***no patient handout*

Pyoderma gangrenosum

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Synopsis

Pyoderma gangrenosum (PG) is an inflammatory, noninfectious, ulcerative neutrophilic skin disease of uncertain etiology commonly misdiagnosed as an aggressive skin infection. Pustules form and give way to ulcers with a necrotic, undermined margin. PG can affect any age and take on a number of differing clinical presentations. PG can have either an acute or chronic course and result in extensive scarring (which can be keloidal or have dyspigmentation, especially in patients with darker skin types). There is no predilection for sex or any population. The disease occurs most often in middle-aged adults.

The two primary variants are a classic ulcerative form, which often involves the lower extremities, and a vesicobullous form, which is more superficial and tends to occur on the upper extremities, including hands. Fever, toxicity, and pain can be associated with the onset of PG. Rarely, PG can involve the eyes as well. Extracutaneous manifestations may take the form of sterile neutrophilic abscesses, such as in the lungs, heart, gastrointestinal tract, liver, eyes, central nervous system, and lymphatic tissue.

Though the exact cause is unknown, neutrophil dysfunction, inflammation, and genetics are all thought to play a role. Additionally, PG has associations with a number of systemic illnesses. In about 50% of cases, there is an association between PG and systemic diseases such as **ulcerative colitis**, **Crohn disease**, **arthritis**, **myeloma**, leukemia, **monoclonal gammopathy**, **granulomatosis with polyangiitis** (formerly known as Wegener granulomatosis), collagen vascular disease, **metabolic syndrome**, and **Behçet disease**, among other disorders. Surgery by itself can be a precipitating cause. **Levamisole-contaminated cocaine** has been associated with PG lesions ranging from vesicopustules to bullae to larger ulcers; most patients demonstrated positivity for antiphospholipid or anticardiolipin antibodies.

PG tends to be self-limited. First-line therapies are widely accepted, while alternative therapeutic recommendations are largely based on anecdotal evidence. Surgical intervention is a common exacerbating factor because PG demonstrates pathergy, a phenomenon by which skin trauma can lead to worsening disease.

Codes

ICD10CM:
L88 – Pyoderma gangrenosum

SNOMEDCT:
74578003 – Pyoderma gangrenosum

Look For

PG typically begins as an extremely painful solitary nodule or deep-seated pustule that ruptures and forms a shaggy ulcer. Often, especially in patients with inflammatory bowel disease (IBD), there are pustules that do not progress to ulcerative lesions. The border of the ulcer has a deep violaceous or dusky color and is usually undermined. The ulcer extends peripherally with a bright erythematous or violaceous halo. Necrosis is a common feature. As the ulcer progresses, a purulent coating commonly forms over the center of the ulcer. The ulcer may become secondarily infected and have a foul odor.

PG typically occurs on the extremities. PG may also occur around a stoma (peristomal PG). More than one active ulcer may be seen.

There are four main subtypes of PG:

- Ulcerative – Painful ulcer with purulent base and erythematous undermined border. This is the classic form of PG.
- Pustular – Discrete pustules with surrounding erythema, most often seen in patients with IBD.
- Bullous (also known as atypical PG) – Rapidly evolving vesicles that coalesce into bullae on an erythematous base. Lesions can evolve rapidly and there can be central necrosis. This subtype is most commonly seen in patients with an associated lymphoproliferative disorder.
- Vegetative – Superficial ulcerations without a purulent base or undermined borders.

Rarely, PG can present as a suppurative panniculitis. All variants heal with thin, atrophic, or classically cribriform scars. Patients with darker skin may heal with hypo- or hyperpigmented scars.

Ocular PG presents with ulcerative lesions involving the scleral, corneal, orbital, and periorbital tissue, with a predilection for patients older than 60 years. The disease is typically unilateral. Associated findings include peripheral ulcerative keratitis, eye redness, impaired visual acuity, and lagophthalmos (impaired ability to close eyelids completely).

PG may also present as a component of genetic conditions such as PAPA syndrome (pyogenic arthritis, PG, and acne), PASH syndrome (PG, acne, hidradenitis suppurativa), and PAPASH syndrome (pyogenic arthritis, PG, acne, hidradenitis suppurativa).

Oral aphthae, ulcerative lesions of the oral mucosa (pyostomatitis vegetans), and ulcerative lesions of the vulva and eyes may also be seen.

Diagnostic Pearls

Frequently, PG is a diagnosis of exclusion, and other more common causes of ulcers including vascular disease and infectious diseases should be carefully considered. There are diagnostic criteria under study. The past or present history or the presence of IBD may be suggestive of PG

but should not limit a full diagnostic workup.

The characteristic ulcer edge is undermined, and the base can be deep and is usually purulent. PG shares with Behçet disease and Sweet syndrome the occurrence of pathergy. Pathergy is the invocation of lesions by trauma to the skin such as a needle stick, biopsy procedure, or even insect bites. Therefore, it is **not** recommended to debride a PG ulcer because this will only result in increasing its size.

Differential Diagnosis & Pitfalls

Ulcers:

- Infection – As many infectious processes can cause a similar picture (eg, progressive bacterial synergistic gangrene, **North American blastomycosis**, other deep fungal infections, **amebiasis**, **sporotrichosis**, **atypical mycobacterial infection**), pyoderma gangrenosum is a diagnosis of exclusion. If a patient has traveled to tropical countries within the last 6 months, diagnoses such as leishmaniasis (**Old World** and **New World**), tropical ulcer, and **Buruli ulcer** must be considered.
- **Calciphylaxis** – Rapidly progressive, can be associated with eschars.
- **Chancroid** – Usually present around genital skin.
- **Eosinophilic granulomatosis with polyangiitis** (Churg-Strauss syndrome)
- **Herpes simplex virus** (HSV) – Usually grouped, punched-out erosions.
- **Ecthyma**
- **Ecthyma gangrenosum**
- **Squamous cell carcinoma** – Associated with keratotic plaques.
- **Lymphoma**
- **Venous** or **arterial ulcerations**
- **Granulomatosis with polyangiitis**
- Traumatic ulceration
- **Necrobiosis lipoidica** – Usually associated with atrophic plaques.
- **Tertiary syphilis**
- **Factitial ulcer** – Sharp geometric borders.
- **Factitial panniculitis**

Pustules / nodules:

- **Cellulitis**
- **Folliculitis**
- **Furuncle**
- **Insect** or **spider bite**
- **Sporotrichosis**
- ***Mycobacterium marinum* infection**
- Impetigo (**bullous**, **non-bullous**)
- **Panniculitis**
- **Sweet syndrome**
- **Bromoderma**

Pyostomatitis vegetans:

- **Aphthous stomatitis**

The differential diagnosis for an immunocompromised patient also includes:

- Chronic **HSV**
- Ulcerative **Kaposi sarcoma**

Ocular PG:

- Cellulitis (**orbital**, **preseptal**)
- **Endophthalmitis**
- **Abscess**
- **Seborrheic keratosis**
- **Stye**
- **Chalazion**

- **Granulomatosis with polyangiitis**
- **Basal cell carcinoma**
- **Squamous cell carcinoma** (SCC) (see also **corneoconjunctival SCC**)

Best Tests

Skin biopsy with culture for bacteria, atypical mycobacteria and fungi should be performed to rule out infectious etiologies. *Leishmania* culture and viral studies (swab for direct fluorescent antibody and viral culture) should be considered when the index of suspicion is high for these infectious causes. It is important to note that secondary infections in PG ulcers may lead to positive bacterial cultures, despite the fact that this infection is not the primary cause of the ulcers. Histopathology typically reveals a dense neutrophilic skin infiltrate, necrosis, and hemorrhage. Leukocytoclastic vasculitis may be observed in some biopsy specimens.

Testing should be undertaken to rule out similar or associated disorders. Routine investigations to evaluate for systemic disease may include the following:

- CBC +/- peripheral blood smear
- Serum electrolytes
- Liver function tests
- Urinalysis
- Antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), antiphospholipid antibody, and rheumatoid factor
- Serum and/or urine protein electrophoresis

Frequently, PG is a diagnosis of exclusion, and other more common causes of ulcers including vascular disease and infectious diseases should be carefully considered. The past or present history or the presence of IBD may be suggestive of PG but should not limit a full diagnostic workup.

Management Pearls

The choice of wound care dressing depends on the appearance of the ulcer, including the amount of associated exudate and necrosis. Consider a consultation with a wound care nurse or center.

The IBD that may be associated with PG can be subtle and requires a full evaluation, even in the absence of signs and symptoms. Referral to a gastroenterologist is indicated for possible endoscopy and management. The lesions of PG respond to treatment of underlying rheumatoid arthritis or IBD. Improvement of the underlying inflammatory disease may clear or make treatment of the PG easier.

Surgical therapy and elective surgeries should be avoided, if possible. Debridement should be avoided. If surgical therapy is required, it should be performed only in conjunction with immunosuppressive therapy. Autologous skin grafts should be avoided due to the risk of inducing PG at the donor sites.

Patients with more deeply pigmented skin may heal with significant hypo- or hyperpigmentation associated with scarring.

Ocular PG is treated with corticosteroids, followed by surgical reconstruction if necessary after disease stabilization. PG involving the eye or orbit should be treated aggressively, as the lesions carry a high risk for recurrence.

Other consultants may be needed: ophthalmologist, rheumatologist, oncologist, general, or plastic surgeon. Evaluate on a case-by-case basis.

Therapy

Effective treatment of any underlying medical condition will often ameliorate the lesions of PG. Referral to dermatology for management is often indicated for multiple lesions or widespread disease.

Systemic corticosteroids are the mainstay of therapy, as corticosteroids can arrest the rapid enlargement of the ulcers of PG.

First-line options include:

- Prednisone 0.5-2 mg/kg p.o. divided 2-4 times every 24 hours; taper over weeks to months as symptoms resolve, or
- Methylprednisolone 0.5-1 mg/kg every 24 hours, or
- Methylprednisolone pulse dosing 1 g every 24 hours for 1-5 days (requires close inpatient monitoring), or
- Cyclosporine-A 5 mg/kg every 24 hours divided twice daily (often induces a rapid response and marked improvement in pain), or
- Combination of systemic steroids PLUS cyclosporine at the doses described above is also considered a good first-line therapy.

For mild disease, first-line agents include:

- Intralesional corticosteroids, eg, triamcinolone acetonide 10 mg/mL, or
- High-potency topical corticosteroids, eg, clobetasol propionate cream 0.05% (not usually effective as stand-alone agents but can be used under occlusion to treat early lesions), or

- Topical tacrolimus (0.1% ointment), especially for peristomal PG.

Alternate therapies include tumor necrosis factor-alpha inhibitors (prior exposure to tuberculosis should be measured by a PPD before beginning these therapies):

- Infliximab may be used at 5 mg/kg and is infused at weeks 0, 2, 6, and every 8 weeks after that or every 2 weeks. Due to common infusion reactions, systemic steroids (100 mg methylprednisolone IV) are recommended to be given concurrently. This therapy may be combined with oral steroids or other immunosuppressants such as methotrexate or azathioprine.
- Adalimumab has also been used at 40 mg weekly, 40 mg monthly, 40 mg twice monthly, 80 mg weekly for 2 weeks followed by 40 mg per week, and other regimens have been shown to result in ulcer healing. The evidence supporting the use of adalimumab is not as strong as that for infliximab and is mostly from individuals with concomitant IBD or rheumatoid arthritis.
- Etanercept has been used as well at 50 mg given at home subcutaneously twice weekly, but there is far less supportive evidence for this medication than infliximab.

Alternate therapies also include:

- Mycophenolate mofetil 1.25-3.0 g/day has been used, generally in combination with other agents such as prednisone or cyclosporine.
- Dapsone 200-400 mg every 24 hours may be combined with systemic steroids in patients with normal glucose-6-phosphate dehydrogenase levels. CBC should be carefully monitored.
- Minocycline 100 mg every 12 hours, usually as an adjunct to systemic steroids.
- Sulfasalazine 0.5-2 g every 6 hours.
- Thalidomide 200-400 mg every 24 hours (teratogenic, neuropathy side effects).
- Clofazimine 300-400 mg every 24 hours (side effects can include pigmentary changes).
- Tacrolimus (FK506) 0.1 mg/kg every 24 hours.
- Methotrexate 2.5-25 mg p.o. or IM weekly.
- Intravenous immunoglobulin (IVIG) 1.5-2.0 g/kg IV monthly, generally as adjuvant therapy with systemic corticosteroids or immunosuppressants.

- There is emerging evidence for the use of canakinumab 150 mg subcutaneous injection once with or without a second dose 2 weeks later. However, to date the only evidence for these therapies is from small case series.

Ocular PG:
While there is no standard therapy, systemic corticosteroid is the mainstay of treatment. Alternative immunomodulatory agents, such as cyclosporine, dapsone, and azathioprine, may be tried for maintenance therapy. Topical corticosteroid preparation may be helpful. Adjuvant reconstructive surgery is performed only in stabilized disease due to risk of pathergy.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
adalimumab	1
Anthelmintic	1
Antimetabolite	1
azacitidine	1
cocaine	1
ipilimumab	1
Isotretinoin	1
levamisole	1

Medication	Citations
Retinoid	1
rituximab	1
sunitinib	3