

Pyoderma Gangrenosum: A Cause of Nonhealing Ulcer Over Lower Extremities

Patel Trusha M¹, Shah Aishni J², Nair Pragma A³

Author Affiliation:

¹3rd Year Resident, ²1st Year Resident ³Professor & Head, Dept of Dermatology, Venereology & Leprosy, Pramukhswami Medical College, Shree Krishna Hospital, Karamsad, Anand, Gujarat 388325, India.

Corresponding Author:

Nair Pragma A, Professor & Head, Dept of Dermatology, Venereology & Leprosy, Pramukhswami Medical College, Shree Krishna Hospital, Karamsad, Anand, Gujarat 388325, India.

E-mail: pragyaan@charutarhealth.org

Received on: 27.11.2018

Accepted on: 14.12.2018

Abstract

Chronic lower limb ulcer is a wound that shows no tendency to heal after 3 months of appropriate treatment or is still not fully healed at 12 months. There are various causes of non-healing ulcer which include vascular insufficiency, diabetic ulcer and various infections. One such cause is Pyoderma gangrenosum, which is a chronic, relapsing, ulcerative inflammatory neutrophilic dermatosis with distinctive clinical manifestations. It shows a strong association with systemic diseases like inflammatory bowel disease, seronegative arthritis and lymphoproliferative disorders. No specific investigations are available for the diagnosis which mainly depends on clinical features. Corticosteroids and immunosuppressant therapy are mainstays in treatment. Here, we present a case of pyoderma gangrenosum in a 55 year old female over lower limb, treated with cyclophosphamide pulse therapy and showed good improvement.

Keywords: Pyoderma gangrenosum (PG); neutrophilic dermatoses; non healing ulcer.

Introduction

An ulcer is a breach in continuity of skin and mucous membrane. Chronic ulceration of lower limb is a frequent condition leading to pain and discomfort. Most common cause of lower limb ulcer is venous insufficiency in 70% cases followed by arterial in 10% mixed in 15% and others in 5% [1]. One such cause is Pyoderma Gangrenosum (PG). It is a neutrophilic, ulcerative inflammatory skin disease of uncertain etiology and is also known as phagedena geometrica, dermatitis gangrenosa, phagedenic pyoderma. It is frequently associated with systemic conditions and has incidence of 3 to 10 cases per million per year. PG can occur at any age, with peak incidence at age group of 20-50 years. Women are slightly more susceptible than men [2].

Case report

A 55 year old female patient presented to skin outpatient department with 6 months old history of non healing ulcers over buttocks, perianal area,

right knee and right ankle. H/o joint pain and swelling with morning stiffness involving large and small joints present. She was been treated with systemic steroids on & off for the same. Patient was a freshly diagnosed case of diabetes mellitus and hepatitis C Virus (HCV). On general examination, she was found to be emaciated and pale without any lymphadenopathy. She has excessive weight gain, buffalo hump, moon face, hypertrichosis and abdominal distention. On local examination ulcer of 5*5 cm in size with raised, undermined, boggy violaceous borders and necrotic slough at the periphery was present over lateral malleolus [Figure-1a]. Multiple ill defined undermined ulcers



Fig. 1a: Ulcer of 5*5 cm in size with raised, undermined, boggy violaceous borders and necrotic slough at the periphery over lateral malleolus

ranging from 1*1 to 2*3 cm were present over both buttocks and perianal area with multiple scattered depigmented macules and patches [Figure -1b] Her baseline investigations, histogram, renal functions test, urine routine micro, serum electrolytes were in normal limits. Serology for HIV and syphilis were negative, RA factor was positive, Cryoglobulinemia and C-ANCA were negative, but P-ANCA was positive. C reactive protein, vitamin b12, ESR were deranged. Based on P-ANCA, HCV and clinical history of patient, pyoderma gangrenosum was suspected and biopsy was taken. Histopathology showed acanthosis, ulceration with neutrophilic debris in upper dermis. The rete ridges show saw toothing with marked histiocytic proliferation, perivascular lymphoplasmacytic infiltration and vascular proliferation which was suggestive of pyoderma gangrenosum. [Figure-2] Patient was started on cyclophosphamide pulse therapy as steroid sparing treatment. Five pulses of inj cyclophosphamide 750 mg IV was given to her under cover of MESNA (2-mercaptoethane sulfonate Na) and hydration at 21 days interval and she showed good improvement [Figure-3a and 3b]



Fig. 1b: Multiple ill defined undermined ulcers ranging from 1*1 to 2*3 cm over both buttocks with multiple scattered depigmented macules and patches.

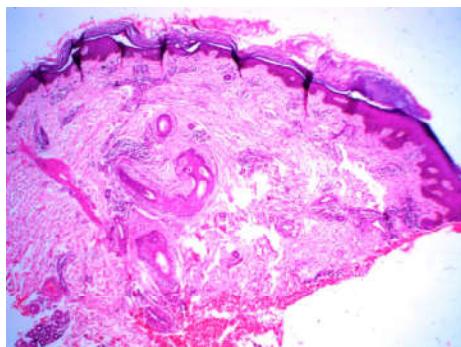


Fig. 2: Upper dermis showing acanthosis and ulceration with neutrophilic debris, saw toothing of rete ridges with marked histiocytic proliferation, perivascular lymphoplasmacytic infiltration and vascular proliferation.



Fig. 3a:



Fig. 3b:

Fig. 3a and 3b: Resolved lesions after treatment

Discussion

Chronic leg ulcer (CLU) is a wound that shows no tendency to heal after 3 months of appropriate treatment or is still not fully healed at 12 months [3]. There are multiple causes of chronic non healing ulcers. (Table 1)

Common sites for non-healing wounds are feet, ankles, and calves but for the non-ambulatory, common places include hips, thighs and buttocks. Pyoderma gangrenosum is also a chronic ulcerative condition, which should be kept as one of the differentials in lower limb nonhealing ulcer. In 50% to 70% cases, PG is associated with systemic diseases like inflammatory bowel diseases (ulcerative colitis and Crohn's disease), rheumatoid arthritis, multiple myeloma, leukemia, chronic active hepatitis, Behcet's disease, malignancies, HIV infection and immunosuppression in transplant recipients [4]. Its aetiopathogenesis is not completely understood. Possible causes include: an abnormal immunological response to undefined triggers, cross-reactivity, T cell-dysregulation, elevated pro-inflammatory

Table 1: Various causes of non healing lower limb ulcers.

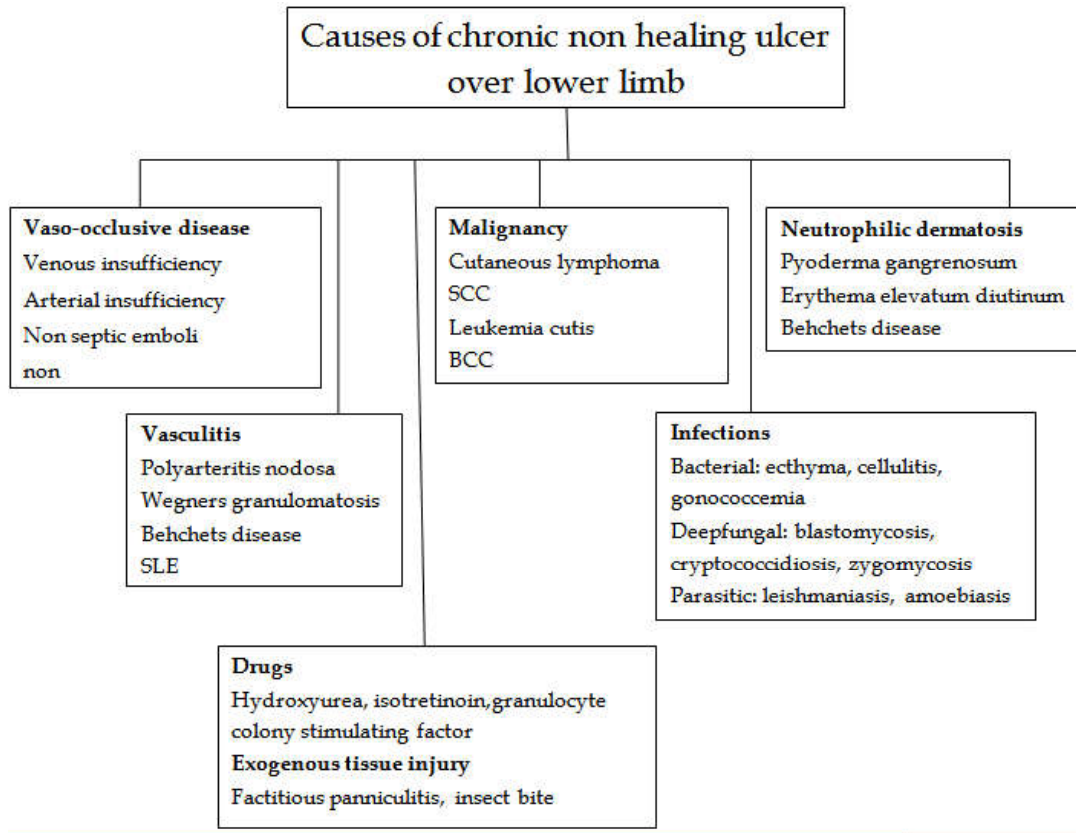


Table 2: Newer Diagnostic criteria for pyoderma gangrenosum

Major Criteria	A biopsy from the ulcer edge demonstrating a neutrophilic infiltrate
Minor Criteria	<ul style="list-style-type: none"> ➤ Exclusion of infection ➤ Pathergy ➤ Personal history of inflammatory bowel disease or inflammatory arthritis ➤ History of papule, pustule, or vesicle that rapidly ulcerated ➤ Peripheral erythema, undermining border, and tenderness at site of ulceration ➤ Multiple ulcerations (at least one occurring on an anterior lower leg) ➤ Cribriform or “wrinkled paper” scar(s) at sites of healed ulcers ➤ Decrease in ulcer size within one month of initiating immunosuppressive medications

cytokines and chemokines or genetic abnormality which is supported by the presence of PG lesions in patients with: PAPA syndrome (pyogenic sterile arthritis, PG, and acne); PAPASH syndrome (pyogenic sterile arthritis, PG, acne, and hidradenitis suppurativa) and PASH syndrome (PG, acne, and hidradenitis suppurativa). Characteristic lesion of

PG begins as painful deep nodule or a hemorrhagic superficial pustule, followed by dark red or painful, purplish inflammatory ulcerative lesion. PG is most commonly seen on the lower limbs, namely the pretibial area, but other areas like head, neck, breasts, genitalia, and upper extremities can be involved. In our case, the lesions are present over both buttocks,

perianal area and lateral malleoli. Four major clinical variants of PG have been described: ulcerative (classic), pustular, bullous, and vegetative (superficial). Clinically, the classical form (ulcerative) is characterized by rapidly progressing, painful ulcers with well defined, violaceous, undermined borders. The base of the ulcers has granulation tissue, which may be necrotic and covered by purulent exudates. The pustular type presents as is commonly associated with IBD. Bullous PG presents with grouped vesicles, which coalesce to form large bullae that ulcerate. The most uncommon and least aggressive is vegetative (superficial) type which presents as erythematous, ulcerated plaque without the characteristic undermined border.

When ulcer of PG heals, new epithelial growth connects the ulcer bed to the surrounding normal skin and finally results in cribriform scars. Many times the lesions appear after minor trauma, such as injections, insect bites, biopsies, or surgical incisions like breast surgery or caesarian section. This phenomenon is known as pathergy. It is an aberrant exaggerated inflammatory response to cutaneous tissue antigenically altered by trauma, and is observed in up to 30% of PG cases [5]. PG is an uncommon ulcerative, inflammatory disorder that can be challenging to diagnose. Diagnostic criteria for ulcerative pyoderma gangrenosum have been revised in March 2018 (Table 2). A Delphi consensus of international experts have given new, validated diagnostic criteria which helps in the diagnosis of PG [6].

At least the major criterion and four minor criteria must be fulfilled for diagnosis of PG. The new criteria represent our preferred approach to the diagnosis of PG. In our case, the major criteria and all the minor criteria except pathergy are fulfilled. Treatment of PG includes local wound care, topical and systemic therapy. Local wound care reduces pain, provides protection and promotes healing and includes dressing with hydrocolloid/vaseline gauze or skin grafting. Topical therapy includes cromolyn sodium, topical glucocorticoids, tacrolimus, or hyperbaric oxygen. Alternative local therapies are intralesional injections of glucocorticoids, cyclosporine or tacrolimus. Systemic therapy may be required for severe cases or those refractory to local treatment. Initial therapy includes high dose corticosteroids, but if there is incomplete response to corticosteroids, then first choice is cyclosporine A or azathioprine. Second choice is mycophenolate mofetil, dapsone, chlorambucil, sulfasalazine or minocycline. For recalcitrant PG, cyclophosphamide, infliximab, thalidomide,

tacrolimus can be used [7]. Cyclophosphamide, an anticancer drug, is now commonly used in many dermatologic disorders like bullous disorders, vasculitis and connective tissue disorders. Cyclophosphamide has immunomodulatory effects. It is thought to have these mechanisms of action [8]: elimination T regulatory cells (CD4⁺, CD 25 + T cells) in the host and induction of T cell growth factors, such as IFN-1. A major side effect of cyclophosphamide is haemorrhagic cystitis, caused by the metabolite Acrolein, which is why it is given under the cover of Mesna (2 Mercapto Ethane Sulfonate Sodium) [9].

Biologics like TNF- α inhibitors (infliximab, adalimumab and etanercept) may be used. Surgical intervention like debridement and skin grafting may be harmful as there is risk of pathergy, but used when there is extensive necrosis of the skin or vital tissues like tendons and ligaments, are exposed at the ulcer bed. The prognosis of PG for most patients is generally good.

Conclusion

Pyoderma Gangrenosum is a chronic ulcerative condition for which specific laboratory investigations are not available. So it is mainly a diagnosis of exclusion and one needs a thorough knowledge of its types and clinical presentations.

References

1. Casey G. Causes and management of leg and foot ulcers. *Nursing Standard* 2005;23:601-11.
2. Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol.* 2009;23(9):1008-17.
3. B. Kahle, H. J. Hermanns, and G. Gallenkemper, Evidence-based treatment of chronic leg ulcers. *Deutsches Ärzteblatt International* 2011;108(14):231-37.
4. Banga F, Schuitemaker N, Meijer P. Pyoderma gangrenosum after caesarean section: a case report. *Reprod Health* 2006;3:1-5.
5. Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am J Clin Dermatol.* 2012; 13(3):192-11.
6. Zouboulis CC, Okun MM, Prens EP, Gniadecki R, Foley PA, Lynde C et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year

- results of a phase 3 open-label extension study, *J Am Acad Dermatol*. 2018.05.040.
7. Gettler S, Rothe M, Grin C, et al. Optimal treatment of pyoderma gangrenosum. *Am J Clin Dermatol* 2003;4:597-608?
 8. Sistigu A, Viaud S, Chaput N, Bracci L, Proietti E, Zitvogel L. Immunomodulatory effects of cyclophosphamide and implementations for vaccine design". *Seminars in Immunopathology*. 2011;33(4):369-83.
 9. Korkmaz A, Topal T, Oter S. Pathophysiological aspects of cyclophosphamide and ifosfamide induced hemorrhagic cystitis; implication of reactive oxygen and nitrogen species as well as PARP activation. *Cell Biol Toxicol* 2007;23:303-12.
-

Subject Index

Title	Page No
A Clinical Study of Melasma and the Effect of Different Therapeutic Modalities in its Treatment	65
A Clinico-Epidemiological Study of Dermatophytosis	79
A Hospital-Based Study of Epidemiological Patterns of Vitiligo	20
Acne Vulgaris and Quality of Life	37
Dermatophytosis: Correlation Between the Site of Involvement and the Causative Agent	73
Modified Maintenance Fluid in Pediatric Electrical Burns	11
Mycological Study of Tinea Versicolor at a Tertiary Care Centre	24
Noninfectious Dermatoses Among Hivpatients: Clinical Descriptive Study	28
Pediatric Herpes Zoster: A Study of 64 Case	5
Psychiatric Disorders with Dermatological Symptoms: An Open, Cross Sectional, Observational Study	14
Pyoderma Gangrenosum: A Cause of Nonhealing Ulcer Over Lower Extremities	85
Skin Diseases in HIV Positive Patients Attending the Skin and STD OPD at a Tertiary Care Hospital	33
Study of Prick Test in Chronic Spontaneous Urticaria	61
The Impact of Pruritus on the Quality of Life of Patients with Chronic Plaque Psoriasis	53

Author Index

Name	Page No	Name	Page No
Adavi Vijayakumara	20	Payal Chakravarty	5
Aggarwal A	11	Pragya Nair	37
Amin Syed Moinuddin	53	Rajesh Kataria	53
Arwinder Kaur Brar	14	Raju G. Chaudhary	14
Ashish Jagati	14	Raksha Patel	61
Chaitnaya Naamdeo	53	Ramya KN	73
Deepshikha Khanna	5	Ramya KN	79
Elankumar S	11	Ravi Kumar Chittoria	11
Gupta S	11	Rima joshi	61
Harshavardhana KN	73	Santoshdev P. Rathod	14
Harshavardhana KN	79	Shah Aishni J	85
K. Devendrappa	24	Sharath Chandra B Athanikar	65
Kalgi D. Baxi	14	Soham B. Buch	14
Kira Pariath	37	Sonal Patel	61
Konda Sireesha Reddy	11	Subhash Bharti	5
Lakshmipathi Y Pattar	28	Suma D Gudi	28
Lakshmipathi Y Pattar	33	Suma D Gudi	33
Likhitha R	11	TukaramSori	65
Mohammed Waseem Javed	24	Varadaraj V Pai	65
Nair Pragya A	85	Vijetha Rai	65
Naveen KN	65	Vinayak Chavan	11
Patel Trusha M	85	Vishalakshi S. Pandit	20