.

Of the five cases, four were treated with systemic corticosteroids and one with a potent topical steroid cream (patient 5). Two cases (patients 2 and 3) were treated with systemic corticosteroid monotherapy (oral prednisolone 1–2 mg/kg/day) with progressive reduction on healing of the ulcers. Patient 3 continued oral prednisolone 5 mg daily after tapering over 17 weeks in view of her associated diseases (SLE and APS). Patient 4 was given both topical and systemic corticosteroid treatment (intravenous [IV] hydrocortisone 100 mg QDS which was converted to oral prednisolone 1–2 mg/kg/day with progressive reduction, and betamethasone dipropionate ointment) with healing of the ulcers. Patient 5 was prescribed oral sulfasalazine and betamethasone dipropionate cream. Systemic antibiotics were started for all five cases to cover for possible secondary skin infection.

Immunosuppressants were prescribed in combination with corticosteroid therapy for two cases (patients 1 and 4). Patient 1 received oral tacrolimus and mycophenolate mofetil (MMF) as a steroid-sparing treatment after oral prednisolone was tapered and discontinued. Patient 4 was restarted on oral mesalazine and azathioprine in view of prior poor compliance to his treatment for UC. Patient 2 was already on 10 weekly 300 mg infliximab injections (5 mg/kg) for his CD at another hospital for 3 years before the development of PG. The duration between the last dose of infliximab and the development of PG was 4 weeks.

Adjunctive treatment included local wound dressings which was instituted for all cases. Urgotul[®], Aquacel Silver[®], and Mepilex Silver[®] dressing were used depending on the wound condition.

Surgical treatment was performed in two cases. Patient 4 underwent debridement of the lesions on bilateral lower limbs. Patient 5 had wound debridement followed by a split-thickness skin graft.

Response to treatment was favorable with all cases recovering well, and no recurrences noted. Complete healing was achieved in all patients, ranging from one to 3 months after diagnosis.

Discussion

Introduction and demographics

Pyoderma gangrenosum is rare^[1] as evidenced by five cases over a 3-year period. The overall incidence of PG is estimated at 6/million in the population.^[14] PG mainly affects adults aged between 20 and 50 years, but children may rarely be affected.^[2,10] This neutrophilic dermatosis has a female preponderance.^[8] In our study, there were three males and two females, aged between 19 and 58 years (mean age 38 years). Only one case occurred before the second decade and the rest, after it. Although the age group of our patients corresponds to that of the literature, there was a slight male preponderance (male:female ratio of 1:5). In a report by Bhat *et al.*, their male:female ratio was 1.25:1,^[15] also showing male predominance. More studies need to be done to ascertain if there is a higher risk for males in the Asian population.

All our cases had lesions on the lower limbs and were of the ulcerative subtype. This is in agreement with the literature as the most commonly reported anatomical site and subtype of PG.^[6,15]

A unique feature of PG is pathergy that is defined as an inflammatory reaction in the skin induced by trauma, and reportedly seen in 50% of PG patients.^[13] This was evident in one of our cases who had a previous debridement done at the lesion site. Pustular PG can have a similar appearance to an abscess that is a potential source of a dilemma for clinicians in terms of management.

Diagnosis

The diagnosis of PG is challenging as doctors must take into account a long list of differential diagnoses that have to be excluded. This is because PG in essence is a diagnosis of exclusion.^[4] Differentials such as necrotizing fasciitis, other infections (bacterial, fungal, amoebic), vasculitis and cutaneous malignancies have to be excluded.^[4,5] Our patients who were diagnosed with PG fulfilled the diagnostic criteria set forth by Su *et al.*^[16] [Table 2].

When doing routine blood tests, it is not surprising to see raised inflammatory markers in PG. This was explained by Schotanus *et al.*^[11] C-reactive protein participates in the clearance of necrotic and apoptotic cells and levels rise in response to inflammation. Leukocytosis is also due to tissue necrosis caused by PG. Such results can mimic an infection, thus cultures need to be taken.

Table 2: Diagnostic criteria for PG^[23]

Major criteria

- Rapid (a) progression of a painful, (b) necrolytic cutaneous ulcer (c) with an irregular, violaceous, and undermined border
- Other causes of cutaneous ulceration have been excluded (d)

Minor criteria

- History suggestive of pathergy (e) or clinical finding of cribriform scarring
 - Systemic diseases associated with PG (f)
 - Histopathologic findings (sterile dermal neutrophilia, \pm mixed inflammation, \pm lymphocytic vasculitis)
 - Treatment response (rapid response to systemic steroid treatment) (g)
- (a) Characteristic margin expansion of 1-2 cm/day, or a 50% increase in ulcer size within 1-month
- (b) Pain is usually out of proportion to the size of the ulceration
- (c) Typically preceded by a papule, pustule, or bulla
- (d) Usually necessitates skin biopsy and other investigations to rule out causes and for work-up
- (e) Ulcer development at sites of minor cutaneous trauma
- (f) Inflammatory bowel disease, arthritis, IgA gammopathy, or underlying malignancy
- (g) Generally responds to a dosage of prednisolone 1 mg/kg to 2 mg/kg/day, with a 50% decrease in size within 1-month

Requires both major criteria and at least 2 minor criteria PG: Pyoderma gangrenosum

They are generally negative unless there is secondary infection.^[11] Delayed diagnosis or misdiagnosis can lead to serious morbidity and hence should be made as soon as possible.^[14]

Although there are no histopathological findings specific to PG, a skin biopsy must always be performed to rule out other differentials.^[11] Of the four cases that had a biopsy done, three showed dense neutrophilic infiltrate while one showed leukocytoclastic vasculitis. These two are common histologic patterns seen in PG. Histopathologic findings vary with the site biopsied. Lymphocytic vasculitis is predominant at the erythematous area peripheral to the ulcer. Specimens taken more centrally will show neutrophilic infiltrate and abscess formation.^[11]

Associated conditions

Up to 50–70% of PG cases have an associated systemic disease.^[9] Inflammatory bowel disease and arthritic conditions (e.g., rheumatoid arthritis) are the more commonly associated ones.^[7] Our case series revealed a close association with underlying systemic disease. Four had inflammatory bowel disease, and one had both SLE and APS. A case with inflammatory bowel disease was also positive for hepatitis C, which is a known association.

Management

If left untreated, PG may last for months to years. Treatment should be directed at both the skin lesion and underlying systemic disease.^[17] Due to the lack of randomized controlled trials, treatment is empirical and consists of a combination of topical and systemic drugs (such as corticosteroids, immunosuppressants, analgesia) and local wound care.^[17,18]

Corticosteroids are considered first-line treatment for localized, as well as disseminated PG. It is particularly effective for acute and rapidly progressive forms.^[7,15] Potent topical (like in patient 5) and intralesional corticosteroids are effective in localized PG.^[7] Cases with disseminated PG should be started on systemic corticosteroids.^[7] In chronic and steroid-resistant cases, immunosuppressants like cyclosporine 2 mg/kg/day are usually added due to side effects of the prolonged use of corticosteroids.^[19] All five of our cases received steroid therapy.

Thalidomide, MMF, tacrolimus, dapsone, azathioprine, infliximab, IV immunoglobulin, and hyperbaric oxygen therapy are effective in treating PG.^[18,20,21] It is interesting to note that patient 2 developed PG while still on infliximab therapy for his CD, despite it being a treatment option for PG. This is similar to the case presented by Rallis *et al.*^[22] Although the specific mechanism for this phenomenon is unknown, the usage of other anti-tumor necrosis factor- α agents such as etanercept and adalimumab has been efficacious in the treatment of PG.^[22] In steroid-refractory PG, these agents should also be considered.^[17]

On tapering prednisolone, patient 1 was started on tacrolimus and MMF as a steroid-sparing treatment regime. Compared with corticosteroids and cyclosporine, MMF has fewer side effects which are generally not serious in nature, is mostly well-tolerated and can be used long-term.^[23]

Wound dressings were instituted for all five cases and were continued after the patients were discharged till the ulcers were fully healed. Local wound care is essential to prevent and treat possible secondary bacterial infections.^[21]

While some argue that debridement is contraindicated in suspected, and untreated PG as the trauma of surgery can be sufficient to induce pathergy,^[24] others deem gentle debridement beneficial. This consists of removing nonviable tissue and the application of allogeneic cultured dermal substitutes.^[11]

Surgical reconstruction of PG is indeed challenging as the treatment itself has the potential to induce pathergy. Split-thickness skin graft, like what one of our cases underwent, is a commonly used surgical technique. A team in Korea reported a groin free flap reconstruction for PG of the face, achieving rapid wound closure and a favorable cosmetic appearance.^[19]

It is reported in some patients for pain to be out of proportion to the size of the lesion.^[9] This warrants adequate analgesia in the management.^[17] Two out of our five cases complained of pain and were given analgesia accordingly.

Many patients may receive corticosteroid treatment for longer periods and higher doses than is clinically necessary. Clinicians have to differentiate active disease from an inactive residual ulcer that is often slow to heal. Landis *et al.* proposed Gulliver's sign, which is defined as the point where "edges become more even with the surrounding skin and one can make out string-like

growths of epithelium, which straddle the border between the ulcer bed and the normal surrounding skin.” When this is present, inflammation is controlled, and clinicians should begin tapering doses of corticosteroid and immunosuppressive therapy. This decreases the risk of side effects of systemic treatment, while obtaining maximum benefit.^[25]

Prognosis

C-reactive protein levels can be used to monitor disease activity and treatment response. Complete wound healing may range from weeks to a year. Once fully healed, a cribriform scar is produced. Prognosis of PG is generally good but is still a potentially lethal disease.^[11,17] Older patients and males have a poorer outcome.^[23] In patients presenting with lone PG, it is important for clinicians to look for an underlying systemic disease.

Comorbid conditions like diabetes mellitus might contribute to the development of PG and worsen local healing processes, especially so on the lower limb.^[9] The possibility of underlying malignancy (mostly hematological malignancies such as myeloproliferative or myelodysplasia) must be considered in patients with persistent PG.^[6,17]

Conclusion

As family physicians may encounter patients with PG, who frequently present with a rapidly progressing ulcer on the limbs, it is crucial to recognize this condition early and make timely referral to dermatology. A multidisciplinary approach^[14] to management involving the dermatologist, surgeon, gastroenterologist, wound nurse, and the pain team will undoubtedly improve the prognosis of this condition.

References

- Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: An updated review. *J Eur Acad Dermatol Venereol* 2009;23:1008-17.
- Pereira N, Brites MM, Gonçalo M, Tellechea O, Figueiredo A. Pyoderma gangrenosum - A review of 24 cases observed over 10 years. *Int J Dermatol* 2013;52:938-45.
- Weizman A, Huang B, Berel D, Targan SR, Dubinsky M, Fleshner P, *et al.* Clinical, serologic, and genetic factors associated with pyoderma gangrenosum and erythema nodosum in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2014;20:525-33.
- De Menezes D, Yusuf E, Borens O. Pyoderma gangrenosum after minor trauma in a pregnant woman, mistaken for necrotizing fasciitis: Report of a case and literature review. *Surg Infect (Larchmt)* 2014;15:441-4.
- El-Kehdy J, Haneke E, Karam PG. Pyoderma gangrenosum: A misdiagnosis. *J Drugs Dermatol* 2013;12:228-30.
- Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum: A review of 86 patients. *Q J Med* 1985;55:173-86.
- 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.
- von den Driesch P. Pyoderma gangrenosum: A report of 44 cases with follow-up. *Br J Dermatol* 1997;137:1000-5.
- Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: A retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol* 2011;165:1244-50.
- Dos Santos Sousa MC, Lima Lemos EF, Oliveira De Moraes O, Silva Leite Coutinho AS, Martins Gomes C. Pyoderma gangrenosum leading to bilateral involvement of ears. *J Clin Aesthet Dermatol* 2014;7:41-3.
- Schotanus M, van Hout N, Vos D. Pyoderma gangrenosum of the hand. *Adv Skin Wound Care* 2014;27:61-4.
- Farrell AM, Black MM, Bracka A, Bunker CB. Pyoderma gangrenosum of the penis. *Br J Dermatol* 1998;138:337-40.
- Satoh M, Yamamoto T. Genital pyoderma gangrenosum: Report of two cases and published work review of Japanese cases. *J Dermatol* 2013;40:840-3.
- Langan SM, Groves RW, Card TR, Gulliford MC. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: A retrospective cohort study. *J Invest Dermatol* 2012;132:2166-70.
- Bhat RM, Nandakishore B, Sequeira FF, Sukumar D, Kamath GH, Martis J, *et al.* Pyoderma gangrenosum: An Indian perspective. *Clin Exp Dermatol* 2011;36:242-7.
- Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: Clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol* 2004;43:790-800.
- Tan WC, Ong CK, Lo KS, Leong KN. Pyoderma gangrenosum. *Med J Malaysia* 2007;62:251-3.
- 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.
- Seok HH, Kang MS, Jin US. Treatment of atypical pyoderma gangrenosum on the face. *Arch Plast Surg* 2013;40:463-5.
- Sinnaya S, Hamza S. Pyoderma gangrenosum of the breast treated with intravenous immunoglobulin. *J Dermatol Case Rep* 2013;7:64-8.
- Ueno T, Omi T, Uchida E, Yokota H, Kawana S. Evaluation of hyperbaric oxygen therapy for chronic wounds. *J Nippon Med Sch* 2014;81:4-11.
- Rallis E, Koumantaki-Mathioudaki E, Tsiatoura A, Stavropoulos P, Katsambas A. Pyoderma gangrenosum and tumor necrosis factor α agents. *Cutis* 2013;92:E1-2.
- Li J, Kelly R. Treatment of pyoderma gangrenosum with mycophenolate mofetil as a steroid-sparing agent. *J Am Acad Dermatol* 2013;69:565-9.
- Tay YK, Friednash M, Aeling JL. Acute pyoderma gangrenosum does not require surgical therapy. *Arch Fam Med* 1998;7:377-80.
- Landis ET, Taheri A, Jorizzo JL. Gulliver's sign: A recognizable transition from inflammatory to healing stages of pyoderma gangrenosum. *J Dermatolog Treat* 2014.

How to cite this article: Tay DZ, Tan K, Tay Y. Pyoderma gangrenosum: A commonly overlooked ulcerative condition. *J Fam Med Primary Care* 2014;3:374-8.

Source of Support: Nil. **Conflict of Interest:** None declared.