Journal of Pakistan Association of Dermatologists. 2023;**33(4)**:1694-1700.

Case Report

Propylthiouracil induced p-ANCA+ pyoderma gangrenosum with inflammatory bowel disease in pregnancy

Devi Arofah Mumtazah, Sara Ester Triatmoko*, Larasati Budiyarto

Department of Dermatology and Venereology, Fatmawati Central General Hospital, Jakarta, Indonesia.
* Department of Plastic Reconstructive and Aesthetic Surgery, Fatmawati Central General Hospital, Jakarta, Indonesia.

Abstract Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by painful ulcers with undermined edges and peripheral erythema. The global incidence of PG is estimated to be 3 to 10 cases per million people per year, affecting individuals aged between 25 to 54 years. We here present a case report of a 34-year-old female with deep painful non-healing ulcers on both legs which first appeared during her pregnancy. Prolonged consumption of propylthiouracil (PTU) to treat hyperthyroidism was found. Gastrointestinal symptoms were denied. Histopathological examination revealed intense neutrophilic infiltration of the dermis in the skin biopsy and chronic ulcerative inflammation in the biopsy of ileum and colon. The result of p-ANCA was positive. The patient was diagnosed with drug-induced pyoderma gangrenosum associated with PTU use and inflammatory bowel disease. Combination therapy of systemic corticosteroid, two split-thickness skin graft (STSG) surgeries, oral dapsone, appropriate wound care, and management to eliminate predisposing factors resulted in a favorable outcome. Pyoderma gangrenosum has been considered a challenging disease to diagnose and treat. Clinicians need to enhance their knowledge of diagnosis and management of PG to give proper management and yield a better prognosis.

Key words
Inflammatory bowel disease; Pregnancy; Propylthiouracil; Pyoderma gangrenosum; Split-thickness skin graft surgery.

Introduction

Classic ulcerative pyoderma gangrenosum (PG) is an uncommon neutrophilic dermatosis (ND) characterized by painful ulcers with undermined edges and peripheral erythema (red skin). It is worth noting that the name "pyoderma gangrenosum" is a misnomer because PG is neither an infection ('pyoderma' historically refers to a bacterial skin illness producing pus) nor a typical gangrenous disease. PG is still one of the most challenging dermatological conditions to detect and cure.[1]

The global incidence of PG is estimated to be 3 to 10 cases per million people per year, affecting individuals aged between 25 and 54 years. Children account for around 4% of all cases. The most common subtype was ulcerative PG (68.8% of cases), and the lower extremities were predilection sites of ulcer formation.[2]

A characteristic PG lesion begins as a small, discrete pustule that develops into a sharply marginated ulcer with undermined, violaceous edges and an erythematous zone surrounding it.[2] The diagnosis of PG can be problematic since its

Address for correspondence
Dr. Larasati Budiyarto
Dermatology and Venereology Department,
Fatmawati Central General Hospital,
Jakarta, 12430, Indonesia.
Ph: +6281223704604
Email: larasatib22@gmail.com

symptoms are similar to other infectious and inflammatory diseases, such as wound infection, leukocytoclastic vasculitis, hidradenitis suppurativa, Behçet's syndrome, antiphospholipid syndrome, ecthyma gangrenosum, cutaneous malignancy, and Sweet's syndrome. PG may develop quickly and show resistance to antibiotic therapy and may be worsened by surgical debridement. To avoid major morbidity, prompt diagnosis is crucial.[3]

Case Illustration

A 34-year-old female came with a chief complaint of painful non-healing deep ulcerous wounds on both legs. The lesion started as an erythematous papule which turned into pustules and later turned into ulcers which expanded and spread to adjacent normal skin in the past year. The patient was in the first trimester of pregnancy when the wound first appeared. During pregnancy, she had previously sought treatment from a general practitioner and received oral antibiotics such as amoxicillin, cefadroxil, and clindamycin repeatedly with no improvement. After giving birth, the wounds worsen and grew in size, thus she was referred to a dermatologist.

The patient had a history of hyperthyroidism treated with PTU (Propylthiouracil) 3X100 mg/day for nearly 2 years. The history of the same complaint in the family was denied. There were no gastrointestinal symptoms. The patient had no history of malignancy, infections, and symptoms of autoimmune disease. There was no history of diabetes in the patient.

On physical examination of the bilateral cruris region, multiple ulcers with the size of lenticular to plaque were found. Borders of ulcers were irregular with livid-colored undermined edges. Yellowish (slough) to black necrotic tissue with pus and serum was present. Pain was found on palpation. No eye involvement, oral mucosal disease, nor genital ulceration were found. Two months after the patient's first visit, ulcers on the posterior right leg became deeper, exposing

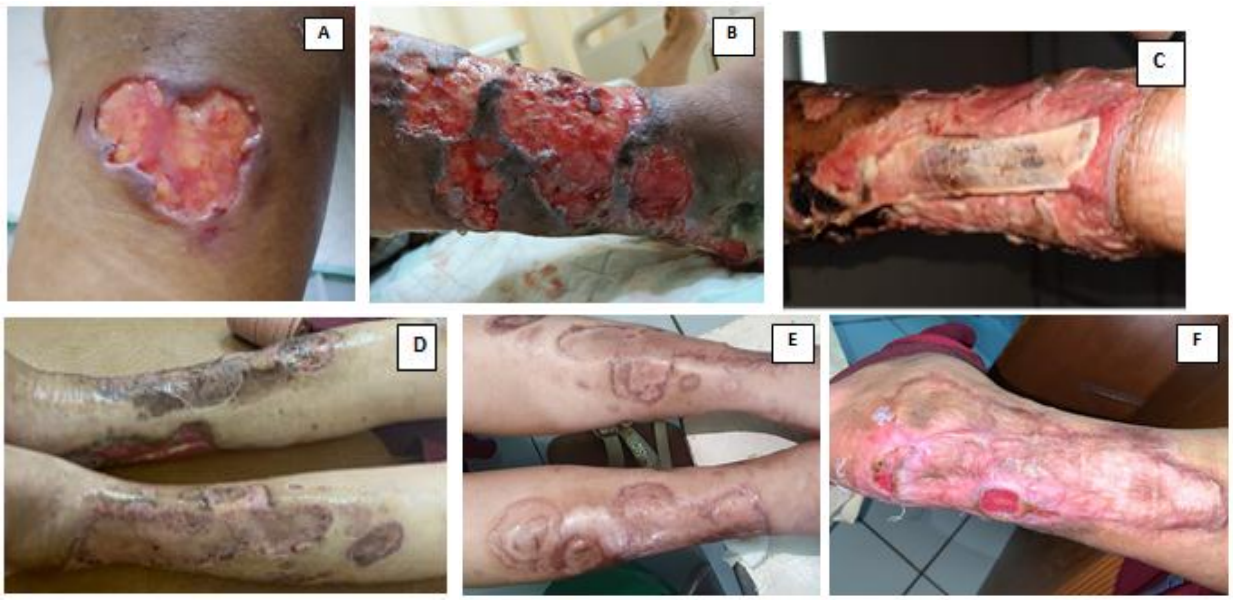

Figure 1 (A) Wounds on the anterior left leg displaying peripheral erythema and undermining borders. (B) Multiple ulcers at right and left lower legs 1 week before surgery. (C) A wound exposing the calcaneus tendon was found on the lower right leg 1 day before surgery. (D) Clinical progress of wounds on the anterior of both legs 1 month after two skin graft (STSG) surgeries. (E) & (F) Wounds at anterior and posterior lower right leg after 11 months of therapy.

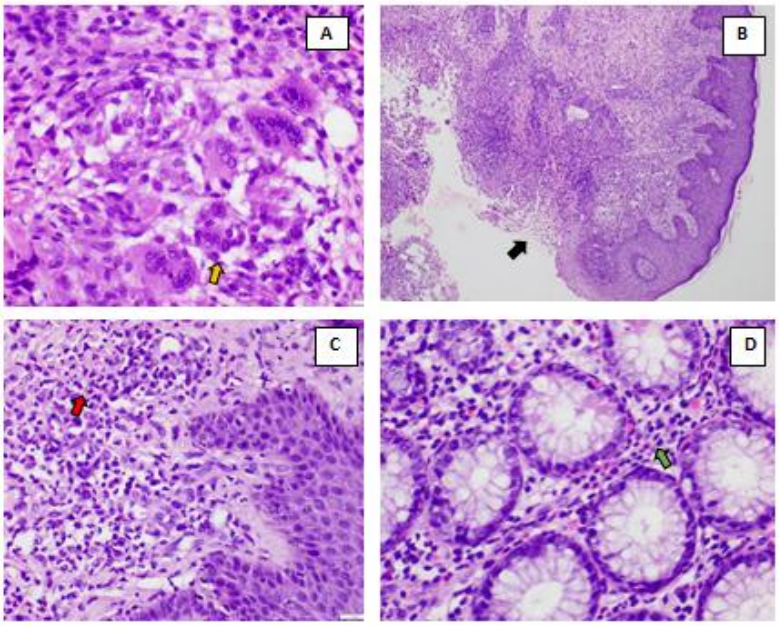

Figure 2 (A) The first skin biopsy showed connective tissue with infiltration of lymphocytes, histiocytic epithelioid cells, and multinucleated datia cells (yellow arrow). (B) The second skin biopsy revealed a stratified squamous layer with signs of ulceration (black arrow), and (C) intradermal neutrophilic abscess (red arrow) with clusters of lymphocytes, eosinophils, and plasma cells. (D) Ileum and colon biopsy presented infiltration of neutrophils, lymphocytes, eosinophils, and plasma cells in the connective tissue surrounding tubular glands (green arrow).

the calcaneus tendon.

The first punch biopsy revealed connective tissue with infiltration of lymphocytes, histiocytic epithelioid cells, and multinucleated datia cells which were concluded as a granulomatous inflammatory reaction. The second punch biopsy presented a stratified squamous layer with signs of ulceration and the formation of an intradermal neutrophilic abscess. The dermis was infiltrated by clusters of lymphocytes, neutrophils, eosinophils, and plasma cells. There was dilation of blood vessels. No malignancy was suspected. Histopathology results suited the description of pyoderma gangrenosum.

The patient was consulted by an endocrinologist and gastroenterologist to seek possible predisposing factors. Biopsy of the colon and ileum revealed chronic non-specific ulcerative inflammation of the ileum and colon surface with a normal composition of tubular glands. Connective tissue was filled with infiltration of neutrophils, lymphocytes, eosinophils, and plasma cells. No malignancy nor specific process was suspected. The level of fecal calprotectin was increased to 109,2, and the IGRA test result was negative. ANA profile results were borderline positive on PM Scl-100 and AMA-M2. p-ANCA was tested after initiation of therapy due to limited resources, the result was positive with 1:10 titer and negative c-ANCA. HbA1c result was 4.5%. There were no abnormal findings on complete blood count (CBC), and liver function tests. TSH and free T4 test results were within normal range.

The patient was diagnosed with pyoderma gangrenosum with risk factors of inflammatory bowel disease and the use of propylthiouracil (PTU). Two months after the patient's first visit, two split-thickness skin graft surgery (STSG) were done on both legs in 4 weeks intervals. During hospitalization, methylprednisolone 125 mg/day IV with a tapered-off dose was administered. After discharge, the systemic steroid was tapered off and replaced with dapsone starting at 2X100 mg/day. Propylthiouracil (PTU) was discontinued and exchanged with thiamazole 10 mg/day. Mesalamine 2 x 250 mg/day was prescribed to treat ulcerative colitis. Vitamin C 500 mg/day, vitamin D3 2000 IU/day, and zinc sulfate 20

mg/day were also given as supplements. The remaining wounds were dressed in saline compresses, covered with super-absorbent silicone foam dressing (Cutimed® Siltec), and wrapped in an elastic bandage (Elastomull®). Most of the wounds showed re-epithelialization after 11 months of therapy.

Discussion

Pyoderma gangrenosum (PG) is a rather uncommon neutrophilic dermatosis distinguished by painful, sterile ulcers that frequently appear on the lower legs and trunk. The majority of cases occur in individuals aged 30-50 years. PG has four primary clinical variants: ulcerative, pustular, bullous, and vegetative, with ulcerative being the most frequent by far.[4,5]

Female sex, pregnancy, surgery, and a history of underlying illness such as IBD or hematologic malignancy are considered risk factors for PG. PG has polygenic and autoinflammatory properties. Physiologic state in pregnancy as seen in this case is related to higher numbers of neutrophils induced by the placenta through the release of granulocyte colony-stimulating factors.[6] Overexpression of interleukin (IL)-1b, IL-17, tumor necrosis factor (TNF)-a, and numerous chemokines enhances the mechanism of neutrophil activation and migration.[4,5] Due to the potential of pathergy and wound healing deficits during delivery and post-partum, it is especially crucial to identify PG and control disease activity in pregnant females.[7]

Pyoderma gangrenosum has been considered a challenging disease to diagnose with no established diagnostic gold standard. Clinical manifestations and laboratory findings, in this case, fulfilled Delphi Consensus Criteria in 2018 which requires a case to meet the major criterion (biopsy with neutrophilic infiltrate) and at least four of eight minor criteria (exclusion of infection on histology; pathergy; history of IBD or inflammatory arthritis; papule/pustule/vesicle which ulcerates rapidly; peripheral erythema, undermining border, and tenderness; multiple ulcerations at least one occurred on the anterior lower leg; cribriform or wrinkled paper scars; and decrease of ulcer size after immunosuppressive treatment).[5]

Histopathology result obtained from skin biopsy in this case suits the major histological presentations of PG which might vary depending on clinical variants as well as the location of the biopsy. In typical ulcerative PG, there may be epidermal and dermis ulcers, with the development of strong neutrophilic infiltration, neutrophilic pustules, and abscess.[8]

ANA profile test in this case revealed results of borderline positive on PM Scl-100 and AMA-M2. This should be recognized because PG may be a sign of chronic autoimmunity. The presence of PG lesions in a female with ANA reactivity predicts a potential connective tissue disease. However, because ANA is also seen in healthy people, this finding in isolated PG might be coincidental.[9]

In this case, the patient received prolonged therapy of PTU, an antithyroid drug to treat hyperthyroidism. Studies found an association between PTU use and the development of PG. PTU has been linked to the formation of antineutrophil cytoplasmic antibodies (ANCA) in 20% of Graves' disease patients. Positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA) result as seen in this case has been linked to several types of vasculitis and neutrophilic dermatoses, including drug-induced vasculitis, Sweet's syndrome, Behçet's disease, and PG.[10]

PG affects 0.5 to 5% of IBD patients and has

previously been proven to be more frequent in women.[11] Despite no gastrointestinal symptoms being found in this case, a biopsy of the ileum and colon revealed chronic non-specific ulcerative inflammation which indicates the presence of ulcerative colitis, an inflammatory bowel disease. Increased inflammatory markers, fecal calprotectin, and endoscopic correlation were used to identify IBD disease activity at the time of a PG episode. Systemic inflammation plays a key role in the pathogenesis of PG along with its association with IBD and other inflammatory diseases. The clinical course of PG may not correspond with the activity of IBD and may even precede a diagnosis of IBD for several years.[12]

PG is a challenging condition to treat. Management of PG focuses on reducing systemic inflammation. PG required a multidisciplinary approach which includes a combination of topical treatments, wound care, surgery, and systemic therapy. Treatment options are tailored according to location, number, and size of the lesion; extra-cutaneous involvement; underlying systemic illness; side effect profiles; cost; and patient preferences.[13]

Following the detection of the possibility of PTU-induced PG, PTU should be brought to cessation before implementing any additional therapy, and any predisposing factors leading to PG should be managed. In this case, PTU use was stopped and mesalamine was prescribed to manage ulcerative colitis (inflammatory bowel disease).

Systemic immunosuppressive therapy is advised for individuals refractory to topical treatment with large and fast-progressing ulcers. Systemic steroids, such as prednisolone (0.75 mg/kg per day), are the most often used first-line therapy for PG. Oral prednisone (1-2 mg/kg/day) therapy is as effective as intravenous methylprednisolone delivery at a dose of 1 g/day for up to 5 days in the early stage.[10]

Other systemic medications include cyclophosphamide, methotrexate, mycophenolate mofetil, sulfasalazine, and azathioprine. A favorable response to the treatment and greatly reduced recurrence after the treatment can be highlighted in patients receiving cyclosporine (2-5 mg/kg/day) treatment.[10]

Traditionally, the inclusion of topical or systemic antibiotics or anti-neutrophilic medicines (dapsone and colchicine) was given depending on the provider's preference.[14] As given in this case, Dapsone acts as an immunomodulator, anti-inflammatory, and anti-neutrophilic drug. The medication is hypothesized to impede neutrophil chemotaxis and interfere with oxidative damage caused by myeloperoxidase.[15]

Superpotent corticosteroids, calcineurin inhibitors (particularly tacrolimus), dapsone, 4% disodium cromoglycate, 5-aminosalicylic acid, and nicotine (usually in a patch formulation) have all been used topically. Intralesional therapy has also been reported to be a successful localized treatment.[13]

In this case, two surgeries of split-thickness skin grafts (STSG) were done on both legs within two weeks intervals. Surgical management of PG ulcers is normally not advisable due to pathergy (the emergence of lesions in areas with microtraumas), which is one of the characteristics of PG, unless there is adequate immunosuppressive medication. A multicenter case study presented 15 patients with PG who were effectively treated with STSG surgery secured by NPWT (negative pressure wound therapy) while receiving appropriate immunosuppression.[12,16]

Biologic agents are increasingly being employed as adjuvant therapy for PG lesions that do not respond to first-line systemic medications. For the treatment of classic PG, infliximab is the only biologic agent that has been tested in a randomized, double-blind, placebo-controlled study which revealed that infliximab 5 mg/kg improved lesions in 20 out of 29 patients. IVIg (with a dosage of 2 g/kg) in combination with systemic steroids is a therapeutic option for patients with refractory PG.[17]

Wound care consisting of gentle wound cleaning, appropriate use of topical antimicrobial medications (if indicated in the event of critical colonization), a moist wound environment, and edema control are all necessary in the treatment of PG. In literature, many dressings have been used to treat PG. The type of dressing used is determined by the features of the ulcer (such as drainage, size, and location). Pain management is critical in the treatment of PG, and it frequently entails the use of nonsteroidal anti-inflammatory medications and opioids.[14]

Conclusion

A case of pyoderma gangrenosum with predisposing factors of PTU (propylthiouracil) consumption and inflammatory bowel disease has been reported. Management of PG relies on a multidisciplinary approach to find out predisposing factors and to treat the wound by reducing systemic inflammation. This case serves as a reminder for clinicians to raise awareness in diagnosing pyoderma gangrenosum and finding out its predisposing factors to provide appropriate early management and yield a better prognosis.

References

1. Maverakis E, Marzano A v., Le ST, Callen JP, Brüggen MC, Guenova E, *et al*. Pyoderma gangrenosum. Vol. 6, Nature Reviews Disease Primers. Nature Research; 2020.
2. Monari P, Moro R, Motolese A, Misciali C, Baraldi C, Fanti PA, *et al*. Epidemiology of pyoderma gangrenosum: Results from an Italian prospective multicentre study. Int Wound J. 2018 Dec 1;15(6):875–9.
3. Clayman E, Marcet K, Kuykendall L, Atisha D. Pyoderma Gangrenosum Following Bilateral Deep Inferior Epigastric Perforator Flaps. J Reconstr Microsurg Open. 2016 Sep 28;01(02):125–7.
4. Wang JY, French LE, Shear NH, Amiri A, Alavi A. Drug-Induced Pyoderma Gangrenosum: A Review. Vol. 19, American Journal of Clinical Dermatology. Springer International Publishing; 2018. p. 67–77.
5. Haag C, Hansen T, Hajar T, Latour E, Keller J, Shinkai K, *et al*. Comparison of Three Diagnostic Frameworks for Pyoderma Gangrenosum. Journal of Investigative Dermatology. 2021 Jan 1;141(1):59–63.
6. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. Vol. 14, Expert Review of Clinical Immunology. Taylor and Francis Ltd; 2018. p. 225–33.
7. Vigl K, Posch C, Richter L, Monshi B, Rappersberger K. Pyoderma gangrenosum during pregnancy – treatment options revisited. Journal of the European Academy of Dermatology and Venereology. 2016 Nov 1;30(11):1981–4.
8. George C, Deroide F, Rustin M. Pyoderma gangrenosum-a guide to diagnosis and management. Vol. 17, MEDICINE Clinical Medicine. 2017.
9. Shrestha S, Aryal A. Pyoderma Gangrenosum with Positive Antinuclear Antibody, in the Absence of Systemic Association. Nepal Journal of Dermatology, Venereology & Leprology. 2018 Mar 29;16(1):66–9.
10. Köken Avşar A, Karakaş A, Uslu S. Propylthiouracil induced p-ANCA pyoderma gangrenosum: Case report and review of literature. Maltepe Tıp Dergisi. 2020 Aug 31;12(2):59–62.
11. Weizman A v., Huang B, Targan S, Dubinsky M, Fleshner P, Kaur M, *et al*. Pyoderma gangrenosum among patients with inflammatory bowel disease: A descriptive cohort study. J Cutan Med Surg. 2015 Mar 1;19(2):125–31.

12. Plumptre I, Knabel D, Tomecki K. Pyoderma gangrenosum: A review for the gastroenterologist. Vol. 24, Inflammatory Bowel Diseases. Oxford University Press; 2018. p. 2510–7.
13. Garieri P, Marcasciano M, Greto Ciriaco A, Spagnuolo R. Pyoderma Gangrenosum and inflammatory bowel disease: a combined medical and surgical approach – case report and literature review. 2022.
14. Fletcher J, Alhusayen R, Alavi A. Recent advances in managing and understanding pyoderma gangrenosum. F1000Res. 2019;8.
15. Feldman SR, Lacy FA, Huang WW. The safety of treatments used in pyoderma gangrenosum. Vol. 17, Expert Opinion on Drug Safety. Taylor and Francis Ltd; 2018. p. 55–61.
16. Pichler M, Larcher L, Holzer M. Surgical treatment of pyoderma gangrenosum with negative pressure wound therapy and split thickness skin grafting under adequate immunosuppression is a valuable treatment option: case series of 15 patients. J Am Acad Dermatol. 2016 Apr 1;74(4):758–60.
17. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. Vol. 14, Expert Review of Clinical Immunology. Taylor and Francis Ltd; 2018. p. 225-33.