An Overview on Pyoderma Gangrenosum Presentation and Management Approach in the Emergency Department

Eid Hussein S. Alshahrani[1]*, Mohammed Salamah Alabid[2], Mohammed Amer A Alsmail[3], Hanan Abdullah A Almowallad[4], Taha Abbas Almohammad[5], Adnan Mubarak M Aldhabab[6], Nora Khalid M Khayat[7], Sultan Abdulaziz S Alahmad[8], Yara Nasser R. Alanazi[2], Malek Yahya Mohtasib[9], Adel Mohammad Hakami[10]

[1] Faculty of Medicine, University of Bisha, Bisha, KSA
[2] Faculty of Medicine, Al Jouf University, Al Jouf, KSA
[3] Faculty of Medicine, Medical University of Silesia, Katowice, Poland
[4] Faculty of Medicine, Medical University of Lodz, Lodz, Poland
[5] Emergency Department, Oyun City Hospital, Al Ahsa, KSA
[6] Faculty of Medicine, King Abdulaziz University, Jeddah, KSA
[7] Faculty of Medicine, Umm Al Qura University, Makkah, KSA
[8] Faculty of Medicine, King Faisal University, Al Ahsa, KSA
[9] Faculty of Medicine, King Saud bin Abdulaziz for health sciences, Jeddah, KSA
[10] Emergency Department, Samtah General Hospital, Jazan, KSA

ABSTRACT

Pyoderma Gangrenosum is a rare neutrophilic dermatosis with multiple different clinical presentations and associated comorbidities. Historically, it has been a challenging disorder to diagnose, as it is difficult to establish this condition based on a clinical presentation. Recently, several studies have attempted to define the prevalence of clinical manifestations of PG in order to improve diagnostic accuracy leading to the development of new diagnostic criteria rather than the traditional approach of a diagnosis of exclusion. Moreover, new biologic treatment modalities have been introduced. **Objective:** In this study, we aimed to evaluate the management and diagnostic approach of pyoderma gangrenosum in the emergency department. **Methodology**: PubMed database was used for articles selection, and the following keys were used in the mesh ((“Pyoderma Gangrenosum "[Mesh]). **Conclusion**: There is no diagnostic gold standard. However, PARACELSUS has been adopted as a novel diagnostic tool. Although the pathophysiology of PG is still incompletely understood. The discovery of new inflammatory cytokines and signal cascades has led to the development of a novel biologic therapy. However, significant research is needed in biologic therapy as it is difficult to assess long-term efficacy, adverse events, and remission rates as outcome measures for PG.

Key Words: *Pathergy, Pyoderma Gangrenosum, Biologic therapy, Corticosteroids, Diagnostic criteria.*

eIJPPR 2020; 10(6):110-114

HOW TO CITE THIS ARTICLE: Eid Hussein S. Alshahrani, Mohammed Salamah Alabid, Mohammed Amer A Alsmail, Hanan Abdullah A Almowallad, Taha Abbas Almohammad, Adnan Mubarak M Aldhabab and *et al.* (2020). “An Overview on Pyoderma Gangrenosum Presentation and Management Approach in the Emergency Department”, International Journal of Pharmaceutical and Phytopharmacological Research, 10(6), pp.110-114.

INTRODUCTION

Pyoderma Gangrenosum (PG) is a rare inflammatory disorder often associated with inflammatory bowel disease (IBD), inflammatory arthropathies, and hematologic malignancies. In the general population, it equally affects patients of both sexes, however, some female dominance is suggested, and it can affect any age group. PG has an overall incidence of 5.8 per 100,000 individuals and a mortality rate of up to 30%. This high rate was found in some series mainly due to complications including infection, scarring, uncontrolled pain, depression, and loss of mobility. [1]

Corresponding author: Eid Hussein S. Alshahrani
Address: Faculty of Medicine, University of Bisha, Bisha, KSA.
E-mail: Dr.eid996 @ gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 26 July 2020; **Revised:** 26 November 2020; **Accepted:** 03 December 2020

However, given the lack of a gold standard for diagnosis, the exact prevalence has yet to be elucidated since PG is commonly under- or over-diagnosed. [2] The aetiopathogenesis of PG is currently unknown and is hypothesized to be multifactorial, involving both the adaptive and innate immune systems as well as having genetic factors in play. Proper analgesia, wound care, and compression therapy are all important tenets in the management of Pyoderma Gangrenosum. Topical and systemic therapies are used empirically, but no targeted or specific treatment exists, and current therapy largely depends on the severity and progression of the disease. [3, 4]

This review will highlight updates in diagnosing, managing this disease, and will assist physicians in better understanding PG and ultimately improving patient care overall.

METHODOLOGY:

PubMed database was used for articles selection, and the following keys used in the mesh ((“Pyoderma Gangrenosum "[Mesh]). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; pyoderma gangrenosum diagnosis and management. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review:

The name pyoderma gangrenosum has a historical origin, firstly described by Broque in 1916. In 1930, the disease was given the name PG when it was reported and confirmed as a streptococcal infection. However, it does not cause gangrene and is not an infection (pyoderma). Although this disease affects both sexes, there may be some female dominance [5]. All ages may be affected by the disease, but it predominantly occurs in the fourth and fifth decades of life. The prognosis of PG is commonly good provided that complications are minimal. However, residual scarring and also recurrence are prevalent even after proper treatment. [6, 7]

Pathophysiology and Associations:

Even after a century, the etiology and pathophysiology of the disease have not been fully understood although it is thought to be a reaction to the dysregulated innate immune system, abnormal chemotaxis, phagocytosis, and neutrophil immigration. Moreover, a lot of genetic factors and mutations have been associated with this condition and have been proposed as possible causes and/or risk factors in the pathophysiology of PG. (Table 1) There is also evidence in PG association with other disorders related to neutrophilic dysfunction, such as IBD [8], rheumatoid arthritis (RA), seronegative arthritis, hematologic disorders, and malignancies such as acute myeloid leukemia (AML). [3, 9] IL-6, a pro-inflammatory cytokine that plays a role in the activation and accumulation of neutrophils, has been found to be elevated in patients with PG lesions. [10]

Approximately 50% of patients presenting with PG are usually having systemic diseases, the rest are mostly idiopathic. [11] These diseases may follow, precede, or occur simultaneously with pyoderma gangrenosum. Moreover, the classification of pyoderma gangrenosum is dependent on the associated conditions into para inflammatory, paraneoplastic, hematologic, idiopathic, and Drug-induced. Drugs that may be concerned as PG triggers include propylthiouracil, isotretinoin, cocaine, and sunitinib (protein kinase inhibitor). [12]

The most common associations with this condition are IBD, arthritis and hematologic. PG is usually associated with mild IBD and represents as the second most cutaneous manifestation occurring in 0.5% of all IBD patients. It is also frequently associated with RA, sometimes as high as 37% of PG cases having RA. Furthermore, the association between hyper-IgE and PG is rare, but high levels of IgE have never been observed in RA-induced PG. [13, 14].

Bullous PG is typically associated with hematological malignancies, especially acute myelogenous leukemia. Other conditions that are often associated with this condition are lymphoma, monoclonal gammopathy, and myelodysplastic syndrome. 70% of the bullous PG follow, accompany, or precede hematological malignances. [15]

Table 1: Pyoderma gangrenosum (PG)-associated genetic syndromes and their specific gene mutations. [3]

Acronym	PG-associated syndrome	Gene mutation
PAPA	Pyogenic arthritis, PG, acne	*PSTPIP1**
PASH	PG, acne, suppurative hidradenitis	*PSTPIP1, NCSTN**
PASS	PG, acne conglobata, suppurative hidradenitis, seropositive spondyloarthropathies	N/A*
PAPASH	Acne, PG, pyogenic arthritis, suppurative hidradenitis	*PSTPIP1**
PsAPASH	Acne, PG, pyogenic arthritis, suppurative hidradenitis	N/A*

*N/A: not available; NCSTN: codes for nicastrin, a protein essential for chemical signaling pathways and for normal immune system functioning; PSTPIP1: proline-serine-threonine phosphatase-interacting protein 1.

Clinical Variants and Features:

Four clinical variants are recognized based on their clinical and histopathological features: ulcerative (including

peristomal), bullous, pustular, and vegetative. Peristomal PG (PPG) is a rare neutrophilic dermatosis that comprises about 15% of all cases of pyoderma, characterized by painful, necrotic ulcerations occurring in the area surrounding an abdominal stoma. On the other hand, pustular pyoderma gangrenosum is rare; it often begins as a pustule or group of pustules that later coalesce and ulcerate. Moreover, it mostly occurs with IBD and tends to occur on the trunk and extensor surfaces of the limbs. The other type, bullous pyoderma gangrenosum, presents with rapidly evolving vesicles or bullae with central necrosis affecting the face and upper limbs more than the lower limbs. It is associated mostly with hematological disorders and malignant neoplasms. Lastly, vegetative PG commonly occurs on the trunk as a multiple or single, non-painful lesion and it usually presents in a less aggressive manner than the other varieties. These vegetative lesions often occur as a single lesion in patients who respond to topical treatments better than the other types and are otherwise well [16].

PG generally starts quite suddenly, usually at the site of a minor injury, Thus it may be triggered by surgical procedures; this phenomenon is often referred to as pathergy. The lesion resulted from surgical scars usually begins as a papule, pustule, or blood blister, which breaks down into a collection of small ulcers with a “cat paws” appearance. It is also characterized by a violaceous border that over hags the ulcers bed, which is usually erythematous and indurated. These coalesce and then the central area undergoes necrosis resulting in a single ulcer. Several ulcers may develop simultaneously over months to years. [16-19].

Patients are often presenting with myalgia, arthralgia, malaise, and fever. Lesions are commonly painful, which can be severe. The lesions usually heal with scarring, often in a cribriform or criss-cross pattern, and the epithelium from the borders extends into the ulcer (referred to as Gulliver’s sign). However, the bullous variant of PG may heal with no scars. Early diagnosis and rapid treatment decrease the risk of disfigurement and scarring. [17, 20]

Diagnosis:

The diagnosis is rather difficult and challenging and the condition is frequently misdiagnosed. The diagnosis process usually requires clinicopathological correlation and often is a diagnosis of exclusion, after ruling out the common causes of skin ulceration by histopathology. However, the histopathological differentiation of PG from other ulcerative processes with dermal neutrophilia is challenging and sometimes impossible. [20]

Numerous literature used the proposed diagnostic criteria for classic ulcerative PG by Su *et al*. (2004). However, in 2018, diagnostic criteria for pyoderma gangrenosum were made following a Delphi consensus, which highlighted 1 major criterion and 8 minor criteria. However, Jockenhöfer *et al*. developed PARACELSUS score as a separate diagnostic tool for PG (Table 2). [21–23]

Table 2: Proposed diagnostic criteria

Su *et al*. criteria [21]	**The Delphi Consensus of International Experts [23]**	**PARACELSUS score [22]**
Major criteria		
Other ulcerating conditions excluded (that is, biopsy and other investigations)	Biopsy	Exclude other differential diagnoses
Typical clinical presentation of classic pyoderma gangrenosum	-	Reddish-violaceous ulcer border
-	-	Progressive ulceration (developed in <6 weeks)
Minor criteria		
Histopathology findings	Histopathology findings	Histopathology findings
Typical systemic diseases present	Typical systemic diseases present	Typical systemic diseases present inflammatory bowel disease, inflammatory arthritis
Treatment responsive to systemic steroids	Cribiform scarring	Improvement in symptoms by immunosuppressants
History of pathergy and cribriform scarring	Pathergy	Pathergy
-	Pain, undermined border, peripheral erythema	Undermined border
-	Vesicle, pustule, or papule that ulcerated	Pain
-	Multiple ulcerations (at least one on lower leg)	Irregular ulcer shape

Management:

Treatment and management of PG are considered to be challenging as there is no specific protocol for this issue. However, the mainstay of PG treatment is immunosuppressive therapy and corticosteroids. The most commonly used first-line treatment in the management of PG is systemic steroids. In systemic therapy, typical monotherapy can be used in mild cases. [24] Topical and intralesional steroids are used as ulcer size was an important predictive factor in lesion resolution alongside other systemic therapies (ex, prednisone) as improvements are very slow and relapses are very prevalent. [25] Steroids are less effective in treating PG with comorbid IBD when compared with biological therapy. Multiple different biological agents have been proposed for the treatment of PG. Agents targeting TNF-α are the best studied and the main example is Infliximab, which has a rule in associated RCT and restoring the ability of T-regulatory cells to inhibit aberrant cytokine production. The discovery of new inflammatory cytokines and signal cascades has led to the development of novel biologic therapy. These include IL-12 and -23 antagonists, IL-6 antagonists, intravenous immunoglobulin therapy, and phosphodiesterase 4 inhibitors, which had been shown to have satisfying results in healing and in the complete resolution of the PG lesions. However, the whole healing process might be of a more chronic nature can even take years. [20]

Even though treatment of pyoderma gangrenosum is mainly non-surgical. The necrotic tissue should be removed surgically. During the active stage of PG, wide surgical debridement should be avoided as it may lead to the enlargement of the ulcer. Skin grafting and other surgical procedures may be carried out when the active phase of the disease has settled, with special care to minimize trauma. [20]

CONCLUSION:

Pyoderma gangrenosum is a rare non-infectious inflammatory disorder and was usually diagnosed based on the apparent clinical findings and by the exclusion of other ulcerative skin disorders, resulting in misdiagnosis of the condition in many patients. There are no golden standard diagnostic criteria approved for this condition, however, multiple criteria have been proposed to improve the accuracy of diagnosis, most notably PARACELSUS, which is a novel diagnostic tool. Although the pathophysiology of PG is not yet fully understood, multiple treatment options have been adapted with good results in patients. Corticosteroids and biologic therapy are the mainstay of therapy with more options such as inflammatory agents' antagonists emerging as other options. Nevertheless, more research is needed in these recent treatment models (biologic therapy) as it is difficult to assess long-term efficacy, adverse events, and remission rates as outcome measures for PG are not widely available.

REFERENCES

[1] 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(9):2166–70.

[2] Cohen PR. Neutrophilic Dermatoses: A Review of Current Treatment Options. Am J Clin Dermatol.2009;10(5):301–12.

[3] Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma Gangrenosum: An Update on Pathophysiology, Diagnosis and Treatment. Am J Clin Dermatol. 2017;18(3):355–72.

[4] McKenzie F, Arthur M, Ortega-Loayza AG. Pyoderma Gangrenosum: What Do We Know Now? Curr Dermatol Rep. 2018;7(3):147–57.

[5] Sheikh HM, El-Hamshary OI. Phenotype And Genotype Changes Effects of the Fungicide Benlate On Bacterial Antagonistic Against Pathogenic Fungi Causing Dermatological Diseases. Pharmacophores. 2018;9(2):25-34.

[6] Bhat RM, Nandakishore B, Sequeira FF, Sukumar D, Kamath GH, Martis J, Furtado S. Pyoderma gangrenosum: an Indian perspective. Clinical and Experimental Dermatology: Clinical dermatology. 2011 Apr;36(3):242-7.

[7] Xu A, Balgobind A, Strunk A, Garg A, Alloo A. Prevalence estimates for pyoderma gangrenosum in the United States: An age-and sex-adjusted population analysis. Journal of the American Academy of Dermatology. 2020 Aug 1;83(2):425-9. doi: 10.1016/j.jaad.2019.08.001.

[8] Aldosari MS, AlOtaibi FF, AlHuzaimi AM, Khalil NK, Faden NA, Thaniah SY. Patient Awareness of Extra intestinal Manifestations of Inflammatory Bowel Disease in Riyadh, Saudi Arabia. Int. J. Pharm. Res. Allied Sci. 2018;7(1):72-9.

[9] You HR, Ju JK, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Paraneoplastic pyoderma gangrenosum associated with rectal adenocarcinoma. Annals of dermatology. 2018 Feb 1;30(1):79-82.

[10] McKenzie F, Cash D, Gupta A, Cummings LW, Ortega-Loayza AG. Biologic and small-molecule medications in the management of pyoderma gangrenosum. Journal of Dermatological Treatment. 2019 Apr 3;30(3):264-76.

[11] Prystowsky JH, Kahn SN, Lazarus GS. Present status of pyoderma gangrenosum: review of 21 cases. Archives of dermatology. 1989 Jan 1;125(1):57-64.

[12] Wang JY, French LE, Shear NH, Amiri A, Alavi A. Drug-induced pyoderma gangrenosum: a review.

American Journal of Clinical Dermatology. 2018 Feb 1;19(1):67-77.

[13] Agarwal AL, Andrews JM. Systematic review: IBD-associated pyoderma gangrenosum in the biologic era, the response to therapy. Alimentary pharmacology & therapeutics. 2013 Sep;38(6):563-72. doi: 10.1111/apt.12431. Epub 2013 Aug 5. Review.

[14] Mir-Madjlessi SH, Taylor JS, Farmer RG. Clinical course and evolution of erythema nodosum and pyoderma gangrenosum in chronic ulcerative colitis: a study of 42 patients. American Journal of Gastroenterology. 1985 Aug 1;80(8)..

[15] Sullivan SN. Bullous Pyoderma Gangrenosum and Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018;24(5):e16–7.

[16] George C, Deroide F, Rustin M. Pyoderma gangrenosum–a guide to diagnosis and management. Clinical Medicine. 2019 May;19(3):224. doi: 10.7861/clinmedicine.19-3-224.

[17] Goldust M, Hagstrom EL, Rathod D, Ortega-Loayza AG. Diagnosis and novel clinical treatment strategies for pyoderma gangrenosum. Expert Rev Clin Pharmacol. 1 2020;13(2):157–61.

[18] Maniei M, Aghababaeian H, Karimi H, Firozzadeh K, Amirgholami N, Moghaddam AS, Kiarsi M, Zakeri O, Kalani L. The Use of Aloe Vera after Infrared Therapy in the Treatment of a Diabetic Foot Ulcer: A Case Report. J. Biochem. Technol. 2019;10(2):43-9.

[19] Sardari M, Esmaeili R, Ravesh NN, Nasiri M. The impact of pressure ulcer training program on nurses' performance. J. Adv. Pharm. Educ. Res. 2019;9(3):145-9.

[20] Fletcher J, Alhusayen R, Alavi A. Recent advances in managing and understanding pyoderma gangrenosum. F1000Research. 2019;8. pii: F1000 Faculty Rev-2092. doi: 10.12688/f1000research.19909.1. eCollection 2019. Review.

[21] Su WD, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. International journal of dermatology. 2004 Nov;43(11):790-800.

[22] Jockenhöfer F, Wollina U, Salva KA, Benson S, Dissemond J. The PARACELSUS score: a novel diagnostic tool for pyoderma gangrenosum. British Journal of Dermatology. 2019 Mar;180(3):615-20. 10.1111/bjd.16401.

[23] Maverakis E, Ma C, Shinkai K, Fiorentino D, Callen JP, Wollina U, Marzano AV, Wallach D, Kim K, Schadt C, Ormerod A. Diagnostic criteria of ulcerative pyoderma gangrenosum: a Delphi consensus of international experts. JAMA dermatology. 2018 Apr 1;154(4):461-6.

[24] Fitzmaurice S, Duong C, He Y, Fergus J, Raychaudhuri SP, Shirakawa Garcia M, Maverakis E. Effective strategies for the management of pyoderma gangrenosum: a comprehensive review. Acta dermato-venereologica. 2015 May 1;95(5):525-33.

[25] Thomas KS, Ormerod AD, Craig FE, Greenlaw N, Norrie J, Mitchell E, Mason JM, Johnston GA, Wahie S, Williams HC, Barnes J. Clinical outcomes and response of patients applying topical therapy for pyoderma gangrenosum: a prospective cohort study. Journal of the American Academy of Dermatology. 2016 Nov 1;75(5):940-9.