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Case Report

Pyoderma gangrenosum: mis-diagnosed as necrotizing fasciitis and review of local experience in patients' characteristics, associated disease and therapy

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Abstract

Pyoderma gangrenosum (PG) is a rare non-infectious, inflammatory neutrophilic dermatosis that can be idiopathic or associated with underlying autoimmune or neoplastic disorders. It is often diagnosed by exclusion with no gold standard for diagnosis and treatment. We described a 38-year old diabetic lady who presented with rapidly deteriorating ulceration over right foot with extensive suppuration, misdiagnosed as 'necrotizing fasciitis' with multiple surgical debridement and amputation was planned. A clinical diagnosis of PG was made after skin biopsy reviewed. She responded significantly after systemic pulsed methylprednisolone therapy and her leg was salvaged. In our local experience of 12 cases with PG follow-up in 5-year period, 83.3% were associated with underlying systemic disease and lower limbs (91%) were the most common site of involvement. Non-healing ulcer (100%) was most frequent presenting symptoms followed by pustule or blister formation. An average of 1.67 skin biopsies were performed for diagnosis. The mean duration of disease before remission was 13.2 ± 6.4 months. Importantly, one-third of cases had experienced relapse. Systemic corticosteroid was mostly given during acute phase, followed by cyclosporin, mycophenolate, azathioprine and anti-tumor necrosis factor (TNF).

Conclusion: PG should be considered in patients with non-healing ulcers, especially over lower limbs after exclusion of other cause(s). Systemic corticosteroid during acute phase followed by immunosuppressants resulted in disease control. Continuous monitoring is required as relapse may occur.

Introduction

Pyoderma gangrenosum is a rare inflammatory condition with varying clinical presentations and severity. Typically, it presents as a papule or pustule that rapidly evolves to a classical ulcerative lesion with irregular, erythematous to violaceous edges. Other subtypes include bullous, pustular, vegetative, drug-induced, post-surgical, peristomal or mixed. Pathergy is a characteristic feature of pyoderma gangrenosum as lesions often occur at sites of trauma. PG has an estimated annual incidence of 3–10 cases per million people [1]. It affects people of any age, but incidence peaks between fourth and fifth decades and affect both sexes with slight female predominance [2,3]. Although pyoderma gangrenosum can be found independently, it is more commonly found in association with an underlying disease. In fact, more than 50% of pyoderma gangrenosum cases are associated with inflammatory bowel diseases, inflammatory arthritis, or haematological disorders [2,3]

The diagnosis of pyoderma gangrenosum is challenging, as it is a diagnosis of exclusion such as infection, malignancy, vasculitis, vasculopathy, collagen-vascular disorder or venous insufficiency [4,5]. Diagnostic criteria for pyoderma gangrenosum was proposed by Su et al which require two major and two out of four minor criteria to establish the diagnosis (Table 1) [6]. Major criteria include rapid progression of painful, necrolytic, cutaneous ulcer with an irregular violaceous border and exclusion of other causes of cutaneous ulceration [7]. Minor criteria include history suggestive of pathergy or clinical findings of cribriform scarring,

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systemic diseases associated with pyoderma gangrenosum, compatible histopathological findings, and response to treatment [6]. Recently, Maverakis et al proposed new criteria based on a consensus of international experts, requiring one major and four out of seven minor criteria (Table 2) [7] .This revised diagnostic tool emphasize the histological finding of neutrophilic infiltrate over ulcer edge and i) exclusion of infection, ii) history of inflammatory bowel or arthritis, presence of iii)pathergy, iv)cribriform or wrinkle scars at healed ulcer sites, v) papule, pustule or vesicle ulcerating within 4 days of appearing vii) peripheral erythema, undermining border and tenderness at ulcerations site v) multiple ulcers , at least 1 on anterior lower limbs, viii) that improve significantly (reduced by 50%) after corticosteroid or immunosuppressants with in 1 month [7]. Receiver operating characteristic (ROC) analysis revealed that 4 of 8 minor criteria maximized discrimination, yielding sensitivity and specificity of 86% and 90%, respectively. Although the exact pathophysiology of pyoderma gangrenosum is poorly understood but is believed to be a combination of genetics, irregular activation of inflammatory cytokines, and both innate and adaptive immune systems [8]. There is a variety of disorders associated with pyoderma gangrenosum, and review of literature revealed that the frequently associated conditions include inflammatory bowel disease; rheumatological conditions such as rheumatoid arthritis (RA), seronegative arthritis, psoriatic arthritis, ankylosing spondylitis; solid organ malignancies and haematological disorders such as myelodysplasia, monoclonal gammopathy, polycythaemia vera [2,3,5].

Table 1. *Diagnostic tool for Pyoderma gangrenosum (2004 Su et al)*

Major criteria
• Rapid Rapid progression of a painful necrolytic cutaneous ulcer with an irregular, violaceous and undermined border • Other causes of cutaneous ulceration excluded
Minor Criteria
• History of pathergy or cribriform scarring clinically • Associated systemic disease (inflammatory bowel disease, arthritis, IgA gammopathy or underlying malignancy) • Classic histopathological findings • Treatment response (rapid response to systemic steroid treatment – 50% improvement in 1 month)

Table 2. *Revised Diagnostic Tool for Pyoderma gangrenosum (2018 Maverakis et al)*

Major criteria
• Biopsy of ulcer edge demonstrating neutrophilic infiltrate
Minor Criteria
• Exclusion of infection • Pathergy (induction of skin lesion after trial trauma) • History of inflammatory bowel disease or inflammatory arthritis • Peripheral erythema, undermining border, and tenderness at ulceration site • Papule, pustule or vesicle ulcerating within 4 days of appearing • Multiple ulcerations (at least one on anterior lower leg) • Cribriform or 'wrinkled paper' scar(s) at healed ulcer sites • Decreased ulcer size within 1 month of initiating immunosuppressive medication(s)

Case

We presented a 38-year old lady presented with abrupt onset of tender erythema over her right ankle after minor sprain injury. Blisters and pustule formations were noted within few days after injury. The lesions rapidly deteriorated after aspiration of the 'abscess' and 'blisters' by a podiatrist. She then developed fever and was given oral amoxicillin/clavulanic acid. She had known history of diabetes mellitus, proteinuria and mild renal impairment. Her usual medication included lisinopril, metformin, and protaphane insulin injection.

On admission, she was febrile (38.5°C) and had marked leukocytosis (white cell counts 26 x 109 with neutrophil predominant, raised C-Reactive Protein level of 34.8 mg/dl (Normal range < 0.76mg/dl). Other blood parameters included creatinine level 122 umol/L (normal range <82 umol/L) and glucose level 7.8 mmol/L. The blood culture was repeated twice with negative results. The wound swab culture grew pseudomonas aeruginosa and diphtheroids species. Intravenous piperacillin and tazobactam was started for her after admission. Initial working diagnosis included ecthyma gangrenosum and necrotizing fasciitis. in view of rapid deterioration, multiple debridement surgeries were performed by the orthopedic surgeon but no improvement was reported. Computed tomographic scan of right foot showed significant collection of pus over right foot with inflammatory change. Radiological diagnosis of right foot abscess, however, need to rule out necrotizing fasciitis was suggested. Amputation of right foot was, therefore, planned. Dermatologist was consulted before the operation. Clinically there was giant ulcerations over right foot with peripheral erythema, undermining edge and pustules formation over surrounding edematous skin (Figure 1). Skin biopsy was performed on edge of ulceration over right dorsal foot which showed neutrophilic predominant infiltrates with ulcerations. Pathergy test was positive. A clinical diagnosis of PG was made. The patient responded significantly shortly after 2 doses of systemic pulsed methylprednisolone therapy (250mg daily). She was followed by tailing dose of prednisolone from 1mg/kg/day (50mg daily) and cyclosporine (2.75 mg/kg/day) was given. Other workup including autoimmune profile (Anti-nuclear Antibodies, double-stranded DNA, Anti-nuclear cytoplasmic antibodies, Rheumatoid factor, anti-cyclic citrullinated protein (anti-CCP), interferon gamma reactive antigen (QuantiFERON) test were all negative. Stool for occult blood was negative.

On reviewing her past medical history, she has similar episode about 10 years ago with persistent progressive left foot ulcer responded to systemic prednisolone up to 60mg daily and mycophenolate mofetil 1000mg b.d. Prednisolone was tapered off after 2 years while low dose MMF of 250mg daily was maintained. She denied of arthritis, diarrhea, hematochezia, abdominal pain nor bowel habit change all along. There was no significant personal or family history of inflammatory bowel disease or inflammatory arthritis.

At 4-month follow-up post-discharge, she was on prednisolone 10mg daily and adalimumab 40mg alternate weekly with right ankle ulcer reduced in size and symptoms resolved.

Local experience of PG

Twelve cases of pyoderma gangrenosum followed up in a dermatological center of a tertiary hospital in Hong Kong during 2015-19 were identified. The mean age was 60.8 ± 16.1 (range 34-88) and the mean age of onset was 54.2 ± 15.3 (range

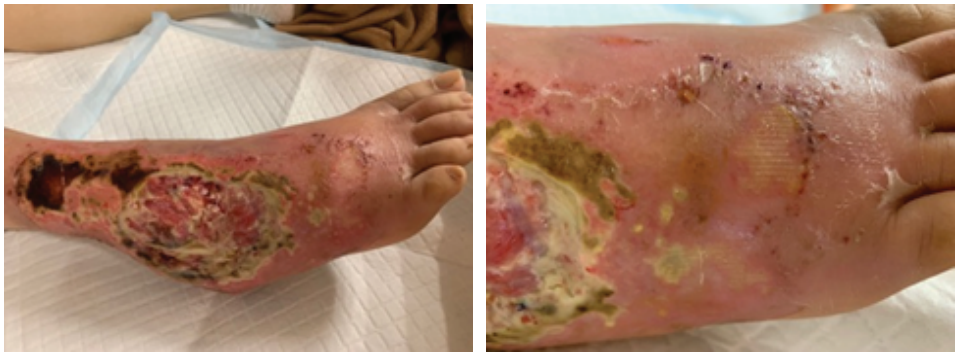

Figure 1. *Persistent ulcerations over right foot with peripheral erythema, undermining edge and pustule formations over surrounding edematous skin.*

Table 3. *Characteristics of pyoderma gangrenosum in a tertiary hospital, 2015-2019 (n =12).*

	Mean ±SD
Age, years	60.8 ±16.1 (34-88)
Onset, years	54.2± 15.3 (24-80)
Gender	2F:1M
Associated diseases	10 (83.3%)
Rheumatological disease^	5 (41.7%)
IBD[a]	2 (16.7%)
Haematological disease[#]	3 (25.0%)
Unknown	2 (16.7%)
Presenting symptoms	
Non-healing persistent ulcers	12 (100%)
Pustules	3 (25%)
Bullae/blisters	2(16.7%)
Sites	
Lower limbs	11 (91.6%)
Face or upper limbs	2 (16.7%)
Pathergy documented	2 (16.7%)
Relapse /recurrent course	4 (33.3%)
Duration till remission(months)	13.2 ± 6.4(6-24)
Treatment	
Corticosteroid	10 (83.3%)
Cyclosporine	5 (41.7%)
Mycophenolate	4 (33.3%)
Anti TNF (Adalimumab, infliximab)	4 (33.3%)
Azathioprine	3(25%)
Methotrexate	2 (16.7%)
Hydroxychloroquine	2 (16.7%)
Skin biopsy	
Number of skin biopsy performed	1.67 ± 0.65 (1-3)

^Rheumatological disorders included rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE); aInflammatory bowel disease included Crohns' disease and ulcerative colitis. # Haematological diseases included myelodysplastic disease (MDS), myeloproliferative disease (MPD), Monoclonal gammopathy with unknown significance (MGUS.)

24-80) (Table 1). PG affected both sexes with female to male ratio 2:1. Most (83.3%) of patients had underlying associated autoimmune or hematological disorders: rheumatological disease (41.7%), hematological disorders (25%) and inflammatory bowel disease (16.7) (Table 3). The most common presenting symptoms were non-healing ulcers (100%), pustule (25%) and blisters formation (16.7%).

Lower limbs were most frequently affected (91.6%). Positive pathergy was documented in 2 cases with rheumatoid arthritis. About one-third of cases had recurrent course of disease with flare after initial improvement and remission. The mean duration of clinical remission lasted for 13.2 ± 6.4 months (range 6-24). Systemic corticosteroid was mostly used (83.3%), especially during acute phase (methylprednisolone 250mg-1000 mg daily for 2-3 doses; prednisolone 0.5-1.5 mg/kg/day). Other than corticosteroid, systemic cyclosporine (41.7%), mycophenolate mofetil (33.3%), azathioprine (25%), methotrexate and hydroxychloroquine were given orally for disease control. Anti-tumour necrosis factor (TNF), were used in one-third of cases. Skin biopsies were done in all cases with average of 1.67 skin biopsies (range 1-3) performed for diagnosis.

Discussion

Our patient had clinical manifestations compatible with classic ulcerative or pustular pyoderma gangrenosum with initial pustules formation rapidly progressive into non-healing ulcers over right foot after repeated surgical debridement. It should prompt early recognition of PG in cases of persistent suppurative ulcers to avoid misdiagnosis of Necrotising fasciitis and limb amputation and devastating complications. Rapid clinical improvement was observed in this case with reduction of ulceration diameter and dry-up of suppuration after initiation of pulse methylprednisolone, cyclosporine and subsequently anti TNF alpha antagonist. She was then maintained with 40mg alternate weekly dose of Adalimumab and gradual tapering of prednisolone , from 50mg to 10mg daily.

In our case series, the most common associated systemic disease was rheumatological disorders (4 RA and 1 lupus erythematosus), followed by inflammatory bowel disease (1 Crohn's disease and 1 Ulcerative colitis). Haematological disorders were mostly observed among those elderly PG cases (1 myelodysplastic disorder, Myeloproliferative disease, Myelogammopathy of unknown significance MGUS. One

hematological cases deceased during acute phase with presentation of uncontrolled MPD and PG. Usually more than one skin biopsy has to be performed before a definite diagnosis is made. Majority of PG has fair-good prognosis after systemic immunosuppressant and corticosteroid retreatment and underlying disorder controlled. However, it was worth -noting that as one third of cases relapsed after 1 year of immunomodulating agents. Continuous monitoring is required and maintenance treatment shall be considered to prevent relapse.

Conclusion

PG should be considered in cases with non-healing ulcers, especially over lower limbs after exclusion of other causes. Systemic corticosteroid during acute phase followed by immunosuppressants are effective in disease control. Maintenance dosage and continuous monitoring is required as relapse may occur after initial remission.

Conflict of interest

There is no competing conflict of interest for the authors.

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