Pyoderma Gangrenosum:
Treatment Options

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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U093 – Update on Management of Unusual Neutrophilic Dermatoses

DISCLOSURES

I do not have any relevant relationships with industry.
Outline

• Overview of pyoderma gangrenosum
  • Clinical presentation
  • Subtypes of pyoderma gangrenosum
  • Differential diagnosis
  • Systemic associations

• Topical treatments

• Systemic treatments
Background

• Rare inflammatory neutrophilic dermatoses

• **Pathogenesis** – poorly understood, neutrophil dysfunction

• **Age:** 30-50 yo

• **Sex:** Females > Males (76%)

• **Location:** Lower legs (78%)

• **Number of ulcers:** >1 (65%)

• **Pathergy** – (31% of cases)

Clinical Presentation

• Begin as tender bump on skin or sterile pustule → quickly progresses into painful ulcer

24-48 hrs

Uptodate.
Types of Pyoderma Gangrenosum

Classic

Bullous

IBD

Vegetative

Peristomal

Brooklyn T, et al. BMJ. 2006
240 pts with PG
95 pts misdiagnosed
Consider alternative diagnosis when refractory to treatment
Repeat biopsy

Differential Diagnosis

- Vascular occlusive disease
- Infection
- Vascularitis
- Factitial
- Cancer
- Inflammatory disease

References:
Diagnosis (of exclusion)

• No specific lab or histopathologic findings
• Clinical history/physical exam
• Review of Systems – to evaluate for underlying systemic conditions
• Labs
  • CBC, ESR, SPEP, ANCA, RF, antiphospholipid Abs
• Colo/EGD (based on hx)
• Biopsy – non-specific
  • Edema, neutrophilic infiltrate, necrosis and hemorrhage
• Tissue culture – to r/o infection

Konopka CL. J Vasc Bras. 2013.
**PAPA**

- First described in 1997
  - Pyogenic sterile
  - Arthritis
  - Pyoderma gangrenosum
  - Acne (nodulocystic type)
- Autosomal Dominant
- Mutation in PSTPIP1
  - Increase Il-1β

**PASH**

- New entity coined in 2012
  - Pyoderma gangrenosum
  - Acne
  - Suppurative
  - Hidradenitis
- Mutation not identified
- May respond to IL-1β blockade

Case #1

• 23 yo F presented with 1-month history of an ulcer on the lower extremity
  • Painful 10/10
  • +Pathergy

• PMH: SLE

• Meds:
  • Azathioprine
  • Plaquenil

• SH: undergraduate student

• FH: non-contributory
Which of the following is NOT commonly associated with PG?

A. Inflammatory bowel disease
B. Depression
C. Thyroid Disease
D. Hematologic disorders
E. Arthritis
Systemic Associations

- Systemic conditions (1/2 of cases)
  - IBD (34%)
  - Hematologic disorders (20%)
  - Arthritis (19%)
  - Depression (19%)
  - Psoriasis (11%)
  - Hepatitis (9%)
  - CTD/SLE
  - Behcet disease
  - HIV
  - Pregnancy

Binus AM. BJD. 2011.
Patient declines systemic therapy... Now what?

**Topical Therapy!**

**Can topical therapy be used alone for the treatment of PG?**
- Topical corticosteroids and tacrolimus (0.03% or 0.1%)
- 43.8% healed on topical medication alone, 33.3% concomitant systemics
- Median time to healing 145 days
- Initial ulcer size was a predictor of time to healing
- *Apply to inflamed ulcer edge*
- *Caution with topical tacrolimus (systemic absorption)*

**Bottom line:** Yes, topical corticosteroids or tacrolimus can be used for small localized lesions.

Thomas K. JAAD. 2016.
Intralesional Triamcinolone

- Triamcinolone 6mg-40mg/cc
- Inject ulcer edge
- q4-6 weeks
- Monitor closely for signs of pathergy

Case Continued

• Patient started on clobetasol 0.05% ointment daily x 3 months
• Ulcer no longer painful, growing, or with surrounding erythema → however still present

• What is the next best step in management?
Becaplermin

- Recombinant PDGF
  - FDA approved for diabetic ulcers
  - Black box warning
- **Becaplermin 0.01% gel**
- Apply to ulcer edge
- 2 published reports of using becaplermin for PG

Cost: 1000-1100$/15gm tube

Topical Timolol

- ß2-adrenergic receptor antagonist
- **Timolol 0.5% gel or solution**
- 1 drop every 2 cm to ulcer edge
- MOE: improves keratinocyte migration

**Case report (Liu et al)**
- 77 yo F p/w painful, ulcer on right medial ankle
- Collagenase 250U/g ointment and timolol 0.05% gel (to edge)
- After 36 days → completely re-epithelialized

Other Topical Agents

- Dapsone
- Cyclosporine
- 5-Aminosalicylic acid
- 1% sodium cromoglycate
- Nitrogen mustard

Local Wound Management

• Avoid wet-dry dressings
• Careful with enzymatic debridement
• Moisture-retentive dressings (ie hydrogels)
  • Induce collagen production
  • Facilitate autolytic debridement
  • Promoted angiogenesis
  • Less permeable to external infection
• Exudative wounds
  • Alginate necessary to reduce risk of maceration

Patient would like to undergo an elective breast augmentation, how should you counsel the patient?

- Retrospective study - Brigham and Women’s and Mass Gen Hospital from 2000-2015
- 5.5% risk of PG by procedure (33 developed PG/601 surgeries)
- 15.1% of patients experienced postsurgical recurrence/exacerbation
- Risk increased with more invasive procedures and chronic PG
- Immunosuppression, time elapsed since original PG diagnosis, and procedure location did not significantly influence risk

- Risk is low, but certainly significant given invasive nature of procedure

Xia FD, et al. JAAD. Accepted 2018.
Case #2

• 79 yo M with h/o MGUS
  • Cyst on right knee → I&D
  • Rapidly progressed to painful ulcer
  • Clinically consistent with PG
• ROS: Night sweats and hemoptysis
• CT scan showed mass-like pulmonary consolidations
• Lung biopsy – acute inflammation and necrosis
  • Extracutaneous PG

Which organ is most commonly affected in extracutaneous PG?

A. Eyes
B. Upper airway
C. Lung
D. Liver
E. Bone
Extracutaneous PG

• Typically follows skin lesions
• Lung is most common
  • SOB, hemoptysis
• Upper airway, spleen, eyes, bone, muscle

What is a reasonable first line therapy for this patient?

- Prednisone 1-2mg/kg/day
- Cyclosporine 3-5mg/kg/day
  - May be better for patients with idiopathic disease

Which of the two is better?

• STOPGAP: Multicenter, blinded, RCT
• Prednisolone 0.75 mg/kg/d vs. cyclosporine 4mg/kg/d
• At six months:
  • Cyclosporine: 28/59 (47%) – ulcers healed
  • Prednisolone: 25/53 (47%) – ulcers healed
• Adverse reactions similar for both groups (2/3 of pts)
• Bottom line: No statistical difference in outcomes

What is the only medication that has undergone a randomized placebo controlled trial?

A. Adalimumab
B. Cyclosporine
C. Prednisone
D. Infliximab
E. IVIG
Infliximab

• Only randomized, placebo-controlled trial of systemic therapy for PG

• Infliximab 5mg/kg vs Placebo

• Week 2: 46% of infliximab improved, 6% in placebo

• Total of 29 patients got infliximab, 69% had beneficial clinical response

• 67% with IBD respond, 73% without IBD respond

TNF-alpha Inhibitors

- **Infliximab**
- **Adalimumab**
  - 40mg weekly
  - 40mg twice monthly
- **Etanercept**
  - 25mg-50mg twice weekly
- Hx of IBD or RA
- Fonder *et al* - patient failed infliximab, responded to adalimumab

Anakinra

- Interleukin receptor 1 antagonist
  - Lowers levels of IL-1β
- Shown to be effective in PAPA and PAPASH
- Recent case series of 3 patients successfully treated with anakinra (with RA and SLE)
- Dose: Anakinra 100mg sq daily
- Rapid response → within days!!

The patient has tried and failed prednisone, cyclosporine, and a TNF-alpha inhibitor. What else can you try?

- Systematic review investigated treatment of refractory PG with IVIG
  - Majority also receiving systemic glucocorticoids (88%)
  - Complete response: 26/49 patients (53%)
  - Complete/Partial response: 43/49 (88%)
  - Mean time to initial response 3.5 weeks
  - 92% of patients tapered off of steroids while on IVIG

What can you try for rapidly progressing PG?

- Methylprednisolone 1gm IV x 1-5 days
- Cyclosporine 3-5mg/kg IV x 7 days

Combination Therapy

• Retrospective, multicenter cohort study out of Germany, looked at 121 patients with PG
  • 88.5% of patients initially responded to glucocorticoids, however majority eventually required additional agent
  • PG healed in 72.7% of patients
  • Mean healing time was 7.1 months
  • On average – patients required 2 (or more) different systemic therapies

Other Systemic Therapy

- Dapsone (if normal G6PD levels)
- Mycophenolate mofetil (good adjunct therapy)
- Methotrexate (good adjunct therapy)
- Minocycline (good if you suspect underlying infection)
- Ustekinumab
- Azathioprine
- Tacrolimus
- Thalidomide
- Cyclophosphamide
- Chlorambucil
- Alefacept

After ustekinumab

Pain Control

• Debilitating pain
• Important to monitor patient’s level of pain as marker of treatment efficacy
• Multispecialty approach is often helpful to address chronic pain
• Screen for depression

Summary

• Consider alternative diagnosis if PG not responding to treatment
• If the ulcer is small, localized, or vegetative subtype – consider topical therapy
• Becaplermin and timolol can be useful for wound advancement
• IVIG for refractory disease
• Multiple systemic agents often required
• Pain control, screen for depression
Questions?

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