2019 update on pyoderma gangrenosum

Kanade Shinkai, MD PhD
University of California, San Francisco

F106: Updates in neutrophilic and pustular dermatoses

I have no conflicts of interest to disclose. I will be discussing off-label use of medications during this lecture.

2019 updates

Diagnosis

New PG diagnostic criteria?

*Histopathology
Using literature-based characteristic validation
Comparison to other criteria ongoing


Does age matter?

• Multicenter retrospective cohort study (n=365)
• Associated comorbidities (67%)
• Patients >65 yrs:  - pathergy (36% vs 24%, p=.02)
  - RA, AS, malignancy, hemod disorders
• IBD more common in <65 yrs (47.7% vs 26.6%; p<.001)

2019 updates

Pathogenesis

Are there different pathogenic pathways?

- Malignancy
- Neutropenia
- Medication
- Autoimmune
- Infection
- Autoinflam
- Pathergy
- Immunodeficiency

Neutrophils
T cells (Th17)
Cytokines
Genes

Neutrophil recruitment

Neutrophil homeostasis

PG plus shock physiology

- 69yo M
- History of MDS
- Repeated debridement
- Multiple IV antibiotics (5), antifungals (2), valacyclovir:
  - cultures negative
  - lesion expanding
- Shock physiology

Does this case fit PG diagnostic criteria?

- *PG major criteria
  - Classic ulcer
  - Dx of exclusion
  - Pathergy, cribiform
  - Systemic associations
  - Histopathology
  - Response to steroids

NND: distinct subset of ND with shock physiology

- PG/ Sweet syndrome
- PG+shock/ Necrotizing Sweet
  - Necrotizing
  - Neutrophilic
  - Dermatoses


Necrotizing neutrophilic dermatoses

• Shock physiology mimicking necrotizing fasciitis
• High misdiagnosis rate (91% given antibiotics as initial rx)
• Morbidity: amputation, leukemoid reaction, satellite lesions


How do we explain the necrotizing phenotype?

2nd signal?

IL-1
IL-8
Rantes

Adam and Colikoglu (2004) JEADV
Sifa et al (2007) JAMA Derm

Necrotizing neutrophilic dermatosis vs infection?

Markers of infection:
• Tissue cultures (43-98%)
• Blood cultures (18-66%)
• Universal PCR
• Procalcitonin
• Presepsin
• ESR/CRP ratio (low ratio)
• CD64 + PCT + IL-10

Adam and Colikoglu (2004) JEADV
Sifa et al (2007) JAMA Derm
Could there be a genetic basis for NND?

- Novel heterozygous variants in NFKB1 (p50/p105)
- Spectrum of phenotypes: autoimmunity/autoinflammatory
  

Somatic mosaicism in NLRP3 inflammasome

- Regulates IL-1 cytokine production
  

Drug-induced PG

- Onset: may be years after drug start, no pattern suggests drug
  
Levamisole-induced PG: distinct pathophysiology?

- Levamisole → retiform purpura, PG (neutropenia, ANCA+, APLA)
- Rapid response to brief, low-dose steroids (<0.5mg/kg x 1-2 wk)


Drug-induced neutrophilic dermatosis

Similar or distinct pathophysiology?

Malignancy 
Neutropenia 
Medication 
Autoimmune 
Infection 
Autoinflam 
Pathergy 
Immunodeficiency

Neutrophil recruitment 
Neutrophil homeostasis

Keratinocyte apoptosis

Wu et al (2017) BJD, 177: 72-83
2019 updates

Best practices for PG management

WOUND + INFLAMMATION

Additional goals:
- Reduce pain
- Evaluate for/ treat associated systemic condition(s)

Limited evidence for PG treatment

- Topical: level II evidence
  - clobetasol propionate 0.05%
  - tacrolimus 0.03 or 0.1%

- Systemic: level Ib evidence
  - prednisone
  - cyclosporine
  - TNF-alpha (infliximab)
What's new in PG treatment? Case reports

• Apremilast (Laird et al, 2017, JAAD Case reports)*
• Tocilizumab (Lee et al, 2016, JEADV)*
• JAK inhibitors
  - Tofacitinib (JAK1/3) (Kochar et al, 2019, Clin GE & Hep)*
  - Ruxolitinib (JAK2) (Nasifoglu et al, 2018, BJD)

Do PG variants require distinct treatment?

GI lymphoma PAPA Peri-stomal IgA vasculitis

2019 updates
Special site: PG after breast surgery

- Systematic review
- Median onset: post-op day 7
- Risk factors:
  - reduction/reconstruction
  - malignancy (37%)
  - autoimmunity (17%)
- Treatment: 4.7 months


Aesthetic breast implant augmentation and attempts to cover defect by pedicle flap

Special site: Peri-stomal PG

- Systematic review (n=335)
- 0.6-1.5% (4.3% in IBD)
- Risk factors:
  - younger age
  - wound infection
  - bowel obstruction
  - hernia
  - female
  - increased BMI
  - autoimmune disease
- Onset: 23 months (mean)

Surgery for PPG: (Re)location, location, location

Surgical approaches:

- ostomy closure: 15 cases  
  100% healing
- stoma revision/relocation: 36 cases  
  86% healing*
- debridement: 34 cases  
  53% healing


Other surgical strategies: grafting


2019 updates

- Diagnosis
- Pathogenesis
- Treatment
- Special scenarios

Ashchyan et al (2018) JAA, online release Dec 2019
Future directions

(Re)considering diagnostic criteria to group & define similar and distinct conditions
Pathogenesis: elucidating pathways, diagnostic markers, distinguishing from infection
Understanding which treatments work and whether they work broadly

Q&A