Pyoderma Gangrenosum: A Practical Approach 2017

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PG – a Diagnosis Made By Clinical Appearance and Exclusion of Other Diseases

- **PG** – an autoimmune disease.
  - Typical clinical presentation
    - Ulcer with undermined borders, gunmetal gray borders, cribriform appearance, “oily” exudate.

- **Epidemiology**
  - 4 main types
  - Ulcerative – most common
    - Also vesiculobullous, pustular, superficial granulomatous, pyostomatitis vegetans.
  - Most common on legs.
  - Slight female predominance
    - ages 20 – 50
    - 4% in children
  - All ethnicities.
  - Incidence 3 to 10/million/year
  - 30% associated with “pathergy”
    - Occur in areas that have experienced trauma.
  - 50% associated with other underlying condition
    - Inflammatory Bowel Disease
    - Connective Tissue Disease
      - RA, SLE, Sjogrens
    - Hematologic disorder
      - IgA monoclonal gammopathy
      - Leukemia
        - Particularly AML
      - myelodysplasia
DDX of non-healing wounds
DI/DNTHEAL

- Diabetes
- Infection
- Inflammation – added by JLM not in original mnemonic
- Drugs – steroids, antimetabolites
- Nutritional
- Tissue necrosis – local or systemic ischemia
- Hypoxia
- Excessive tension - post-surgical or dynamic location
- Another wound – competition between several areas
- Low temperature – i.e. on extremities
  - Adapted from Stillman, RM. Wound Care: emedicine General Surgery
Inflammatory Leg Ulcers
Differential Diagnosis

• Six major disease categories may imitate the clinical appearance of PG:
  – **Vascular Disease**
    • Arterial insufficiency
    • Venous insufficiency
    • Calciphylaxis - particularly painful and rapidly evolving. Similar to PG.
  – **Other inflammatory diseases:**
    • Vasculitis – Small vessel, medium vessel (Polyarteritis nodosa), Large vessel (Wegener’s), Behcet’s, Antiphospholipid syndrome, etc.
    • Panniculitis
  – **Malignancy**
    • Especially squamous cell carcinoma
  – **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
    • Other – stoma wafers, braces, boots, etc.
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
  – **Typical clinical pattern:**
    • irregular, cribiform, violaceous and/or undermined border.
    • painful
    • rapid progression
  – Other causes of ulceration have been excluded.

• **Minor:** must have 2
  – History of pathergy
  – Clinical findings of cribiform scarring
  – Presence of systemic disease associated with PG
    • Especially inflammatory bowel disease
  – Pathology findings
  – Rapid response to systemic steroids
PG - Workup

- History, ROS and exam:
  - Look for hx, 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
  - Guided by history and exam:
    - ANA survey
    - ANCA
    - Antiphospholipid antibodies
      - Lupus anticoagulant, anticardiolipin antibody, β2 microglobulin
    - PT/PTT
    - SPEP
    - CXR
    - RPR or VDRL
  - Colonoscopy or other stool studies?
    - Anti-Saccharomyces cerevisiae antibodies – may be a specific marker for Crohns + 68%
    - O&P
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.

• 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.

• 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

• Pain
  – PG ulcers are very painful.
    • Pain clinic referral is essential for most patients.

• Treat wound colonization or infection
  – 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.
      – Double duty
    • Topical antibiotics as appropriate.
      – Metronidazole or clindamycin will help the odor as well as 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
  – Hydrocolloids/alginites
    • Autolytic debridement.
    • Choose highly absorbent products.
    • Silver containing products decrease bacteria and help with healing.

• 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
- Others
  - Topical nitrogen mustard
  - Topical 1% sodium cromoglycate
  - Topical 0.5% nicotine cream
  - Topical 5-aminosalicylic acid
  - Topical benzoyl peroxide
  - Topical PDGF
  - Topical dapsone
    - Crush tablets or cream
PG – A Practical Approach to Treatment of Inflammation

• Systemic therapies for the treatment of PG:
  – Immune modulatory (less suppressive)
    • Anti-inflammatory oral antibiotics: tetracyclines, macrolides, sulfonamides
    • Specific anti-neutrophil agents: dapsone and/or colchicine.
  • No published data for PG but consider:
    – Pentoxyphylline
      » improve circulation + weak inhibitor of TNF?
    – NSAIDS
    – Sulfasalazine
• Immune suppressive therapies:
  – Rapidly acting:
    • Steroids – gold standard.
    • Oral calcineurin inhibitors (OCIs): cyclosporine A (CsA), tacrolimus
    • Infliximab

  – Better than steroids or OCIs for long term use:
    • 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
      – IL-1 –\( \alpha \) inhibitors - anakinra, canakinumab
      – IL-17 a inhibitors –secukinumab (brodalumab, ixikizumab)?
PG – A Practical Approach to Treatment of Inflammation

• Others
  • IVIG
  • 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)
Practical Algorithm for the Treatment of Rapidly Progressive PG

• **Induction/Initial therapy**
  – Prednisone 0.5 – 1.0 mg/kg/day
    • My experience is that IV forms have most rapid onset.
  – Or calcineurin inhibitor
    • Cyclosporine A (CsA) 3-5 mg/kg/day
      – Remember to use modified or microemulsion
        » Otherwise a steady level is difficult to obtain.
    • Oral tacrolimus 0.1 – 0.2 mg/kg/day
Practical Algorithm for the Treatment of PG

- Which steroid sparing agent?
  - No specific trials for guidance.
    - Combination therapy better than monotherapy?
  - Seems to be relatively equal evidence for the efficacy of:
    - Mycophenolate mofetil
    - Azathioprine
    - Methotrexate
    - TNF-inhibitors
    - Dapsone
    - Reference 11 has a nice review.

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.
A Practical Approach to Treatment of Inflammation in Large or Rapidly Progressive PG

1. Start with rapidly acting induction 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 or infliximab 5-10 mg/kg day 1, 14, 42 then q4-8 wks
   Plan to wean as quickly as possible as the PG improves.

2. Start a steroid sparing agent(s) as well or soon thereafter.
   a. Topical steroid, calcineurin inhibitor or other topical agent.
   b. Add dapsone or colchicine for anti-neutrophil effect.
      Dapsone helps with *pneumocystis* prophylaxis in patients on steroids.
   c. Tetracycline derivative for anti-inflammatory and antibacterial effects.
   d. Add more aggressive immune suppression.
      I happen to like MMF as next agent but TNF- inhibitors, azathioprine or MTX have data as well.
      Give it time to work!

3. Add a TNF inhibitor
   If a+b+c (+/- d) choices do not enable taper of induction agent within 3 months either switch to another immune suppressive agent and/or add anti-TNF – α agent.
   • Because MTX and leflunamide have good data as safe to use with the TNF inhibitor I usually use those in combination.
   • Hepatoscellular T-cell lymphoma with MMF or azathioprine combined with TNF inhibitor so carefull with this regimen.

3. Switch to different biologic agent.
   a. Ustekinumab, secukinumab, ixekizumab

4. IVIG

3. Other agents – thalidomide, INF-α, etc.
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.

3. **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!!

4. 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
    - Intralesional steroids
    - Calcineurin Inhibitors
    - Topical dapsone
    - Antibiotics
      - Erytho, 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
  - Calcineurin inhibitors
  - Infliximab
  - Biologics
    - Adalimumab
    - Etanercept
    - Ustekinumab
    - Secukinumab
    - Ixekizumab
    - Canakinumab
    - IVIG

- **Large/rapidly growing**
  - Topical Therapy
    - Topical steroids
    - Intralesional steroids
    - Calcineurin Inhibitors
    - Topical dapsone
    - Antibiotics
      - Erytho, Metro, Clinda
    - Nitrogen Mustard
    - Cromolyn
    - 5-Sal acid
    - BPO
    - PDGF

  - Consider:
    - Pentoxiphylline
    - NSAIDS
    - Antimalarials
    - Sulfasalazine

  - Biologics
    - Adalimumab
    - Etanercept
    - Ustekinumab
    - Secukinumab
    - Ixekizumab
    - Canakinumab
    - IVIG

  - Systemic steroids
  - Calcineurin inhibitors
  - Infliximab
  - Mycophenolate
  - Methotrexate
  - Azathioprine
  - Leflunamide
  - Thalidomide
  - Cyclophosphamide
  - Chlorambucil
PG: A Practical Approach

References


