Pyoderma Gangrenosum: A Practical Approach
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Pyoderma Gangrenosum (PG): A Practical Approach

• In this session we will:
  – Discuss the evaluation of leg ulcers that are consistent with PG.
  – Discuss the issues involved in treating leg ulcerations, including PG.
  – Discuss a therapeutic ladder for treatment.
DDX of non-healing wounds 

/DIDNTHEAL/

- Inflammation – added by JLM, not in original mnemonic
- Diabetes – wound healing impaired in multiple ways.
- Infection
- Drugs – steroids, antimetabolites, NSAIDs
- Nutrition – protein malnutrition, vitamin deficiency esp. A, C and Zn
- Tissue necrosis – local or systemic ischemia
- Hypoxia – blood volume deficit (anemia)
- Excessive tension - post-surgical or dynamic location
- Another wound – competition between several areas
- Low temperature – i.e. on extremities heal more slowly

- Adapted from Stillman, RM. Wound Care: emedicine General Surgery
Leg Ulcers Mimicking PG: Differential Diagnosis

• 6 major disease categories:

  1. **Vascular Disease**
     • Arterial insufficiency
     • Venous insufficiency
     • Calciphylaxis –
       – Calcific uremic arteriolopathy
         » particularly painful and rapidly evolving.
       – Chronic degenerative vascular disease
     • Livedoid vasculopathy
     • Coumadin Necrosis
Leg Ulcers Mimicking PG
Differential Diagnosis

• 6 major disease categories causing leg ulcerations:

  – **Inflammatory diseases:**
    • Pyoderma gangrenosum
    • Vasculitis – Small vessel, medium vessel (Polyarteritis nodosa), Large vessel (Wegener’s), Behcet’s, Antiphospholipid syndrome, cryoglobulinemia, etc.
    • Panniculitis

  – **Malignancy**
    • Especially squamous cell carcinoma
Leg Ulcers – Differential Diagnosis

- 6 major disease categories causing leg ulcerations:
  - Infection
    - Bacterial – Staph, strep species
    - Deep Fungal – sporotrichosis, etc.
    - Atypical mycobacterial – esp *M. marinum*
    - Tertiary Syphilis (gummas)
    - Deep viral - herpetic infections
    - Anthrax
  - Necrobiosis Lipoidica Diabeticorum
  - Trauma
    - Insect or spider bites can develop into PG.
    - Facticial disease
    - Neuropathy
    - Other – stoma wafers, braces, boots, etc.
Ulcerative PG – a Diagnosis of Clinical Appearance and Exclusion

• Diagnosis
  – Clinical presentation
    • Ulcer
      – undermined borders
      – cribiform morphology
      – gunmetal gray borders
      – “oily” exudate
    • Multiple failed skin grafts or recurrences at same sites.
Ulcerative PG – Epidemiology

Most common on legs.
  • Slight female predominance
  • ages 20 – 50
  • 4% in children

All ethnicities

Incidence 3 to 10/million/year
PG – Epidemiology

- 30% associated with “pathergy”
  - Occur in areas that have experienced trauma.

- 50% associated with another underlying condition
  - Inflammatory Bowel Disease
  - Connective Tissue Disease
    - RA, SLE, Sjogrens
  - Hematologic disorder
    - IgA monoclonal gammopathy
    - Leukemia
      - Particularly AML
    - myelodysplasia
Variants of PG

- Ulcerative
- Vesiculobullous (AKA atypical or bullous)
- Pustular
- Superficial granulomatous
- Pyostomatitis Vegetans
Drug-induced PG-like Leg Ulcers

- Isotretinoin
- Propylthiouracil
- Sunitinib
- Cocaine (probably levamisole)
- Leflunamide
- MTX
- G-CSF
- Sunitinib
Work-Up of Leg Ulcers: Practical Approach #1 – Biopsy Early

• Biopsy:
  – Grayish border if possible.
  – Edge of ulcer in undermined area
    • do not biopsy the interior of the ulcer bed.
    • Send for hematoxylin and eosin (H&E) stain.
    • Prepare to have specimen sent to a trained dermatopathologist.
  – Send tissue culture for:
    • Bacterial, Mycobacterial, Fungal culture
    • Consider viral culture.
Proposed Criteria for Diagnosis of Classic Ulcerative PG

• **Major: must have both**
  1. Rapid progression of a painful cutaneous ulcer with an irregular, cribiform, violaceous and undermined border.
  2. Other causes of ulcer have been excluded (infection, vasculitis, etc)

• 1-2 cm/day or 50% increase/month
Proposed Criteria for Diagnosis of Classic Ulcerative PG

• 5 Minor: must have 2

1. History of pathergy (trauma)

1. Clinical findings of cribriform scarring
Proposed Criteria for Diagnosis of Classic Ulcerative PG

- **Minor: must have 2**

  3. Presence of systemic disease associated with PG.
     - Especially inflammatory bowel disease (IBD)
     - Hematologic
       - Malignancy – myeloma, lymphoma, MDS, PCV
       - Paraproteinemia, esp IgA monoclonal
     - Any other connective tissue disease (CTD)
       - SLE, RA, etc.
Proposed Criteria for Diagnosis of Classic Ulcerative PG

• **Minor: must have 2**

4. Pathology findings
   • Sterile sheets of neutrophils

5. Rapid response to systemic steroids
Diagnosis of PG – The Delphi Group Consensus

• Major: Biopsy of edge of ulcer demonstrating a neutrophilic infiltrate.
Diagnosis of PG – The Delphi Group Consensus

• 8 minor criteria:
  1. Exclusion of infection
  2. Pathergy
     • Present in ~ 30%
  3. Presence of other diseases: IBD, SLE, RA, etc.
     • Present in ~ 50%.
     • Inflammatory Bowel Disease
     • Connective Tissue Disease
        – RA, SLE, Sjogrens
     • Hematologic disorder
        – IgA monoclonal gammopathy
        – Leukemia
           » Particularly AML
        – myelodysplasia
Diagnosis of PG – The Delphi Group Consensus Minor Criteria

4. Papule, pustule or vesicle ulcerating within 4 days of appearing.

5. Peripheral erythema, undermined border and tenderness at site.

6. Multiple ulcerations
   • At least 1 on anterior lower leg.

7. Cribriform or “wrinkled paper” scars at healed sites.

8. Decreased ulcer size within 1 month of starting immune suppressive medications.
Paracelsus Score

• Br J Dermatol 2018
• 3 major criteria:
  – Reddish-violaceous wound border
  – Rapidly progressive disease
  – R/o other causes
• Minor criteria:
  – Improvement with immune suppression
  – Irregular border
  – Pain
  – Pathergy
  – Neutrophilic inflammation on histology
  – Undermined border
  – Associated systemic diseases
PG – Workup

• History, ROS and exam:
  – Look for history, signs or symptoms of IBD, CTD, pathergy
  – PG can occur in extracutaneous areas
    • Eyes, lungs, liver, spleen, GI tract, CNS, bone and heart have been described.

• Labs
  – All patients:
    • Complete metabolic panel and CBC/plt/differential
    • Hepatitis B and C studies
    • HIV
PG – Workup

• Guided by history and exam:
  – Look for other diseases:
    • IBD:
      – Colonoscopy or other stool studies?
      – Anti-Saccharomyces cerevisiae antibodies – may be a specific marker for Crohn's + 68%
      – Stool Guaiac
      – O&P
PG – Workup

• Guided by history and exam:
  – Look for other diseases:
    • ANA survey
    • c-ANCA and p-ANCA
    • ESR
    • RF
    • SPEP
    • Chest X-ray
    • RPR or VDRL
PG – Workup

• Guided by history and exam:
  – Look for other diseases:
    • SPEP/UPEP – myeloma, etc
    • Chest X-ray – lymphoma, etc
    • RPR or VDRL – Syphilis, SLE
PG – Workup

• Guided by history and exam:
• Look for other diseases - coagulopathies
  • Coagulation studies
    – PT/PTT
    – Antiphospholipid antibodies
      » Lupus anticoagulant, anticardiolipin antibody, β–2 microglobulin
    – Others – factor V Leiden, cryoglobulins, methylene tetrahydrofolate reductase
Work-up for PG - Other Testing

• Consider age appropriate cancer workup.
  – PG may be paraneoplastic – particularly myelodysplastic syndrome, myeloma, paraproteins, leukemia.
  – especially considering patient may need immune suppression.

• STRONGLY consider vascular studies to evaluate blood flow.
  – Especially in patients over 50.
    » This may be PG but is the vascular supply sufficient to heal the ulcer?
    » Ankle-brachial index (ABI)– blood pressure in the ankle/blood pressure in arm.
  • If < 0.7 needs vascular surgery consultation.
Work-up for PG - Other Testing

• Consider G-6-PD and thiopurine methyltransferase (TPMT) activity early in work-up in anticipation of treatment options.

• Consider Tuberculosis testing with initial blood work or PPD at first visit.
PG – Diagnosis Made – How to Treat? Practical Approach to Therapy

• 5 major treatment considerations:
  1. Treat the inflammation.
     – Topical
     – Systemic
  2. Treat the ulcer.
  3. Treat the biofilm or any true infection.
  4. Treat the pain.
  5. Treat the underlying disease, if present.
PG – Diagnosis Made – How to Treat? Practical Approach to Therapy

• When is surgical intervention necessary?
  – In general, discourage repetitive debridement +/- grafting
  – 3 scenarios for surgery:
    • Excess necrotic tissue is causing systemic illness
    • Extensive infection.
    • Once PG activity is controlled, for grafting large ulcers.
      – High risk of recurrence in graft donor site as well as in the original site.
PG – Practical Approach to Therapy

• Involve GI, Rheum, Onc for treating underlying disease(s).

• Pain
  – PG ulcers are very painful.
    • Pain clinic referral is essential for most patients.
The biofilm over the ulcers should be swab cultured every few months.

- Try to eliminate an additional driver of inflammation.
- Systemic antibiotics have anti-inflammatory properties.
- Topical antibiotics as appropriate.
  - Metronidazole or clindamycin will help the odor as well and provide moist wound healing.
  - Silver containing products
PG – Practical Approach to Therapy

Treat the Ulcer

• Moist wound healing environment.
  – Due to heavy exudate, most bandages require changing multiple times a day.
  – Minimize trauma
  – Autolytic debridement.
    • Choose highly absorbent products.
    • Silver containing products decrease bacteria and help with healing.
PG – Practical Approach to Therapy
Treat the Ulcer

• Negative – pressure wound therapy
  – Be treating the inflammation.

• Hyperbaric O2
  – Has been shown to help healing and reduce pain.
PG – Practical Approach to Therapy
Treat the Inflammation

• Is systemic therapy required?
  – No specific guidelines.
      • Most cases require aggressive immune suppression.
      • Small, slowly growing – try topical treatment.
      • Moderate size and slowly growing– try topical or less potentially toxic regimens first.
      • Rapidly enlarging – start with aggressive therapy immediately.
• Small, stable ulcers may heal without aggressive systemic immune suppression.

• Locally acting anti-inflammatories
  – Topical or intralesional steroids
    • Clobetasol
  – Topical calcineurin inhibitors
  – Topical antibiotics
PG – A Practical Approach to Treatment of Inflammation

• Locally acting anti-inflammatories
  – Topical nitrogen mustard
  – Topical 1% sodium cromoglycate
  – Topical 0.5% nicotine cream
  – Topical 5-aminosalicylic acid
  – Topical benzoyl peroxide
  – Topical PDGF
  – Topical collagenase ointment + timolol 0.5% gel
  – Topical dapsone
    – Crush tablets or cream
    – 1 report healed in 7 months
Systemic Treatments for PG

- Oral antibiotics
- Specific neutrophil inhibitors
- Disease –Modifying Anti-Rheumatic Drugs
- Steroids
- Cyclosporine A
- Others
PG – Treatment of Inflammation

- Anti-inflammatory oral antibiotics: tetracyclines, macrolides, sulfonamides.
  - Doxycycline 100 mg PO BID
  - Doxycycline 100 mg BID + dapsone 100 mg daily
    • Healed in 45 days (ref 13)
  - Minocycline
Specific anti-neutrophil agents:
- Dapsone 100 mg daily
- Colchicine 0.6 mg BID

Potassium Iodide
- SSKI 1 g/ml -> ~ 50 mg iodide/drop
- Reported doses:
  - 300 mg 3 times a day
  - 1200 mg daily
PG – A Practical Approach to Treatment of Inflammation

• Rapidly acting:
  • Steroids – gold standard
  • Oral calcineurin inhibitors (OCIs): cyclosporine A (CsA), tacrolimus
  • Infliximab
STOP GAP Trial

• Compared CsA with steroids.
  – Oral prednisolone 0.75 mg/kg/day
  – CsA 4 mg/kg/day.

• Healing:
  – Both speed of 0.003 cm² per day
  – 6 weeks 15 % CsA and 21 % pred group healed.
  – 6 mo 47% CsA and 47% pred group healed
Infliximab

- **Systemic Infliximab**
  - Insurance coverage/Prior authorization
  - 5 mg/kg days 1,14,42 then q 4-8 weeks
  - “Response” in 2 weeks in 46%
  - At week 6:
    » remission in 21%
    » no response 31%

- **Infliximab gel**
  - 100 mg infliximab in 5 ml saline in 15 g hydroxyl ethyl cellulose gel
  - Healed large PG ulcer refractory to other therapies.
Tacrolimus

- Much less data
- 0.1 mg/kg showed “rapid response”
Do you need a steroid sparing agent for long term use?

- If using prednisone, CsA or tacrolimus, yes.
- Slower to reach full effect.
- Chemotherapy agents – azathioprine, methotrexate (MTX), cyclophosphamide, chlorambucil, etc.
- Mycophenolate mofetil (MMF), leflunamide
- Thalidomide and lenalidomide
- Biologics
  - TNF – \( \alpha \) inhibitors
  - IL-12/23 inhibitors ustekinumab - higher dose (135 mg q 6 weeks) in 1 paper
  - IL-1 –\( \alpha \) inhibitors - anakinra, canakinumab
  - IL-17 a inhibitors –secukinumab, ixekizumab (brodalumab)?
Practical Algorithm for the Treatment of PG

• Which steroid sparing agent?
  – Seems to be relatively equal evidence for the efficacy of:
    • Mycophenolate mofetil
    • Azathioprine
    • Methotrexate
    • Cyclophosphamide
    • Non-infliximab TNF-inhibitors

Choose the one(s) with which you are most comfortable.
No specific trials for combination therapy.
Try to use combinations that have been studied in other diseases.
PG – A Practical Approach to Treatment of Inflammation

• Others
  • IVIG: 88% partial response, 53% complete response
  • Plasmapheresis, leukocyte apheresis
  • Electron beam therapy
  • Interferon -α
  • In or finished trials:
    – Ixekizumab
    – Secukinumab
    – Xilonix (anti-IL-1α)
    – Canakinumab (anti-IL-1β)
    – Etrasimod (S1P modulator- modulates lymphocyte subpopulations) (Australia)
Vedolizumab

- Binds $\alpha 4\beta 7$ integrin in GI tract
- Effective for PG associated with ulcerative colitis but not PG associated with Crohn’s.
A Practical Approach to Treatment of Inflammation in Large or Rapidly Progressive PG

1. Start with rapidly acting therapy.
   - Prednisone 0.5 – 1.0 mg/kg/day or CsA 3-5 mg/kg/day or tacrolimus 0.1-0.2 mg/kg/day. Plan to wean as quickly as possible as the PG improves.
   OR
   - Infliximab 5-10 mg/kg day 1,14, 42 then q4-8 wks
2. Start a steroid sparing agent(s) as well or soon thereafter.

   a. Topical steroid, calcineurin inhibitor or other topical agent.

   b. Add dapsone and/or colchicine for anti-neutrophil effect. Dapsone helps with *PJP* prophylaxis in patients on steroids.

   c. Tetracycline derivative for anti-inflammatory and antibacterial effects.
Recurrent PG

• Post –op:
  – 15% of patients experienced recurrence/exacerbation.
  – Risk increased with invasiveness of procedures
  – Risk increased with chronic PG (@ 2 years).
  – Prophylactic immune suppression not helpful.

• Review of case reports shows associated with:
  – Malignancy
  – Pregnancy
Summary:
PG- A Practical Approach

1. Biopsy edge of ulcer for pathology and tissue pan-culture.

2. Remember vascular studies (ABI or doppler) – does patient have the circulation to heal the ulcer(s)?

3. Get pain management involved ASAP.

1. Treat the biofilm - colonizing bacteria may be driving some of the immune response.

2. Topical therapy alone may be sufficient for small lesions.
Summary: PG- A Practical Approach

1. Systemic therapy:
   1. Steroids, oral tacrolimus or CsA microemulsion or infliximab for initial therapy
      Taper as quickly as possible.
   2. Consider steroid sparing agents quickly.
   3. Most steroid sparing agents take 12-16 weeks to reach full effect. Give it a chance!!

2. Be flexible – different therapies for different patients.

1. Wean medications slowly after healing – recurrence is not uncommon.
Treatment of PG: Proposed Algorithm

Small/stable
- Topical Therapy
  - Topical steroids
  - Intrallesional steroids
  - Calcineurin Inhibitors
  - Topical dapsone
  - Antibiotics
    - Erythro, Metro, Clinda
    - Nitrogen Mustard
    - Cromolyn
    - 5-Sal acid
    - BPO
    - PDGF

Topical Therapy + Less aggressive systemic
- Antibiotics
  - Dapsone
  - Colchicine
- Consider:
  - Pentoxiphylline
  - NSAIDS
  - Antimalarials
  - Sulfasalazine

Topical Therapy + More aggressive systemic
- Systemic steroids
  - Oral Calcineurin inhibitors
  - Infliximab
- Biologics
  - Adalimumab
  - Etanercept
  - Ustekinumab
  - Secukinumab
  - Ixekizumab
  - Canakinumab
  - IVIG

Large/rapidly growing
- Antibiotics
  - Dapsone
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Topical Therapy + More aggressive systemic
- Systemic steroids
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  - Infliximab
- Biologics
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  - Canakinumab
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References


