Pyoderma Gangrenosum Diagnosis, Differential Diagnosis and Management

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Learning Objectives

• Following this lecture, the attendee will be able to:
  – Effectively diagnose pyoderma gangrenosum
  – Differentiate pyoderma gangrenosum from other causes of cutaneous ulceration
  – Develop an algorithm for effective management of pyoderma gangrenosum
Pyoderma Gangrenosum

- PG is a rare, painful ulcerating condition associated with a variety of co-morbid conditions in roughly 50-60% of patients including IBD, arthritis & hematologic diseases
- Several clinical variants – classic, peristomal, atypical
- PG is a diagnosis of exclusion
- Neutrophilic infiltrates may occur in other organs
- There are multiple treatments, but few have high levels of evidence documenting their efficacy
## PG Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical features</th>
<th>Location</th>
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<tbody>
<tr>
<td>Ulcerative (classic)</td>
<td>Ulcer, undermined violaceous border, purulent base, cribriform scarring</td>
<td>Trunk, extremities</td>
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<tr>
<td>Bullous (atypical)</td>
<td>Bullous → superficial ulcers Hematologic malignancy</td>
<td>Arms, face</td>
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<td>Pustular</td>
<td>Pustules and erosions Inflammatory bowel disease</td>
<td>Same as ulcerative</td>
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<td>Vegetative</td>
<td>Superficial, localized vegetative plaques, ulcers</td>
<td>Head, neck</td>
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<td>Post-surgical</td>
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Clinical features suggestive of PG

- Site: legs or peristomal location
- Presence of systemic disease (e.g. IBD, arthritis, hematologic)
- Presence of pathergy
- Pustular lesions at onset of lesion
- Formation of purulent discharge
- Undermined borders
- Crater-like holes/Cribriform scarring
Diagnostic criteria suggested by Su, et al

**MAJOR (must have both)**
1) Rapid progression of painful ulcer, typically with undermined border
2) Exclusion of other diagnoses

**MINOR (must have 2)**
1) History of pathergy or clinically evident cribriform scarring
2) Associated systemic disease (IBD, arthritis, malignancy, gammopathy)
3) Histologic findings (sterile dermal neutrophilia)
4) Treatment response (rapid to systemic steroids)

• 1 major and 8 minor criteria were identified
• Major criterion – biopsy from the edge revealing a neutrophilic infiltrate

• Minor Criteria
  1. Exclusion of infection
  2. Pathergy
  3. h/o IBD or arthritis
  4. h/o papule, pustule developing into an ulcer w/i 4 days
  5. Peripheral erythema, undermined border & tenderness
  6. Multiple ulcers w at least 1 on the leg
  7. Cribriform scarring
  8. Decreased ulcer size w/i 1-mo of therapy
• 4 Delphi rounds were conducted to develop criteria
• The criteria were then validated using 113 case reports of PG or mimickers published in the literature
• The presence of 4 minor criteria resulted in 86% sensitivity and 90% specificity
Figure 1. Diagnostic Criteria for Classic Ulcerative Pyoderma Gangrenosum

Diagnostic criteria for classic ulcerative pyoderma gangrenosum

- Biopsy of ulcer edge demonstrating a neutrophilic infiltrate
  - Yes
  - Consider rebiopsy if ulcer does not resolve or if patient develops a new lesion

- Histology
  - Exclusion of infection

- History
  - Pathergy (ulcer occurring at sites of trauma)
  - Personal history of inflammatory bowel disease or inflammatory arthritis
  - History of papule, pustule, or vesicle that rapidly ulcerated

- Clinical examination (or photographic evidence)
  - Peripheral erythema, undermining border, and tenderness at site of ulceration
  - Multiple ulcerations (at least 1 occurring on an anterior lower leg)
  - Cribriform or “wrinkled paper” scar(s) at sites of healed ulcers

- Treatment
  - Decrease in ulcer size within 1 mo of initiating immunosuppressive medication(s)
The PARACELSSUS score: A novel diagnostic tool for pyoderma gangrenosum

- Rapidly Progressing disease
- Absence of relevant DDx
- Reddish-violaceous border
- Alleviation by immunosuppressive therapy
- Characteristic bizarre border shape
- Extreme pain (>4 on VAS)
- Localization of lesion at site of trauma (pathergy)
- Suppurative inflammatory on biopsy
- Undermined wound border
- Systemic disease association

• Comparison of clinical history and photos from 60 pts. with PG v. 50 with venous leg ulcers using 10 criteria
• 3 major (3 points each), 3 minor (2 points each) and 4 additional criteria (1 point each)
• A score of 10 or more was effective in differentiating PG from VLE
Review of 240 patients with a presumed diagnosis of PG
49 had a different diagnosis
- Vasculopathy – livedoid vasculitis, APS, venous ulceration, etc.
- Vasculitis – WG, PAN, LCV, Cryo-assoc.
- Malignancy – lymphoma/leukemia
- Infection – deep fungal, Tb, HSV, etc.
- Miscellaneous – NLD, Crohn’s, hydroxyurea-induced, spider bite

» NEJM 2002; 347: 1412-8
Infection
- Bacterial infection (eg, syphilitic gumma)
- Mycobacterial infection
- Fungal infection
- Parasitic infection, (eg, cutaneous amebiasis)
- Viral infection (eg, chronic ulcerative herpes simplex)

Sweet syndrome

Insect bite
- Brown recluse spider bite

Malignancy
- Squamous cell carcinoma
- Basal cell carcinoma
- Cutaneous T-cell lymphoma

Halogenodermia
- Iododerma
- Bromoderma

Factitial ulceration
- Ulcerative necrobiosis lipoidica diabetica

Vascular disease
- Venous or arterial insufficiency
- Antiphospholipid antibody-associated occlusive disease
- Thrombophlebitis with gangrene

Syndrome with vasculitis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Behçet disease
- Wegener granulomatosis
Physical Examination

Histopathologic Evaluation

Evaluation for Systemic Manifestations and Associated Conditions
- complete physical examination, laboratory and diagnostic analyses
- consider bone density studies

Treatment

Inflammatory Stage
- Oral prednisone, begin 1 mg/kg/day*
- +/- Non-immunosuppressive systemic agents
- +/- Immunosuppressive agents

Wound Healing Stage
- Local wound care measures
- Gradient support hose
- Optimize treatment of “microvascular” diseases

* (consider calcium and vitamin D and/or etidronate)

Close monitoring until stabilized
- Addition or change of therapeutic agents according to severity of disease

Slow taper of medications
**Severe** = multiple ulcers, single ulcer equal to or greater than 12 cm, or involvement of the face.

**Celcipt** or another nonsteroidal medication

**Cyclosporine can be combined with prednisona and/or mycophenolate to manage severe cases. IVIG is also a compatible agent. Biologics have**

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<th>Legend</th>
<th>Response</th>
<th>Maintenance therapy</th>
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Start initial therapy, cyclosporine (2.5-4 mg/kg/day) or prednisone (0.5-1 mg/kg/day).

3 weeks after starting biologic, titrate down prednisone or cyclosporine.

Increase frequency of biologic and/or add compatible agent.

Continue biologic, consider transitioning patient to a more cost effective alternative for maintenance therapy.

Reassess wound - if ulcer lacks a surrounding inflammatory border -> maximize wound care.

If inflammatory border is present

1) Consider switching to another biologic
2) Consider increasing or changing the non-biologic therapy.

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* Acta Derm Venereol 2015
Genetic abnormalities in patients with PG might direct therapy

- Protein Tyrosine Phosphatase Nonreceptor Type 6 (*PTPN6/Shp1*) (Am J Pathol 2011; 178: 1434)
- E250K mutation in CD2BP1 gene (PAPA patient) (Clin Exp Rheumatol 2012:452)
- A230T & E250Q in the threonine phosphatase-interacting protein 1 (Anakinra might be useful) (Inflamm Bowel Dis 2011;17: e41)
- Janus kinase 2 (JAK2V617F) mutation (Myelofibrosis patient) (Clin Exp Dermatol. 2013 Jan;38(1):44-6.) (ruxolitinib might be used)
- PSTPIP1 Mutation (PAPA patient) (Canakinumab was used) (JAMA Dermatol 2013; 149(2):209-215)
Treatment of pyoderma gangrenosum: retrospective multicentre analysis of 121 patients
Future therapies?

- Canukinumab - NCT01302795 – completed report in the British J. Dermatol
- Xilonix - NCT01965613 – completed no reports of results
- Gevokizumab - NCT01882504 – studies halted
- Secukinumab – NCT02733094 – Recruiting (Germany)
- Ixekizumab - NCT03137160 recruiting
- Etrasimod - NCT03072953 – recruiting (Australia)

http://clinicaltrials.gov/ct2/results?term=pyoderma+gangrenosum&Search=Search
Conclusions

• PG is a diagnosis of exclusion
• Associated diseases include IBD, RA and other arthritides, hematologic malignancy
• Neutrophilic infiltrates may affect other organs
• Multiple treatments are effective