Pyoderma Gangrenosum Diagnosis, Differential Diagnosis and Management

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Disclosure (previous 12 months)

• Consultant – Amgen, Lilly, Argenx

• Speakers Bureau - Biogen/IDEC (Discussion of Drug Eruptions in patients treated with an approved drug for MS)

• Equity Holdings (Personal/Spouse): Celgene; Pfizer; 3M; Johnson and Johnson; Merck; Abbott Laboratories; AbbVie; Procter and Gamble; CVS; Walgreens; Allergan; Amgen

• None of the above relationships are relevant to my presentation

• I will discuss “off-label” uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.
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%
- Variants – classical, atypical, peristomal, mucosal
- PG is a diagnosis of exclusion
- Associations – IBD, arthritis, hematologic diseases, other
- Neutrophilic infiltrates may occur in other organs
## PG Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical features</th>
<th>Location</th>
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</thead>
<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 $\rightarrow$ superficial ulcers</td>
<td>Arms, face</td>
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<td></td>
<td>Hematologic malignancy</td>
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<tr>
<td>Pustular</td>
<td>Pustules and erosions, Inflammatory bowel disease</td>
<td>Same as ulcerative</td>
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<tr>
<td>Vegetative</td>
<td>Superficial, localized vegetative plaques, ulcers</td>
<td>Head, neck</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 cribiform scarring
2) Associated systemic disease (IBD, arthritis, malignancy, gammopathy)
3) Histologic findings (sterile dermal neutrophilia)
4) Treatment response (rapid to systemic steroids)

• 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
<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Infection</td>
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<tr>
<td>Bacterial infection (eg, syphilitic gumma)</td>
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<tr>
<td>Mycobacterial infection</td>
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<td>Fungal infection</td>
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<td>Parasitic infection, (eg, cutaneous amebiasis)</td>
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<tr>
<td>Viral infection (eg, chronic ulcerative herpes simplex)</td>
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<td>Sweet syndrome</td>
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<tr>
<td>Insect bite</td>
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<td>Brown recluse spider bite</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<tr>
<td>Basal cell carcinoma</td>
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<tr>
<td>Cutaneous T-cell lymphoma</td>
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<tr>
<td>Halogenoderma</td>
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<tr>
<td>Iododerma</td>
</tr>
<tr>
<td>Bromoderma</td>
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<tr>
<td>Factitial ulceration</td>
</tr>
<tr>
<td>Ulcerative necrobiosis lipoidica diabeticorum</td>
</tr>
<tr>
<td>Vascular disease</td>
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<tr>
<td>Venous or arterial insufficiency</td>
</tr>
<tr>
<td>Antiphospholipid antibody-associated occlusive disease</td>
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<tr>
<td>Thrombophlebitis with gangrene</td>
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<tr>
<td>Syndrome with vasculitis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Behçet disease</td>
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<td>Wegener granulomatosis</td>
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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* → Monotherapy → Complete → Yes

Start initial therapy, cyclosporine (2.5-4 mg/kg/day) or prednisone (0.5-1 mg/kg/day)

No → Consider biologics

Add compatible steroid sparing agent**

No → Complete

Yes → Titrated down prednisone

Titrated down cyclosporine

Yes → Complete

Continue combination therapy at lowest dose to maintain remission. If remission is sustained for several months, consider switching to monotherapy.

No → Complete

Reassess wound - if inflammatory border still present, reconsider biologics

Legend:
- Yellow: Response
- Pink: Maintenance therapy

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

No → Complete

Increase frequency of biologic and/or add compatible agent***

Yes → Complete

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

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

** Ceilcept or another nonsteroidal medication

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

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

British Journal of Dermatology (2016) 175, pp1070–1072
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