Systemic Mimickers of Genital Skin Disease

FEBRUARY 19, 2018

Matt Lewis, MD, MPH
Clinical Assistant Professor
Stanford Dermatology
mlewis5@stanford.edu
Disclosures

I have no relevant conflicts of interest
I will discuss off-label uses of medications
Objectives

I. Cutaneous Crohn’s Disease
   • Describe the clinical features, lab testing and treatment

II. Genital Psoriasis
    • Recognize frequency, impact and treatment

III. Genital Pemphigus Vulgaris
    • Recognize frequency and treatment options

IV. Behçet’s Disease
    • Be aware of diagnostic criteria and skin manifestations
Cutaneous Manifestations in Crohn’s

1. Specific (Cutaneous Crohn’s)
   - Contiguous: Fistulae
   - Non-contiguous (Metastatic): Genital, distant sites
   - Oral: Mucosal swelling, cobblestoning, orofacial granulomatosis

2. Reactive
   - Aphthous ulcers
   - Erythema nodosum, pyoderma gangrenosum, cutaneous PAN

3. Associated
   - Psoriasiform eruptions, vitiligo
   - Acquired acrodermatitis enteropathica

Genital Crohn’s Disease

- Painful vulvar edema is most common presentation
- Deep linear “knife-like” fissures - most specific but not always present in mild or early disease
- 60-90% also with perianal mucosal involvement – fissures or tags
- Males with scrotal and penile swelling
- Histology shows noncaseating granulomas (80% of cases)

Non-contiguous Crohn’s (Metastatic)

- In adults, 30% precede intestinal disease
- In peds, 80% precede intestinal disease
- Non-contiguous Crohn’s activity may **NOT** parallel intestinal Crohn’s activity

Laboratory Findings in Crohn’s Disease

• Elevated ESR, CRP
• Thrombocytosis, Anemia
• Hypoalbuminemia
• Elevated fecal calprotectin
• Serology
  • Positive ASCA (Anti-Saccharomyces Cerevisiae Antibody)
  • Negative P-ANCA
    • Specificity 91%, Positive predictive value 88%

Treatment Principles in Cutaneous Crohn’s

• Consider comorbidities (e.g. hidradenitis, psoriasis)
• Collaborate with GI doc involved
• Escalate therapy as if for intestinal Crohn’s disease
  • Topical/intralesional/oral steroids, metronidazole
  • Azathioprine, methotrexate
  • Adalimumab, infliximab, certolizumab
  • Ustekinumab
  • IVIG

Take Away Points for Cutaneous Crohn’s

• Painful vulvar edema is most common sign
• Knife-like fissures are most specific sign
• 30% adult vs. 80% pediatric cases precede intestinal disease
• ASCA, P-ANCA, fecal calprotectin are useful screening tests
• Escalate therapy as if for intestinal Crohn’s disease
Genital Psoriasis

- 30-45% patients with genital involvement
- 45% patients with genital psoriasis did not discuss it with physician
- Associated with:
  - Younger age of onset (<40 years old)
  - More frequent nail, scalp, inverse involvement
- Considerations: Superinfection
- Significant effect on quality of life, psychosexual well-being

Genital Psoriasis - Diagnosis

• A Clinical Diagnosis - Biopsy usually unnecessary
• Biopsy if treatment resistant to exclude SCC, Paget’s

Vulvar Psoriasis

- 201 Vulvar psoriasis patients
  - Symptoms: Itching (95%), pain (45%), dyspareunia (28%)
  - Exam: 90% sharp edge, 20% plaques, 17% scale
  - Superinfection: 20% of adults with C. albicans or S. aureus
  - 94% responded to topical therapy alone

**Treatment**

**Inverse Psoriasis**
- Low to mid potency steroid x 2-4 weeks
- Switch to topical calcineurin inhibitor or Vitamin D analogue
- Consider need for topical antimicrobial
- Consider Botox or Excimer
- Escalate to systemic therapy

**Genital Psoriasis**
- Mid to high potency steroid x 2-4 weeks
- Escalate to systemic therapy

Summary for Genital Psoriasis

- 30-45% of patients have genital involvement
- Biopsy is unnecessary unless refractory
- Huge impact on quality of life
- Treat possible co-infection
- Vast majority of cases may be controlled with topical therapy
  - Brief courses of mid to high potency topical steroids
  - Maintenance with topical calcineurin inhibitors, vitamin D analogues
Pemphigus Vulgaris

• Incidence 1-50 million/year, varies by geographic region
• Increased prevalence:
  – Indians, Iranians (HLA-DQB1*0503)
  – Ashkenazi Jews (HLA-DRB1*0402)
• Triggers may include: infections, medications, tumors
  – CLL, NHL, myeloma
• Loss of tolerance to desmoglein 3
• Majority enter remission within 7-10 years

Genital Pemphigus

• 45-50% PV patients with vulvar involvement
  – labia minora > labia majora > vagina, cervix
• 25-30% show acantholytic cells on Pap smear
• Associated with SEVERE disease, nasal mucosal involvement
• Unclear proportion of men affected – likely similar to women
  – Glans, coronal sulcus most common

Pemphigus Vulgaris

• No universally accepted diagnostic criteria
• Diagnosis
  – (1) Clinical presentation
  – (2) Consistent histology
  – (3) Presence of pathogenic autoantibodies (by DIF, or if needed by ELISA)
• Titers by ELISA or IIF usually correlate with disease activity
• Treatment: Induce remission, then maintain remission

Treatment Principles in Genital Pemphigus

• Topical therapy:
  – R/o superinfection if worsening itch/pain/drainage
  – Dilute bleach baths, as for atopic dermatitis
  – Topical steroids for symptoms
  – Topical pimecrolimus may accelerate healing in the oral mucosa

• Systemic Therapy:
  – Prednisone (1mg/kg) with slow taper to induce remission
  – Start steroid-sparing agent simultaneously to maintain remission

Management of Pemphigus Vulgaris

**Mild**
- Topicals: steroids, lido, pimecrolimus
- minocycline + nicotinamide, dapsone

**Moderate**
- Prednisone 1mg/kg + Rituximab or MMF, AZA

**Severe**
- Prednisone 1-3mg/kg + rituximab +/- IVIG
  - May need to add MMF, AZA, or cyclophosphamide

**Prophylaxis**
- Calcium + Vitamin D + bisphosphonate (in most)
- Clotrimazole troches for oral disease, cream for genital disease
- TMP-SMX 3x/week in moderately immunosuppressed


*MMF=mycophenolate mofetil
AZA=azathioprine*
Take Away Points for Genital Pemphigus Vulgaris

• Genital pemphigus is associated with more severe disease
• Topical steroids are most useful for symptoms
• Pimecrolimus may accelerate healing
• Consider dilute bleach baths
• Increase in pain/itching should raise concern for superinfection
• Rituximab becoming 1st line agent for mod/severe disease
• Majority enter remission within 7-10 years
Differential Diagnosis for Vulvar Ulcer

- **Infectious**
  - Viral (HSV, VZV, EBV, CMV, HIV)
  - Candida
  - Group A Strep
  - Mycoplasma
  - Syphilis

- **Inflammatory**
  - Aphthae
  - Contact dermatitis
  - Lichen planus
  - Lichen sclerosus
  - Hidradenitis
  - Cutaneous Crohn’s
  - Behçet’s

- **Autoimmune**
  - Pemphigus
  - Mucous membrane pemphigoid

- **Reactive/Drug**
  - Bullous fixed drug
  - Erythema multiforme/SJS

- **Malignancy**
  - Squamous cell carcinoma
  - Extramammary Paget’s

- **Genetic**
  - Hailey-Hailey

- **Mechanical**
  - Excoriation
  - Abuse
Behçet’s Disease

- 1937 – Described by Hulusi Behçet
- A vasculitis affecting vessels of all sizes
- Onset 20-30 years old
- Need to be followed over time
- Men>Women in Middle East
- Women>Men in US
- Turkey>Middle east>Asia>US>UK
  – HLA-B51

## International Criteria for Behçet’s Disease

Need ≥4 points to make diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Ocular signs</td>
<td>2</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>1</td>
</tr>
<tr>
<td>Vascular signs</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic signs</td>
<td>1</td>
</tr>
<tr>
<td>Pathergy test</td>
<td>1</td>
</tr>
</tbody>
</table>

Oral Ulcers in Behçet’s

• Occur in 95-100% of cases
• Tongue, lips, buccal mucosa, gingiva, soft palate
• Minor, Major, Herpetiform
• Self-limited, resolves in 1-4 weeks
• Biopsy of a classic aphthous ulcer is not usually helpful, except to exclude other diagnoses
• Within 4 years of oral ulcer onset, 95% meet diagnostic criteria for Behçet’s★

Genital Ulcers in Behçet’s

- 60-80% of cases
- Men: 90% on scrotum
- Women: majority on labia, can be in introitus, cervix
- May be inguinal creases, perineum, perianal skin
- Larger, deeper, fewer than oral ulcers → may scar
- Self-limited, resolves in 2-6 weeks
- More likely to manifest epididymitis

Pustular lesions

- Occur in 50% of cases
- Dome-shaped pustule with a red halo
- Extremities > trunk
- Usually not folliculocentric
- Neutrophilic infiltrate, vasculitis

**Pathergy Test**

1. Cleanse volar forearm with alcohol
2. Use 20 gauge needle, 2-3 puncture sites
3. 24-48 hours later, observe for papule/pustule

Erythema nodosum-like lesions in Behçet’s
Apremilast for Behçet’s Ulcers

Genital Ulcers:
100% in the apremilast group (n=10) vs. 50% in the placebo group (n=6) had resolution of genital ulcers by week 12, P=.04.

Behçet’s Treatment Approach

• Prevent irreversible organ damage
• Minimize morbidity of ulceration
Treatment of Aphthous Ulcers in Behçet’s

Driven by severity of symptoms

1st
- Triamcinolone paste, pimecrolimus
- Lactobacilli lozenges
- Oral corticosteroid taper
- Pentoxifylline (better for oral than genital ulcers)
- Colchicine (better for genital ulcers than oral)
- Apremilast

2nd
- Azathioprine
- Adalimumab, etanercept, infliximab
- Anakinra, canakinumab
- Thalidomide

3rd
- Cyclosporine, interferon-alpha

Take Away Message for Behçet’s Disease

- Use 2013 International Criteria for Behçet’s Disease
- Genital ulcers occur commonly on the scrotum and labia, may heal with scarring
- Escalate treatment for ulcers as much as it bothers the patient
- Colchicine is first line systemic therapy for genital ulcers
- Apremilast is an emerging therapy for aphthous ulcers