

Pyoderma Gangrenosum Associated with Ulcerative Colitis

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SUMMARY We report the case of a 45-year old man with non-healing ulcers located on his chest, lumbal, sacral, retroauricular areas and forehead. Both clinical and histopathological examinations suggested pyoderma gangrenosum (PG). For six months the diagnosis of ulcerative colitis was established. PG in our patient was presented as a rapidly enlarging, painful ulcer with purple, undermined edges and a necrotic, haemorrhagic base. Initially, he was treated with a high dosage of peroral glucocorticosteroid, sulfasalazine, and systemic antibiotics, together with daily wound care. Ulceration partially regressed. Total colonoscopy showed pancolitis. When the dose of glucocorticosteroids was tapered down to 35 mg, new ulcerations on his right thigh and abdomen were formed. He also developed *E. coli* sepsis and flare up of bowel disease. Azathioprine, together with two pulse doses of glucocorticosteroids and antibiotics, were administered. He was scheduled for a total colectomy. The management of PG continues to be a therapeutic challenge.

KEY WORDS: pyoderma gangrenosum, ulcerative colitis, therapy

INTRODUCTION

Pyoderma gangrenosum (PG) is an idiopathic inflammatory disease of unknown etiology, frequently associated with an underlying systemic condition such as inflammatory bowel disease, immunologic disease or haematological malignancy (1,2). Its occurrence tends to parallel exacerbations of the underlying disease.

CASE REPORT

A 45-year-old male patient was suffering from ulcerative colitis when he suddenly developed small erythematous papules then pustules

together with fever and diarrhea. The diagnosis of ulcerative colitis was established for 6 months according to clinical, laboratory, radiological and endoscopic criteria. At that time, he was taking peroral glucocorticosteroid (60 mg prednisone) and sulfasalazine.

Skin ulcerations became larger, located on his chest, lumbal, sacral, left retroauricular region and on his forehead (Figs. 1 and 2). Ulcer borders were irregular, raised, boggy, undermined and very painful.



Figure 1. Multiple PG ulcerations with irregular, raised borders covered with yellow granulomatose tissue

A biopsy specimen from the wound margin showed dense nodular infiltrate of neutrophils extending through the deep dermis (Fig. 3). There was per follicular inflammation, leukocytoclastic vasculitis with fibrin in the wall of venules together with peri- and intra-vascular infiltration of neutrophils with nuclear dust. Tissue bacterial swabs showed *Staphylococcus epidermidis* in one ulceration, while others were sterile. Tissue swabs excluded fungal and mycobacterial infections.

Ulcerative colitis also flared up. A total colonoscopy showed pancolitis with ulcerations and inflammatory pseudopolyps indicating severely active and long-lasting disease.

The patient was initially treated with a high dose of peroral glucocorticosteroid (80 mg prednisone) orally, sulfasalazine, and systemic antibiotic together with daily wound care. Ulcers were gently cleaned by applying wet compresses containing normal saline and covered with moisture-retentive dressings to prolong drug activity and hasten the healing process. On the few smaller ulcers, located retroauricularly occlusive hydrocolloidal dressings were applied. Ulcerations became smaller and shallower; gastrointestinal (GI) symptoms were reduced.



Figure 2. PG ulceration on the left retroauricular region

The glucocorticosteroid dose was gradually tapered down, and at 35 mg, GI symptoms worsened again, presented with diarrhea and fever again. *E. coli* sepsis was diagnosed. Laboratory findings showed a high sedimentation rate, leucocytosis, a high level of C reactive protein concentrations and elevated liver function tests.

Within the following two days, new ulcerations appeared on the abdomen and right thigh. They were up to 15 cm in diameter, with purulent, partially (at the edge) covered by necrotic eschar and

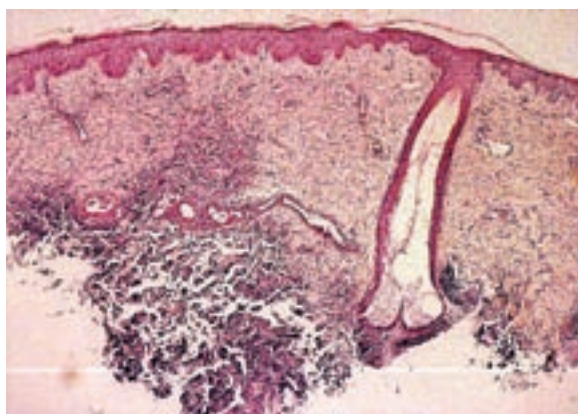


Figure 3. A biopsy specimen from the wound margin showed dense nodular infiltrate of neutrophils extending through the deep dermis. There is per follicular inflammation, leukocytoclastic vasculitis with fibrin in the wall of venules. Haematoxyllin-eosin stain;x25



Figure 4 and Figure 5. PG ulceration with purulent content, partially covered by necrotic eschar, with mild hemorrhagic exudates

mild hemorrhagic exudates (Figs. 4 and 5). Sigmoidoscopy showed multiple pseudopolyps and inflammation changes of bowel mucosa (Fig. 6). A biopsy of the polyp showed low-grade dysplasia, and he was scheduled for a colectomy. He received two pulse doses of methylprednisone i.v., with 100 mg azathioprine. Because of the sepsis, antibiotics were administered as well. A few weeks later, both the skin and GI symptoms improved (Fig. 7). He is now awaiting an operation.

DISCUSSION

Pyoderma gangrenosum was first described in 1930 by Brunsting and coworkers (3). It was originally thought to be a bacterial disease.

The etiology of PG remains unknown. Fifty percent of the cases of PG are associated with chronic disease, including ulcerative colitis and Crohn's disease, chronic active hepatitis, rheumatoid arthritis, seronegative arthritis, monoclonal gammopathy, diabetes or malignancies. The

other 50% of cases have no associated disease and are considered idiopathic (4,5). All ages may be affected, but PG predominantly occurs in the fourth and fifth decades of life. It affects both sexes, but there is a slight predominance in females. Children and adolescents may be affected as well (6). There are four main clinical variants of PG (ulcerative, pustular, bullous, and vegetative), but the ulcerative form is by far the most prevalent (6). An ulcer usually tends to occur on the lower extremities, trunk, and occasionally on the head and neck, and even on genitalia (6-8). Our patient developed ulcers on the abdominal wall and the

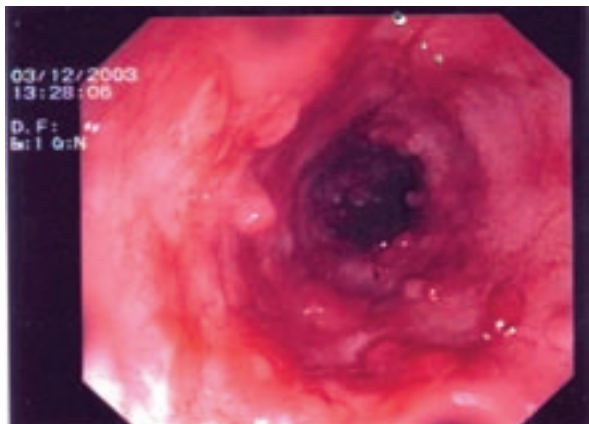


Figure 6. Colonoscopy. Ulceration and multiple inflammatory polyps of sigmoid colon



Figure 7. Cicatrix on the left retroauricular region



Figure 8. A few erosions and cicatricial tissue on the chest region

retroauricular and sternal regions. He later had an exacerbation, and he developed a large ulcer on his right upper leg.

Patients usually describe the initial lesion as a bite-like reaction, with a small, red papule or pustule changing into a larger ulcerative lesion with an undermined and violaceous edge. These ulcers may grow to be as large as 20 cm and may have satellite lesions and multiple ulcers associated with it. In our patient, primary lesions were pustules that rapidly became larger-forming big ulcers. Lesions often result from minor local trauma, which is a process known as pathergy (4). Pathergy is a term that describes ulcer formation that occurs at sites of minimal trauma. Ulcers are very painful, the borders are irregular, undermined, and usually heal with a cribriform scar (5).

No specific pathologic or laboratory finding exists, and the condition may be persistent even with a negative biopsy. The histopathology of PG is non-specific but is useful to exclude other ulcerative and neoplastic disease. Necrosis is characteristically present with neutrophils and fibrin in the superficial vessels, or thrombosis of small vessels. Often it is part of a mixed cellular neutrophilic infiltrate accompanied by lymphocytes, plasma cells, histiocytes and even giant cells, all of which may be distributed around follicles.

For PG diagnosis and treatment, a multidisciplinary approach including a dermatologist, gastroenterologist, pathologist, rheumatologist and podiatrist is often necessary. The treatment of PG is based on the nature and extent of the lesion, and includes therapy for underlying associated disease.

Local therapy is directed toward the relief of pain and the prevention of a secondary wound

infection. Dressings may consist of topical steroids or a hydrogel to promote moist wound healing. Wet-to-dry dressings, rest, limb elevation, potent topical corticosteroids, and intralesional injection are suitable for mild disease (4). If there is secondary infection, the use of topical or oral antibiotics may be appropriate before applying topical steroids.

Systemic corticosteroid therapy is usually needed for more severe disease. Prednisone is the most often used and fastest acting agent. Recurrence is possible after steroid therapy is discontinued. More severe and recurrent disease is treated with immunosuppressive medications, including mycophenolate mofetil (9) and cyclosporine A (10).

Other treatments include recombinant human granulocyte-macrophage colony-stimulating factor (11), plasmapheresis with cyclophosphamide (12), and intravenous human immunoglobulin (13). A novel approach of topical treatment is the use of 0.1% tacrolimus cream twice daily, which is a macrolide antibiotic with an immunosuppressive effect (14,15).

In refractory cases, intravenous pulsed steroids (methylprednisone) or cyclosporine may be beneficial (6). Diaminodiphenyl sulphone (Dapsone) may also be an effective adjunct (6,16-17). Davis *et al.* published a case where hyperbaric oxygen was used to promote healing prior to the application of a skin graft (18). One of the most intriguing new therapies for PG is infliximab. Infliximab is a monoclonal antibody with high affinity and specificity to TNF-alpha which neutralizes its biological activity (19).

Surgical therapy should be avoided because it may exacerbate the disease owing to pathergy (4,5,20). Aggressive debridement of PG wounds is usually contraindicated as well (20). Some patients with ulcerative colitis experience response to total colectomy (15).

The prognosis of PG is generally good. Recurrences may occur, however, and residual scarring is common. Death from PG is rare, but it may occur due to an associated disease or as the result of therapy.

CONCLUSION

The management of PG continues to be a therapeutic challenge. First line treatment is orally administered corticosteroids, sometimes combined with a steroid sparing agent. Early treatment with immunosuppressive drugs is essential to control

the disease and prevent permanent scarring. Lesions may either pursue an acute progressive course or a chronic course with slow extension. It is often difficult to achieve control of aggressive cases of pyoderma gangrenosum. Furthermore, patients recalcitrant to one or many medications are frequently reported. Concomitant disease, intolerance to a class of medications, and the patient's response to prior therapies can help guide a practitioner in choosing the optimal treatment of pyoderma gangrenosum.

References

1. Hickman JG, Lazarus GS. Pyoderma gangrenosum: a reappraisal of associated systemic diseases. *Br J Dermatol* 1980;102:235-7.
2. Holt PYA, Davis MG, Saunders KG, Nuki G. Pyoderma gangrenosum, clinical and laboratory findings in 15 patients with special reference to polyarthritis. *Medicine* 1980;59:114-33.
3. Brunsting LA, Goeckerman WH, O'Leary PA. Pyoderma gangrenosum: clinical and experimental observation in five cases occurring in adults. *Arch Dermatol* 1930;22:655.
4. Callen JP. Pyoderma gangrenosum. *Lancet* 1998;351:581-5.
5. Harris AJ, Regan P, Burge S. Early diagnosis of pyoderma gangrenosum is important to prevent disfigurement. *BMJ* 1998;316:52-3.
6. Crowson AN, Magro C, Mihm MC Jr. Pyoderma gangrenosum: a review. *J Clin Pathol* 2003;30:1-11.
7. Sau M, Hill NC. Pyoderma gangrenosum of the vulva. *Br J Obstet Gynaecol* 2001;108:1197-8.
8. Bennett CR, Brage ME, Mass DP. Pyoderma gangrenosum mimicking postoperative infection in the extremities: a report of two cases. *J Bone Joint Surg* 1999;81:1013-8.
9. Wollina U, Karamfilov T. Treatment of recalcitrant ulcers in pyoderma gangrenosum with mycophenolate mofetil and autologous keratinocyte transplantation on a hyaluronic acid matrix. *J Eur Acad Dermatol Venerol* 2000;14:187-90.
10. Matis WL, Ellis CN, Griffiths CE, Lazarus GS. Treatment of pyodermy gangrenosum with cyclosporine. *Arch Dermatol* 1992;128:1060-4.
11. Groves RW, Schmidt-Lucke JA. Recombinant human GM-CSF in the treatment of poorly healing wounds. *Adv Skin Wound Care* 2000;13:107-12.
12. Kaminska R, Ikaheimo R, Hollmen A. Plasma-pheresis and cyclophosphamide as successful treatments for pyoderma gangrenosum. *Clin Exp Dermatol* 1999;24:81-5.
13. Dirschka T, Kastner U, Behrens S, Altmeyer P. Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998;39:789-90.
14. Wu SJ, Tanphaichitr A, Ly M. Recent advances in dermatology. *Clin Podiatr Med Surg* 2002;19:65-78.
15. Petering H, Kiehl P, Breuer C, Kapp A, Werfel T. Pyoderma gangrenosum: successful topical therapy with tacrolimus (FK506). *Hautarzt* 2001;52:47-50.
16. Jackson JM, Callen JP. Pyoderma gangrenosum. *eMedicine J* 2003;1-14. Available at: <http://www.emedicine.com/DERM/topic367.htm>.
17. Chow RK, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996;34:1047-60.
18. Davis JC, Landen JM, Levine RA. Pyoderma gangrenosum skin grafting after preparation with hyperbaric oxygen. *Plastic Reconstr Surg* 1987;79:200-7.
19. Tan MH, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of pyoderma gangrenosum and psoriasis associated with Crohn's disease with anti-tumor necrosis factor (alpha) monoclonal antibody. *Arch Dermatol* 2001;137:930-3.
20. Spangler JG. Pyoderma gangrenosum in a patient with psoriatic arthritis. *J Am Board Fam Pract* 2001;40:457-61.