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Original Article

Diverse cutaneous manifestations of pyoderma gangrenosum with triple therapeutic trial in a series of 53 cases

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Abstract

Objective To characterize the demographic and the cutaneous features of pyoderma gangrenosum in large series of patients.

Methods This is a case series cross sectional descriptive study with therapeutic trial where 53 patients with pyoderma gangrenosum were seen during the period from September 2013-January 2023.All patients were fully investigated and diagnosed as cases of pyoderma gangrenosum. Still full history and examination were carried out to characterize the clinical pictures. All patients were fully investigated to exclude any associated disease in doubtful diagnosis. Skin biopsy was performed when needed as exclusive measure. Triple therapeutic trial was tried using oral azathioprine, oral dapsone and oral prednisolone.

Results Fifty-three patients were included, their ages ranged from 10-60 years with a mean 45 years, with 39 (73.58%) males and 14 (26.41%) females with ratio 2.78:1. The duration of lesions ranged from 4-12 weeks. The location of these lesions was mostly lower limbs in 31(58.49%) cases. For the rest of the cases, lesions appeared on the trunk including the groin and neck in 14 (26.41%), breast of the female in 3 (5.66%) cases, upper limbs in 2 (3.77%) cases, male genitalia in 2 (3.77%) cases and face in one (1.88%) case. The lesions were single in 36 (67.9.21%) patients while multiple in 17 (32%) cases. The rash had mostly painful ulcerative yellowish surface with undermined edges. The ulcerative subtype was the most frequently recorded in 48 (90.56%) patients. No associated underlying triggering pathologies were noticed during follow up except in seven (13.2%) patients. The therapeutic response was noticed after two weeks but complete clearance of ulcers took several weeks to months according to the size of ulceration.

Conclusion This study showed that pyoderma gangrenosum is a disease of middle-aged males with no well-defined etiological triggering factors except in 13.2% of cases that have been associated with miscellaneous underlying diseases. Accordingly, the etiopathogenesis of pyoderma gangrenosum remains idiopathic, still long follow up might discover many other concealed etiologies. Effective triple therapy was tried and proved its effectiveness.

Key words
Pyoderma gangrenosum; Neutrophilic dermatosis; Triple therapy; Etiopathogenesis.

Introduction

Pyoderma gangrenosum (PG) is an uncommon, chronic, neutrophilic inflammatory dermatosis with the classical ulcerative form typically presenting primarily as a painful pustule, nodule or plaque that progressively enlarging to form an ulcer with elevated, undermined, erythematous

edges.[1,2]

It is most commonly appears between 20 and 50 years of age with female predominance. About 4% of cases of PG occur in pediatrics. Fifty percent of patients have a previous, coincident or subsequent systemic disease, most commonly Crohn's disease, ulcerative colitis, rheumatoid arthritis (RA) or a hematologic disorder.

Although the typical clinical presentation of PG is an ulcer, there are several forms like pustules, bullous and vegetative picture that differ by their clinical appearance, location, and associated diseases. The ulcerative form, which is the most common, is characterized by one or more painful ulcerative cutaneous lesions of variable size and depth with undermined erythematous edges. It occurs most frequently on the lower extremities, especially in the pretibial area, but it can appear any where.[3,4]

Although PG is commonly observed in those with autoimmune diseases such as inflammatory bowel disease (IBD) and RA, which suggests an autoimmune origin, but the precise immunopathogenesis of the condition still remains elusive.[5]

One proposed theory, despite PG being a neutrophilic dermatosis, surrounds the action of T cells, which are inferred to target and cause destruction to pilosebaceous units within the skin. This is concluded in a 2018 study in which PG scars in patients were observed lacking pilosebaceous units. The observation that PG lesions did not tend to occur in regions of the body that did not possess follicular adnexal structures, i.e. the palm of the hands and the soles of the feet, further supported this theory.[6] Contradictory to this however, is recent evidence of PG lesions occurring both on the plantar surface of a metatarsophalangeal joint, as well as on the scar of a past PG ulcer - both regions devoid of pilosebaceous units.[5]

A wider-accepted theory directed towards autoinflammatory origin of where it is associated with several syndromes including PAPA (pyogenic arthritis, PG and acne), which are the result of gene mutations that elevate inflammasome production as protein activators, propagate the innate immune response thereby increasing the formation of interleukin 1 beta, the release of pro-inflammatory cytokines e.g. interleukin-17, and the recruitment of neutrophils. The detection of high levels of interleukin 1 beta and its receptor within PG lesions, as well as the therapeutic effectiveness of an interleukin 1 beta inhibitor (canakinumab), has supported this theory.[5,7]

Nevertheless, as heightened interleukin 1 beta is associated with other skin ulcerating conditions, it has been dismissed as a sole indicator of PG. The study which declares this, instead proposes the overexpression of pattern recognition receptors (PRRs) i.e., toll-like receptors (TLRs) within PG lesions, to be causative of the condition.[8] TLR upregulation, is however, also associated with the autoimmune diseases, RA and IBD. This, therefore, may suggest both an autoimmune and autoinflammatory involvement.[5,8] An over-stimulated innate and adaptive immune response is echoed by a study which further acknowledges the upregulated presence of activator genes e.g. STAT1 and

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+MAPK8, within PG lesions.[9]

Diagnosis of PG is clinical, especially in classical presentation but it is so difficult in non-classical presentation due to the wide range of clinical pathologies that can appear similar. So culture, biopsy and other specific investigations are important to exclude other differential diagnosis.[10,11]

There is neither specific nor uniformly effective treatment for PG. The response to therapy can be variable and has to be altered for each case. The standard therapy of PG is local or combined local and systemic steroid treatment with or without adjunctive systemic treatment.[12]

So the aim of this study is to characterize and describe the demographic and the cutaneous features of pyoderma gangrenosum in large series of patients. In addition, new therapeutic regime was tried.

Patients and methods

This is a case series cross-sectional descriptive and therapeutic study where 53 patients with PG were seen during the period from September 2013-January 2023. A thorough history and physical examination were collected from each patient regarding the following: name, sex, age, address, site, depth and size of the lesion, clinical variants, number of lesions, duration of the lesions, associated systemic diseases and past medical and drug history. Many patients were fully investigated before presentation to us. The following laboratory investigations were done including the following: Complete blood count (CBC), blood sugar, liver function tests , renal function tests , erythrocyte sedimentation rate (ESR), rheumatoid factor, antinuclear antibodies, anti-Ro/La antibodies, antineutrophilic cytoplasmic antibodies (ANCA), antiphospholipid antibody screen, serum protein electrophoresis and immunofixation studies, abdominal sonography and chest X-ray. All patients with ulcers on their legs were undergone bidirectional Doppler or colour-coded duplex sonography to rule out any underlying vascular cause for the ulceration. The clinical diagnosis was uncertain in 6 cases, so skin biopsy was performed in these cases to confirm diagnosis and exclude other diagnoses. The diagnosis was based on clinical features confirmed by pathologic results in doubtful cases with the exclusion of diseases or conditions that produce ulcerations by appropriate studies.

Therapeutic trial was applied using triple therapy like oral azathioprine (50 mg 3 times/ day for adults and 2 mg/kg/day in 2 divided doses for children), oral prednisolone 20 mg once daily and oral dapsone 100 mg/ day for adults and 50 mg/ day for children. Topical antiseptic like povidone iodine was applied twice a day.

After inducing complete clearance of the lesions, the dose of the oral drugs was progressively tapered. Follow-up was done every 2 weeks in the first two months then monthly until complete healing of the lesions.

Results

Fifty-three patients were included, their ages ranged from 10-60 years with a mean 45 years, with 39 (73.58%) males and 14 (26.41%) females (M/F ratio of 2.78:1) **(Table 1)**. Five (9.43%) of these cases were children and their ages ranged from 10-13 years. The duration of lesions ranged from 4-12 weeks. The location of these lesions was mostly lower limbs in 31 (58.49%) cases. For the rest of the cases, lesions appeared on the trunk including the groin and neck in 14(26.41%), breast of the female in 3 (5.66%) cases, upper limbs in 2 (3.77%) cases,

Table 1 Demographic feature of patients with pyoderma gangrenosum.

Demographic	*Number of cases (%)*
Age (years)	
10-26	6 (11.53%)
27-43	7 (13,2%)
44-60	40 (75.47)
Mean age at diagnosis (range).	45 (10-60)
Gender	
Male	39 (73.58%)
Female	14 (26.41%)
Associated diseases	7 (13.2%)
Lymphoma	1 (1.88%)
Leukemia	1 (1.88%)
Mycosis fungoides	1 (1.88%)
Crohn's disease	2 (3.77%)
Behcet's disease	1 (1.88%)
Pulmonary tuberculosis	1 (1.88%)

male genitalia in 2 (3.77%) cases and face in one (1.88%) case. The lesions were single in 36 (67.92%) patients while multiple in 17 (32%) cases. The lesions had mostly painful ulcerative yellowish surface with undermined, erythematous edges (**Figures 1-4)**. The ulcerative subtype was the most frequently recorded in 48 (90.56%) patients. The vegetative variant was observed in 5 (9.43%) cases while no other variants were observed. No associated underlying triggering pathologies were noticed during follow up except in seven (13.2%) patients as one patient developed lymphoma during therapy, one with leukemia, one with mycosis fungoides and two with Crohn's disease, one with Behcet's disease and one with pulmonary tuberculosis. The histopathological results were nonspecific but neutrophilic dermal infiltration, leukocytoclasia and leukocytoclastic vasculitis were seen in some cases **(Figure 1)**.

One child with PG on the back was misdiagnosed by surgeon and was treated by extensive skin grafting that failed after short time and induced exacerbation and enlargement of ulcerations **(Figure 2)**.

The therapeutic response was noticed after two weeks but complete clearance of ulcers took several weeks to months according to the size of ulceration **(Figures 2,4)**.

Discussion

Pyoderma gangrenosum is an inflammatory dermatosis characterized by typical clinical lesion that evolves from pustule to progressively enlarging painful ulcer with erythematous undermined border. As the pathological and immunofluorescent results are not diagnostic, therefore the diagnosis of PG is based on the clinical presentation and evolution of the lesion. [13] Diseases that may produce similar-appearing lesions include, vasculitis, vascular-occlusive or venous disease, atypical mycobacterial infection, cancer, factitial disease, and deep fungal infection, including sporotrichosis, blastomycosis, and cryptococcosis.[14]

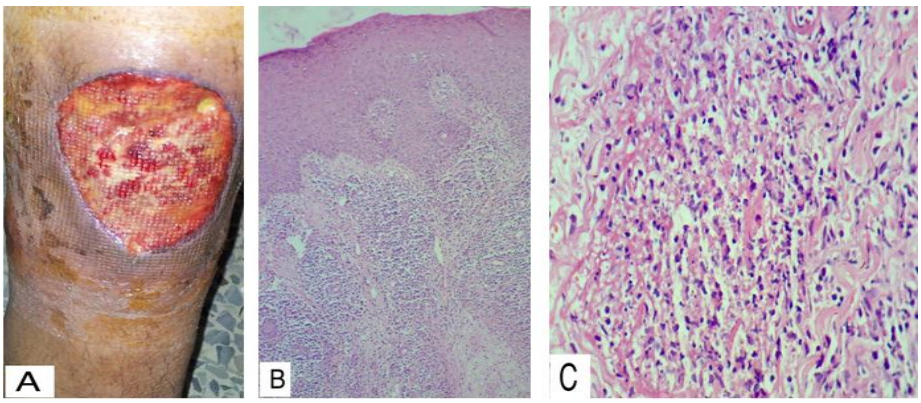

Figure 1 Fifty-three years old male patient showing classic ulcerative type of pyoderma gangrenosum on the right leg(A) and Hematoxylin and Eosin stained section from the same lesion showing dense dermal neutrophilic infiltration with leukocytoclastic vasculitis (B; X10, C; X 40).

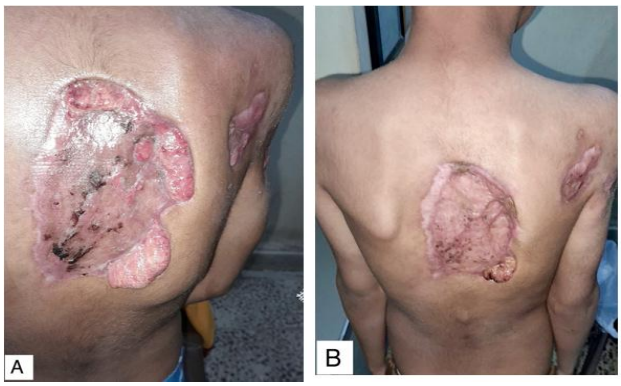

Figure 2 Ten years age male patient showing multiple ulcerative variant of pyoderma gangrenosum on the trunk that was managed by skin grafting. Before treatment(A) and one month after therapy(B).

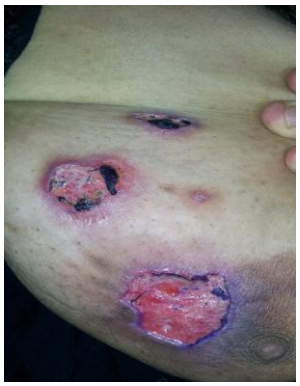

Figure 3 Forty-seven years old female patient showing multiple ulcerative variant of pyoderma ganrenosum on the breast.

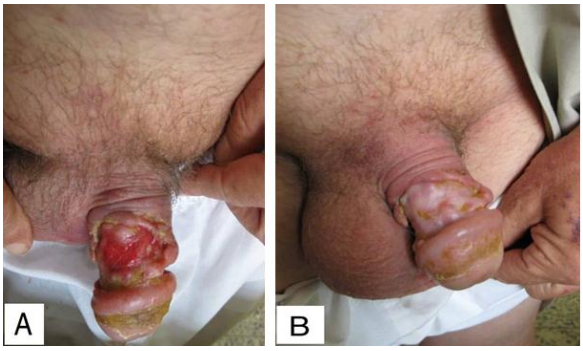

Figure 4 Showing pyoderma gangrenosum of penis shaft (A) before therapy and (B) after therapy.

Regarding the clinical features of PG lesions in the present study, are in agreement with previous reports.[15-19] Male predominance (73.58%) of our cases is the major difference. While this finding is an important controversy with other studies,[15- 19] no single explanation can help solve this issue, but we can speculate that there might due to some genetic buildup of our patients or related to some environmental factors.

The mean age of our patients was 45 years, this result was lower than the reported in previous studies.[20,21] This could be attributed to the presence of 5 children in our cases their ages ranged from 10-13 years.

Ulcerative PG is the most commonly observed form (90.56%) in the present work and this was comparable with other studies.[16,20-23]

In this study, the lower limbs were the most frequently involved in 58.49% of cases, this percentage was slightly lower than other studies which was recorded in 70 to 80%.[16,20,22,24]

The rarity of well designed large scale researches makes the underlying systemic diseases in PG severely hampered. Many dermatological books and expert review recorded associated comorbidities such as IBD, RA, hematological disorders, and solid malignancies in about 50 to 70% of cases.[3,25,26] In a recent textbook publication, the prevalence of IBD, hematologic disease and RA was 20-30%, 15-25% and 20% respectively.[3] While this association was observed in only 13.2% of our cases and as follow: one case with lymphoma, one with leukemia, one with mycosis fungoides and two with Crohn's disease, one with Behcet's disease and one with pulmonary tuberculosis. This low association could not be explained but further studies might give answer.

The association between PG with IBD, RA and hematological disorders including leukemia and lymphomas was supported by many studies and these diseases play an important role in the pathogenesis and occurrence of PG.[16,20-23]

The findings of histopathological studies are nonspecific but can assist to exclude other diseases like vasculitis, infection and malignancy.[3] The histological hallmark of PG is neutrophilic infiltration inside the dermis[3] which is consistent with the result of this study. Biopsy was not performed for all cases, as histopathology is usually non-specific and rarely pathognomonic for PG and biopsy might trigger exacerbation and enlargement of ulcers as patients with PG have positive pathergy test.[27] Furthermore, some patients refused to do biopsy.

Reviewing the old and new studies for immunopathogenesis of PG,[5,6-8,13,28,29] revealed that PG still a matter of complexity and speculations but could be concluded as follow:

1. The immunopathogenesis of PG has not been fully established. Several theories exist about the etiology of PG. Some studies supposed the underlying pathogenesis of PG is a complex interplay between autoimmunity and genetics.
2. Triggers of the immune dysregulation remain unclear but both cellular and innate immunity play a role in the etiology of PG.
3. Neutrophil chemotaxis abnormalities are now considered a consequence of PG but not the driving force.
4. Complexity of immunodysregulation in PG is related to involvement of many immune cells including T cell and neutrophils and many inflammatory mediators (IL)-1β, (IL)-8, (IL)-17, and (TNF)-α.

Treatment of PG is challenging due to lack of wide randomized controlled studies, so the treatment option is based mainly on expert opinion, case series and case report. The treatment option depends on many factors such as location, size and number of the lesions, extra-skin involvement, associated underlying diseases, cost, adverse effect profiles, and patient preference.[29]

In the current work, the treatment option is based mainly on our experience in the treatment of PG for many decades. The use of triple combination therapy like oral prednisolone , oral azathioprine and oral dapsone leads to fast response , low dose of steroid use, minimal or no side effects, and with complete clearance of the lesions within short duration as shown in our cases where all patients revealed complete clearance within several weeks to few months according to the size of ulceration. According to the best of our knowledge, this is the first reported study showing the effectiveness of this new regime of treatment. In addition, the topical antiseptic like povidone iodine was used to prevent secondary bacterial infection.

Finally, PG lesions can mimic many diseases whether infectious or non infectious and there are difficulties in early diagnosis even for expert dermatologists. Accordingly, the patient may attend different medical specialties including surgical field before visiting dermatologist, hence these factors together may delay proper treatment and in some patients might have horrible management like in one patient in the present study who was treated by extensive skin grafting that failed after short time.

Conclusion

This study showed that pyoderma gangrenosum is a disease of middle aged males with no well-defined etiological triggering factors except in 13.2% of cases have associated miscellaneous underlying diseases. Accordingly, the etiopathogenesis of PG remains idiopathic and speculative, still long follow-up might discover many other concealed etiologies. PG lesion can mimic many diseases and the diagnosis will be difficult especially, by non-dermatologist, so improper diagnosis may lead to wrong management and this may worsen the condition.

Effective therapeutic trial was used in this study and this new triple therapy might be tried by other dermatologists in management of their patients.

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