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Case Reports

An Adolescent Boy with Pyoderma Gangrenosum and Ulcerative Colitis

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Abstract Pyoderma gangrenosum (PG) is an ulcerating skin condition that classically associates with inflammatory bowel disease, rheumatoid arthritis and hematological disorders. It is very rare in paediatric population. We report our experience on a 15-year-old Pakistani boy who had rapidly progressive pyoderma gangrenosum associated with acute severe ulcerative colitis. Both diseases were controlled using the combination of systemic corticosteroid, azathioprine, minocycline and aminosalicylates.

Key words Pyoderma gangrenosum; Ulcerative colitis

Introduction

Pyoderma gangrenosum (PG) is a severe ulcerating non-infectious neutrophilic dermatosis which is extremely painful and debilitating. The association with ulcerative colitis is well known but real case is rarely encountered in the paediatric population of Hong Kong. To the best of our knowledge, this is the first reported case locally. We report our experience in the management of this patient with a review of literature on this rare dermatosis. Clinical photos were taken to illustrate the breakdown and healing of skin at different stages.

Case Report

Our patient was born locally at term with normal antenatal and perinatal course to healthy non-consanguineous Pakistani parents. He was the second child of the family and the family history was noncontributory.

He had history of painful per-rectal bleeding with bowel opening a few years ago. He was assessed in surgical out-patient clinic and was managed conservatively with a presumptive diagnosis of constipation and anal fissure.

At the age of 15, he was admitted to surgical ward because of bloody diarrhea (>10 times per day) with fever for a few days and episodic abdominal pain for 4 weeks associated with weight loss. He had no recent travel history and the drug history was negative. Paediatricians were consulted to assess him.

Physical examination showed a sick adolescent boy with growth parameters of 37.3 kg (<3 rd percentile) and 159 cm (10th percentile) on Hong Kong Chinese charts. He had fever and pallor. Abdominal examination found diffuse mild tenderness with no signs of peritonism.

Dermatological examination was normal on admission. 3 days after admission, he started to have tender pustules (Figure 1a) over right shin, left foot and right cubital fossa (venepuncture site). These pustules soon became necrotic. They rapidly broke down and expanded to become large painful ulcers (Figures 1b, 2a, 3a) in 5 days. The skin surrounding the ulcer was erythematous and slight bluish. The base of ulcer (Figure 1b) was covered by purulent materials. There was fresh contact bleeding (Figure 1c) even on gentle wound dressing.

Complete blood picture found hypochromic microcytic

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anaemia with thrombocytosis (Hb 7.5 gm/dL; Platelet 619 x 10^9/L). Blood biochemistry showed hypoalbuminaemia and iron deficiency. The acute-phase reactants were high. (C-reactive protein 190 mg/L; ESR 65 mm/hr) Blood culture, stool culture for bacterial pathogen, amoeba, ova and cyst were all negative. Wound culture was sterile. The Mantoux test was negative.

Oesophagogastroduodenoscopy was normal with no ulcers found. Colonoscopy performed on day 7 of admission showed diffuse erythema with loss of vascular pattern. There were mucosal erosions with contact bleeding suggesting friability. The inflammatory changes were continuous from the anus up to the descending colon without skip area. Further advancement was not possible as limited by pain.

Multiple random biopsies found evidence of chronic and active inflammation together with architectural distortion. These include plasmacytosis in the lamina propria, diffuse cryptitis with occasional crypt abscesses and Paneth cell metaplasia. Distortion in the form of crypts branching and shortening was obvious. No genuine granuloma was identified. These histological changes were compatible with the diagnosis of ulcerative colitis.[1]

After admission, he was started on enteral feeding with commercial nutritional supplement (Ensure®, Abbott Laboratories). The oral intake was poor and so he required intravenous fluid supplement. Ryle's tube feeding was employed to top up his nutrition. Intravenous cefotaxime and metronidazole were used to cover infection empirically.

Sulphasalazine (1 gram tds PO) and mesalazine (1 gram bd PR) were added after colonoscopy. Regular dologesic (1 tab, QID) was prescribed for pain control with acceptable effect.

Three days later, his fever was still swinging. He remained tired with fair general condition. His multiple skin ulcers were increasing in size despite topical treatment with non-adhesive normal saline dressing. Oral prednisolone (20 mg bd), minocycline (100 mg bd) and azathioprine (75 mg daily) were hence chosen for this adolescent in view of the rapidly progressive pyoderma gangrenosum associated with active and severe ulcerative colitis.[2] His fever and general condition improved rapidly in 2 days after the initiation of the above regime. The ulcer progression was also halted. They gradually decreased in size (Figure 1d) and healed over 4 weeks. The systemic corticosteroid can be tapered gradually over 2 months. The cosmetic outcome was good. (Figures 1e, 2bc, 3b)

Discussion

Pyoderma gangrenosum is a rare ulcerating skin disease. It has several variants and may not be easily recognised. The diagnosis will hence be delayed[3] and may lead to unnecessary surgical intervention and considerable morbidity for the patient.[4]

It was first reported by Brunsting, Goeckerman, and O'Leary in 1930. 80 years have lapsed, it is still a poorly understood destructive cutaneous disorder with unknown aetiology. A detailed pathogenesis of the disorder remains obscure. Nevertheless, autoimmune mechanisms are probably implicated.[5]

Exact epidemiologic data are missing, but it is considered to be rare.[6] It is estimated to be 3-10 patients per million population per year.[7] It most commonly occurs on the lower extremities and trunk of adults aged 30-50. However, it can also occur elsewhere including head, neck and genitalia.[8]

PG is very rare in children. Incidence in infants and adolescents constitutes around 4% of all cases.[6,9,10] Since it is not commonly encountered by clinicians including paediatricians, the diagnosis may not be always straightforward.[5]

Around 50-70% of cases are associated with an underlying systemic disease, such as inflammatory bowel disease, arthritis, and haematological malignancies. Inflammatory bowel disease accounts for 10-15% of total cases.[5] Conversely, PG is only occurring in 0.5-5% of patients with inflammatory bowel disease.[11] It may precede, coincide or follow the onset of underlying disease.[12] The exact connection regarding the activity of PG and ulcerative colitis are still lacking. However, the onset of PG is sometimes parallel with activity of bowel disease as in our case.

PG can be classified into four major variants. Our patient has classic form clinically. Classic form usually begins as a tender papulopustule with surrounding halo. It enlarges, ulcerates and breaks down rapidly to form painful ulcer. Fully developed lesions have raised, violaceous, and well demarcated edges.[5] Patients are often systemically unwell and the pain can be severe. When the ulcers heal, the scars are often cribriform.[3] Brooklyn et al had a comprehensive discussion of the remaining clinical variants.[3]

Minor trauma, needle stitches, biopsy or surgery can induce new PG lesions. This is known as pathergy phenomenon.[13] It occurs in 25-50% of cases.[3]

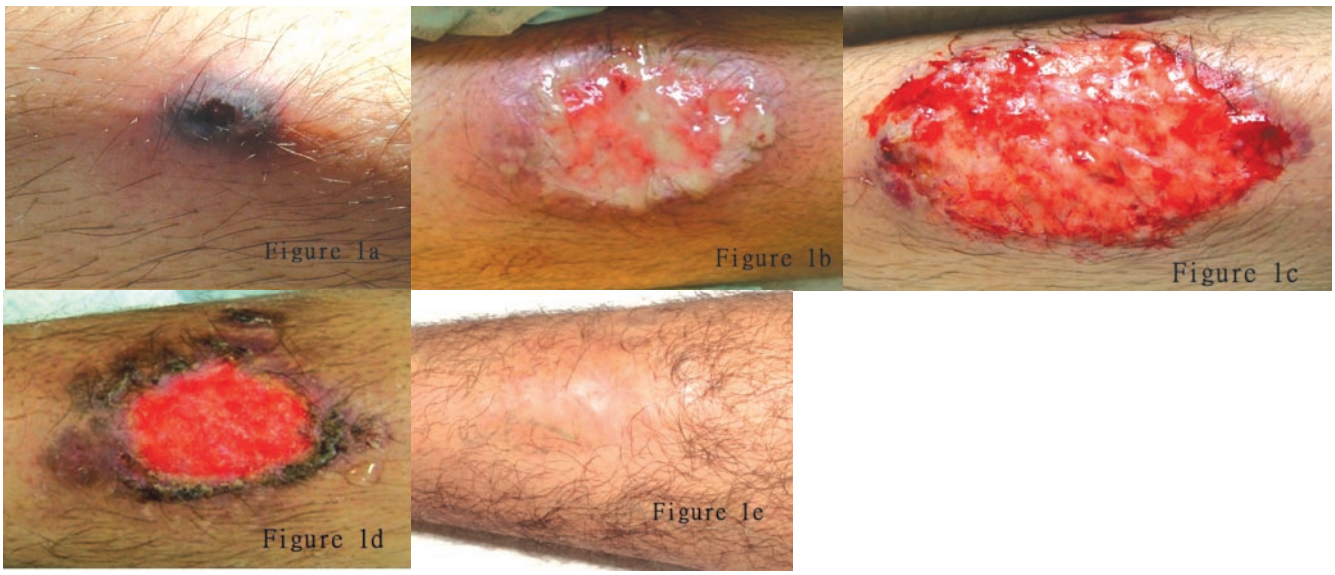

Figure 1 Evolution of a classic pyoderma gangrenosum over right shin.

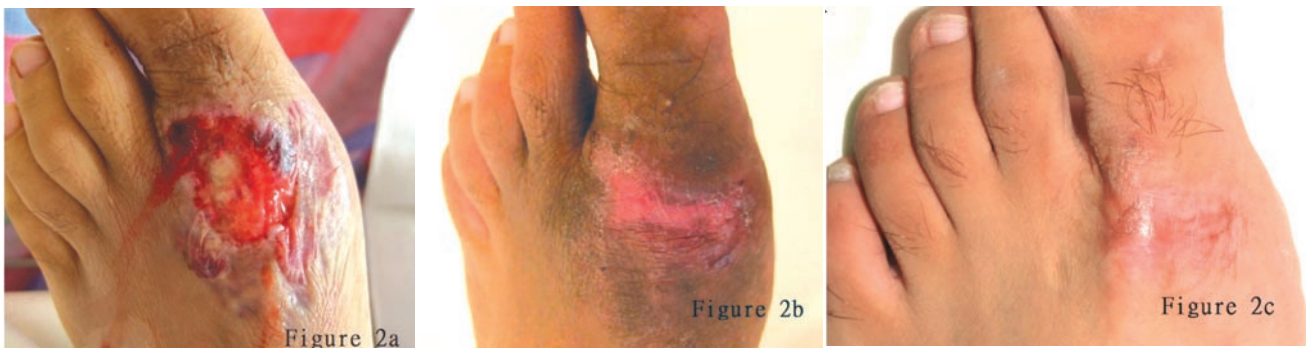

Figure 2 Pyoderma gangrenosum on the left foot.

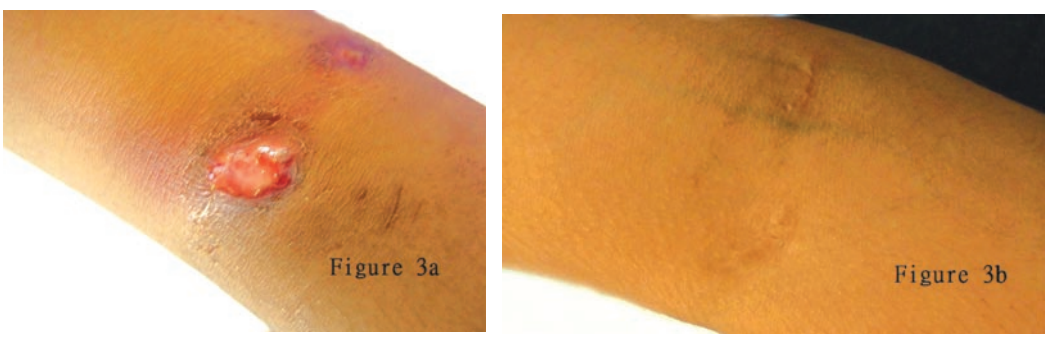

Figure 3 Pyoderma gangrenosum which developed secondary to venepuncture (Pathergic phenomenon) on the right cubital fossa.

Diagnosis

The diagnosis of PG is largely clinical, basing primarily on the presentation and course.[5,8] No laboratory parameters are pathognomonic. Although the appearance is dramatic, it is usually sterile as in our case. However, staphylococci and streptococci may be cultured as a result of colonisation and wound secondary infection.[8]

We did not perform skin biopsy because marked pathergy was observed even in the blood taking site. In clinical setting, the role of biopsy in the work-up of patients with PG is controversial. There is risk of superimposed pathergic response and the pathologic changes are usually not diagnostic. However, it may be of value to differentiate PG from infective, neoplastic and rheumatological ulcers of similar features.[5,8]

Management

Management of PG is challenging. The associated underlying conditions may not be as obvious as in our case and should be sought actively. Treatment targeting the underlying disease usually results in dramatic improvement or complete remission.[5]

In general, the goal is to reduce the inflammation so as to facilitate the wound healing and control the underlying disease if any. Topical treatment may be tried in those mild forms which are not associated with systemic disease.

Local measures like dressing, limb elevation and rest are usually practiced. Moist wound management with non-adhesive material is crucial. It helps to control exudation and improve auto-debridement. It also protects the surrounding skin and offers pain relief. Traumatisation during dressing changes should be cautiously avoided.[6,14]

Topical agents designed to alter the immune response like potent topical steroids, tacrolimus or 5-aminosalicylic acid may be beneficial. Other alternatives that may be useful in controlling the inflammation or promoting wound healing include benzoyl peroxide, disodium cromoglycate and nicotine. Intralesional triamcinolone diacetate twice weekly is likely to be the most effective topical treatment. However, care must be taken to avoid the systemic side effects from large doses. Intralesional ciclosporin has also proved beneficial in some cases.[7]

Although pain management is often overlooked, it is an important aspect of treatment. There is no single pharmacological regime which is universally effective. Hence, it is important to regularly monitor and document the level of pain. Three-step analgesic ladder from World Health Organization can be a useful framework in the management of ulcer pain.[15]

Systemic treatment is mandatory when there is widespread or rapidly progressive disease. Early and aggressive management can reduce morbidity significantly.[6] Our patient has rapidly progressing PG with acute severe ulcerative colitis. Systemic treatment is a must in addition to topical wound management.

Due to the relatively rare and sporadic occurrence, there are no prospective randomised controlled trials for the treatment of PG and only case series have been reported in the literature. No guidelines for the treatment are feasible and treatment is largely empirical with highly speculative mechanism of action. The treatment reported to be usually effective is systemic corticosteroids and ciclosporin. However, their use should be justified, taking into account of the potential risk.[7,15] Infection should also be considered and excluded before the use of immunosuppressant.

Systemic corticosteroids have been the most predictable and effective medication for PG. It hence remains the treatment of choice. It relieves the pain, halts the progression, initiates healing and prevents the development of new lesions.[5,7] It is especially useful when PG is associated with systemic illness like inflammatory bowel disease, as both disease processes can be tackled simultaneously.[16] Prednisolone (1-2 mg/kg) is widely used for initial therapy. The dosage can be tapered once control is achieved. Aggressive PG commonly requires the addition of one or more steroid-sparing agent to prevent disease exacerbation when corticosteroids are tapered. In cases unresponsive to oral corticosteroids, pulse methyprednisolone may be helpful (10-20 mg/kg once daily for 3-5 days).[16]

Ciclosporin, an inhibitor of T-lymphocyte activation, has been used in combination with corticosteroid in widespread PG. Most of the time, ciclosporin can be steroid sparing. Low doses (2-3 mg/kg/day) have been shown to be effective in the management of PG. Potential side effects include nephrotoxicity, hypertension, and opportunistic infection. During the therapy, blood pressure and creatinine levels should be closely monitored.[6,17]

Azathioprine is a commonly prescribed agent. Treatment is usually initiated with dosages of 1-2 mg/kg/day. Clinical response usually is observed after 6-8 weeks. Potential adverse reactions include myelosuppression, gastrointestinal intolerance, infection, hypersensitivity-like reactions and risk for malignancy.[16]

Sulfa drugs are considered to be drugs of second choice and are particular useful in milder forms of PG. Typical

doses range from 100-400 mg daily. Dapsone works by inhibition of neutrophil migration and reactive oxygen species production. It also has other anti-inflammatory activities. However, G6PD status should be checked beforehand. Laboratory testing is required to monitor for potential haematological toxicity including agranulocytosis and haemolysis early in the course of treatment. Folic acid supplement should be prescribed for all patients receiving dapsone to facilitate the replenishment of red blood cells. Dapsone is generally well tolerated but less common side effects like hepatotoxicity, hypersensitivity and peripheral neuropathy do occur.[16]

High dose human intravenous immunoglobulin has been shown to be effective as an adjuvant in case series of severe or refractory PG via its immunoregulatory effects. A total dose of 2 gram per kg is administered over three consecutive days.[18]

Mycophenolate mofetil shows success in a small number of case series. It has been used as monotherapy and in combination with ciclosporin. It is an inhibitor of purine synthesis, reducing the T and B lymphocytes proliferation. Common adverse effects include gastrointestinal or genitourinary symptoms. Leukopenia, anaemia, increased risk of infection and induction of malignant neoplasm are less common and dose related.[6,16,19]

Methotrexate has been reported to be beneficial but is not universally successful. Cyclophosphamide induced remissions in some patients but its significant side effects must be taken into account. Chlorambucil has been used in severe or resistant cases.[7]

In addition, systemic antibiotics such as minocycline or other tetracyclines, rifampicin, vancomycin and mezlocillin have been reported to be useful through their anti-inflammatory mechanism in combination with corticosteroids.[6,20] Especially, minocycline was reported to be useful, regardless of disease severity or underlying disease. Improvement usually happens in weeks. It possibly diminishes the chemotactic responsiveness of neutrophils through inhibition of neutrophil chemotactic factors. Side effects are rarely serious except the potential to raise intracranial pressure.[21]

Infliximab is a chimeric monoclonal antibody that targets the membrane bound precursor of tumour necrosis factor (TNF)-alpha. It prevents the binding of TNF-alpha to its receptor. It has been reported to be particular effective in those cases refractory to corticosteroid and ciclosporin. The onset of clinical response is fast and dramatic.[22] Recently, it is the first-line therapy for those refractory PG associated with concomitant inflammatory bowel disease. Potential adverse reactions include immediate hypersensitivity reactions as well as delayed hypersensitivity events. Patients are at risk for infection including reactivation of tuberculosis.[6-7,16,23]

Tacrolimus has also been tried systemically. It is a novel macrolide antibiotic with similar but much stronger immunosuppressive properties than ciclosporin (10-100 times more potent on gram-for-gram basis). Adverse reactions include neurotoxicity, nephrotoxicity, altered glucose metabolism, infection and malignancy.[16,21]

In the literature, the list of treatments tried is long. Various options and modalities have been reported. Obviously, the choice of which systemic medication to prescribe should be individualised taking into account the severity of the disease, concomitant systemic illness and the safety profile.[16]

Surgery can be an important trigger for PG. Acupuncture, venipuncture and biopsy are all reported to induce the disease as pathergy phenomenon. This is especially true during the acute phase of the disease and near the site of existing lesions. When surgery is unavoidable, the surgeon should be made aware of the risk. Incisions should be kept as short as possible and careful wound closure is important. Concomitant immunosuppression may be needed.[7]

PG often takes a prolonged disease course. In general, it is controllable with medical therapy. However, about 35% of patient will still experience relapsing PG.[13]

Conclusion

In our patient, his underlying disease was acute severe ulcerative colitis (Montreal classification) which can be life threatening.[2] The PG, at the same time, was rapidly progressive. We decided to use the cocktail of immunosuppresives (prednisolone), antimicrobial with anti-inflammatory properties (minocycline) and immune modulator (azathioprine). Azathioprine was prescribed in combination with systemic corticosteroid to achieve acute control, hoping to maintain disease remission when prednisolone was tapered.

We report this case aiming to alert paediatricians of this rare dermatosis. Although uncommon, a high clinical index of suspicion for early recognition is crucial. In typical case, diagnosis can be reached without biopsy. Patients could also be rescued from unnecessary surgical debridement or skin grafting if the diagnosis of PG is considered. Obviously, early institution of appropriate therapy can minimise tissue destruction and scarring.

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