Pyoderma gangrenosum: An update

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ABSTRACT

Pyoderma gangrenosum (PG) is an uncommon, distinctive cutaneous ulceration which is usually idiopathic, but may be associated with many systemic disorders. The etiopathogenesis of PG is still not well understood. Clinically it is classified into ulcerative, pustular, bullous and vegetative types. A few atypical and rare variants have also been described. The diagnosis mainly depends on the recognition of evolving clinical features as investigations only assist in the diagnosis. In view of this a few criteria have been proposed for the diagnosis of PG. The treatment mainly consists of corticosteroids and immunosuppressive agents. A few new agents have also been tried in the management.

Key words: Corticosteroids, pyoderma gangrenosum, ulcerative

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare inflammatory disease of unknown etiology characterized by neutrophilic infiltration of the dermis and destruction of the tissue. [1] PG was first described by Brocq in 1916 as “phagedenisme geometrique” and later named by Brunsting et al. [2] The latter author considered PG to be the dissemination of a distant focus of infection (i.e., the bowel in ulcerative colitis or lungs in empyema). [3] Presently PG is considered a reactive inflammatory dermatosis and part of the spectrum of neutrophilic dermatosis. [4]

ETIOLOGY AND PATHOGENESIS

The precise etiopathogenesis of PG is not well understood. However immunological factors and neutrophil dysfunction can be considered to be involved in etiopathogenesis of PG. [5]

Immunological factors

The following immunological factors can be considered:
1. Frequent association of PG with autoimmune diseases.
2. Pathergy phenomenon indicating an abnormal response to an inciting stimuli such as trauma. [1]
3. Defective cell-mediated immune response in PG. [6]
4. Deposition of immunoglobulins in the dermal blood vessels. Monoclonal or polyclonal hyperglobulinemia may also be associated with PG. [3]

However, the immunological abnormalities associated with PG are not always consistently observed in all patients and it is unclear whether or not they are an epiphenomena. [3]

Neutrophil dysfunction

PG is considered part of the spectrum of the neutrophilic disease. Impaired phagocytosis by neutrophils has been suggested in the pathogenesis of PG. Neutrophil analysis in PG showed evidence of abnormal neutrophil trafficking and aberrant integrin oscillations. [4]
is a rare subset seen around enterostomy/colonostomy in patients with IBD. It is considered a pathergy phenomenon due to irritation to the peristomal skin caused by leakage of faecus or by the adhesive stomal appliance.[13]

**Genital involvement in PG** may be seen in association with ulcers elsewhere in the body. Vulvar, penile, and scrotal involvement has also been described as a solitary manifestation of PG.[14,17] When genital lesions are present Behcet’s disease has to be ruled out in addition to other causes of genital ulcers.[13] Genital and buttock PG present more in the infantile age group than in others. PG in association with HIV infection may show involvement of perineum complicated by secondary bacterial infection.[18]

**PG in infants** and children is rare (4% only).[19] However in our case series we had a higher percentage of cases in children. In children, the lesions are generalized and with involvement of genital areas. However, clinical appearance, location, and response to treatment resemble those of the classic lesions in
adults. The possible differences between adults and children are depicted in Table 1.

**Extracutaneous neutrophilic disease** refers to sterile neutrophilic infiltrates occurring in various internal organs. Pulmonary neutrophilic infiltrates are the most commonly reported extracutaneous sign.[3,20]

*Pyostomatitis vegetans* is considered as oral pustular PG characterized by a pustular, vegetative process of mucous membrane.[21] The oral lesions usually coincide with the active exacerbations in IBD (Table 2).[3]

The “pathergy,” first described by Blobner, refers to the localization of PG to sites of skin damaged by trauma, surgery or venepuncture.[22] It probably represents a localized, misdirected host-mediated effector cell response to cutaneous tissue antigenically changed by trauma in a patient with altered immune reactivity.[10] Pathergy is seen in nearly 25% of the patients with PG.[4] We have reported that pathergy is more common in PG associated with systemic disease.[2]

### Table 1: Differences between childhood and adult form of pyoderma gangrenosum

| Feature                  | Children | Adults          |
|--------------------------|----------|-----------------|
| Morphology of initial lesion | Pustules | Macules/papules |
| Site                     | Generalized | Legs           |
| Associated diseases      | Absent   | Present         |
| Pathergy test            | Absent   | Present         |
| Prognosis                | Good     | Variable        |

**Associated diseases**

Approximately 50% of patients with PG have an associated systemic disease. These diseases may precede, follow or occur simultaneously.[23] Depending upon the associated conditions PG was also be classified as follows:

- Parainflammatory (paraimmune) (associated with IBD, collagen vascular diseases, arthritis, etc)
The most common associations are IBD, arthritis, and hematologic diseases. PG associated with IBD is characterized by ulcerative or pustular PG. Oral and peristomal PG can also occur. PG in association with myeloproliferative diseases may present with bullous PG. In patients with HIV infection, perineum is the most common site of involvement and ulcers are often secondarily infected with bacterial organisms [Table 3].

Criteria for the diagnosis of pyoderma gangrenosum

Criteria for the diagnosis of pyoderma gangrenosum [19]

4. Malignancies - lymphomas, leukemia.
5. External tissue injury - insect bites, factitious panniculitis.
6. Other neutrophilic dermatoses - atypical Sweet’s syndrome, Behcet’s disease.
7. Drug reaction - pustular drug reaction, halogenoderma.

Treatment

The diagnosis mainly depends on recognition of the evolving clinical features and is only supported by histopathology.[6] The histopathologic changes depend on the type of the lesion being studied, the stage of the evolution of the lesion, and the site from which the biopsy specimen is obtained in a given lesion. The histopathologic distinction of PG from other ulcerative processes with dermal neutrophilia is challenging and at times impossible.[25] Massive neutrophilic infiltration (authors prefer to call it as “sea of neutrophils”), in the absence of vasculitis and granuloma formation, is typical of PG.[25] However it has been shown that PG lesions when associated with Crohn’s disease may contain granulomatous foci.[26,27] The histopathology of various morphologic types of PG is summarized in Table 5.

PG has to be differentiated from the following categories of diseases:
1. Vaso-occlusive and venous diseases.
2. Systemic vasculitis - Wegener’s granulomatosis, livedoid vasculitis, polyarteritis nodosa, etc.
3. Infections - subcutaneous mycoses, tuberculosis, syphilis, ecthyma gangrenosum.

Table 2: Clinical features of pyoderma gangrenosum

| Type       | Site             | Associated diseases | Pathergy | Prognosis | Morphology                                         | Treatment                                      |
|------------|------------------|---------------------|----------|-----------|----------------------------------------------------|-----------------------------------------------|
| Ulcerative | Lower extremities/trunk | IBD/arthritis       | Positive | Variable  | Tender, large ulceration with undermined border     | Aggressive systemic (immunosuppressive) therapy |
| Pustular   | Lower extremities/trunk/oral mucosa | IBD | Variable | Good      | Multiple sterile pustules surrounded by a halo       | Treatment of underlying disease               |
| Bullous    | Arms/face        | Myelogenous leukemia | Positive | Poor       | Rapidly evolving tender vesicles/bullae with central necrosis and erosions | Systemic immunosuppressive therapy            |
| Vegetative | Head and neck    | Nil                 | Absent   | Good       | Verrucous and ulcerative lesions                     | Topical/intralesional or less aggressive systemic therapy |

Table 3: Pyoderma gangrenosum (associated diseases)

| Para inflammatory | Hematologic | Paraneoplastic | Drug induced |
|-------------------|-------------|----------------|--------------|
| Inflammatory bowel disease (IBD) | Leukemia | Internal malignancy | Pegfilgastrin (granulocyte stimulating factor) |
| Arthritis (rheumatoid arthritis, ankylosing spondylitis) | Myeloproliferative diseases and myelodysplasia | Carcinoid tumor | Gefinib (epidermal growth factor receptor inhibitor) |
| Collagen vascular disease | Polycythemia vera | Propylthiouracil | Isotretinoin |
| Miscellaneous - HIV, Hidradinitis suppurrativa | Gammanopathies | Phenylalanine | |

Various topical and systemic agents used in the treatment of PG are enumerated in Table 6. The exhaustive list indicates that there is no single agent which is useful in all cases of PG.
Table 5: Histopathology of pyoderma gangrenosum

| Clinical types     | Histopathology                                                                 |
|--------------------|-------------------------------------------------------------------------------|
| Ulcerative         | Edema, neutrophilia, secondary lymphocytic vasculitis                          |
| Bullous            | Epidermal necrosis with neutrophilia, subepidermal bulla                       |
| Pustular           | Epidermal and dermal neutrophilia                                              |
| Vegetative         | Neutrophilic and eosinophilic and histiocytic mixed infiltrate, intra- and subepidermal granuloma formation |

Table 6: Treatment of pyoderma gangrenosum

| Topical agents                  | Cyclosporine                  |
|---------------------------------|-------------------------------|
| Corticosteroids                 | 10% 5 – aminosalicylic acid   |
| Tacrolimus (0.5%)               | Sodium cromoglycate (2%)      |
| 2.5% Benzyol peroxide           | Granulocyte macrophage colony stimulating factor |
| Nitrogen mustand (20%)          | Hyperbaric oxygen             |
|                                  | Phenytoin sodium 2%           |
|                                 | Bectolathasone inhaler spray  |
| Intralesional agents            | Nicotine                      |
| Triamcinolone acetonide         | Cyclosporine                  |

Systemic agents

1. Immunosuppressive agents
   - Corticosteroids → oral
   - Pulse therapy
   - Tacrolimus
   - Cyclosporine
   - Azathioprine
   - Cyclophosphamide
   - Methotrexate
   - Chlorambucil
   - Mycophenolate mofetil
   - Cytosine arabinoside
   - Daunorubicin
   - Melphalan

   Antimicrobial agents:
   - Sulfasalazine
   - Sulfapyridine
   - Sulfamethoxy pyridazine
   - Dapsone
   - Rifampicin
   - Clofazimine
   - Vancomycin
   - Mezlocillin
   - Minocycline

Biologic agents:
- Infliximab
- Alefacect
- Adalimumab
- Etalizumab
- Etenerecept
- Antiinflammatory:
  - Thalidomide
  - Mesalazine
  - Colchicine
  - Heparin
  - Potassium iodide
  - Trierygium willfordii multiglycoside (TWG) (Chinese herb)
  - Isotretinoin

Other immunomodilators:
- Intravenous immunoglobulin
- Interferon
- Granulocyte apheresis

With the exception of the study by Brooklyn et al., there are no placebo-controlled trials in the treatment of PG. This may be because of rarity of PG and ethical consideration involved in giving a placebo to a patient with PG.[29]

Local therapy

Local therapy is an important adjunct to systemic therapy and may provide relief from symptoms. As most of the ulcers show heavy exudates, foam/laminate dressings are recommended. In the case of sloughy or purulent ulcers wet compresses with saline and alginite dressings are useful.[7] Aggressive surgical debridement or skin grafting is discouraged because of the
risk of a pathergic response. Although some topical agents such as tacrolimus, potent corticosteroids, and cyclosporine have reported efficacy, evidence from large clinical trials is lacking.[29,30] Applications of beclomethasone inhaler 4 puffs to the peristomal PG have been reported to be successful.[31] Phenytoin sodium 2% solution has also been reported to be beneficial.[32] Hyperbaric oxygen therapy is thought to benefit PG elevating oxygen tension in the ulcers either through the greater arterial oxygen supplied to the capillary bed or through the local delivery of oxygen to the ulcer surface.[33] Skin grafting or microvascular flap grafting may be successful in nonprogressive disease or a systemic steroid cover is given. Cultured keratinocyte autografts and allografts have also been reported to be useful in some cases [Table 6].[30]

**Systemic therapy**

Systemic corticosteroids have been the most predictable and effective treatment of acute, rapidly progressive form of the disease. High doses of prednisolone or pulse therapy with suprapharmacologic doses of methylprednisolone/dexamethasone may have to be used in resistant disease.[3,30] Among the immunosuppressive agents cyclosporine which does not cause significant myelosuppression has proved to be a useful substitute therapy for PG resistant to steroid treatment.[28] Sulfa drugs may be used either alone or as a steroid sparing agent to maintain improvement in PG.[29]

More recently, tumor necrosis factor – alpha (TNF-alpha) blockers and other injectable biologics have been demonstrated to be successful.[29] Infliximab (5 mg/kg/week intravenously at weeks 0, 2, 6 and at every 6-8 weeks), adalimumab (40 mg subcutaneously weekly), all seem to be effective in PG –especially in association with IBD.[34] Infliximab is the only biologic reported to be efficacious in a randomized double blind placebo control trial.[29] Adalimumab has also been reported to be successful in recalcitrant PG with comparable efficacy to infliximab.[26] Two of the patients who showed recurrence also responded to adalimumab. Biologics like efalizumab and alefacept have also been used successfully in the management of PG.[30] Even though isotretinoin is used successfully in the treatment of superficial PG, it has also been reported to cause PG.[8,36]

The various systemic agents used in the treatment of PG are listed in Table 6. We have presented an algorithm for the treatment of PG [Figure 6].

**CONCLUSION**

Thus, although PG is clinically characteristic, it remains an enigma with regard to its etiopathogenesis. There are various clinical and histological variants of the disease. Criteria have been proposed to diagnose PG. The various therapeutic agents including biologics have been used in the management of the disease.

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**Figure 6:** Suggested treatment algorithm for pyoderma gangrenosum
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