Inflammatory Dermatopathology: A Case-based Update

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

No relevant disclosures
Case 1
4 month old infant; r/o viral, mast cell, LCH
Dx: Superficial and deep perivascular dermatitis
T. pallidum IHC
Additional photos
Syphilis

• Caused by spirochete *T. pallidum*
• Genome sequenced in 1998
• Incidence decreased in 1980s but now increasing since mid-1990s
• Congenital
  — Rare but incidence increasing
• Acquired

1. Primary – chancre, 21 days after sexual exposure
2. Secondary – mucocutaneous, condyloma lata lesions 4-8 weeks after
   • T. Pallidum IHC (sensitivity of 71% versus 41% Warthin-Starry stain)
   • Histopathology
     – *Vascular changes – endothelial cell swelling
     – Elongated rete ridges
     – Plasma cells variable
     – Interstitial infiltrate
     – Epidermal changes (spongiosis, psoriasiform, lichenoid reaction)
     – Exocytosis of neutrophils

3. Latent – no signs or symptoms

4. Tertiary – cardiovascular, CNS, skeleton, less likely skin (nodular or chronic gummatous ulcer)

Congenital syphilis

- Transplacental infection
- Diagnosis: immunoblotting for T. palladium-specific IgM
- Early or late
  - Early
    - Prematurity
    - Low birth weight
    - Rhinorrhea
    - Mucocutaneous lesions
      - Macular rash, vesiculobullous or scaling lesions predominantly on palms and soles
      - Condyloma lata

*27 states reported sex of partner data for 70% of reported cases of primary and secondary syphilis for each year during 2007–2014.

† MSM = men who have sex with men; MSW = men who have sex with women only.
Congenital Syphilis — Reported Cases by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2005–2014

CS* cases (in thousands)  

<table>
<thead>
<tr>
<th>Year</th>
<th>CS Cases</th>
<th>P&amp;S Rate</th>
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<tr>
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</table>

* CS=congenital syphilis; P&S=primary and secondary syphilis.
Why are the rates of syphilis climbing again?

• Increase of infection in medically hard to reach groups, with partners difficult to locate
• Growing role of technology in people’s sex lives – apps that facilitate casual sex
• Most Americans don’t think of it as a threat since the worst epidemics happened centuries ago, when the infection had no known cause or cure
• Syphilis can be difficult to recognize or can go unnoticed, especially if the chancre (the primary lesion of syphilis) presents on a non-genital location and because the chancre is painless
Oral Sex and HIV Risk

Fast Facts
- There is little to no risk of getting or transmitting HIV from oral sex.
- Other STDs and hepatitis can be transmitted during oral sex.
- Latex barriers and medicines to prevent and treat HIV can further reduce the very low risk of getting HIV from oral sex.

Replace Intercourse with Oral Sex

The risk of HIV transmission from oral sex is extremely low. However, the presence of cuts, bleeding gums, or any STD elevates the risk. Options for lowering the risk of transmission during oral sex include using a barrier like a condom or dental dam. If a client does not want to use condoms, not allowing partners to ejaculate into the mouth offers some protection.

https://www.cdc.gov/hiv/risk/oralsex.html
http://www.johnyfit.com/can-i-get-hiv-from-oral-sex/
Take home points

• Remember to consider syphilis in your differential diagnosis as many of the histologic features are subtle

• *T. Pallidum* IHC (71% versus 41% Warthin-Starry stain)

• As a result of this case we changed our comment for cases signed out as “Superficial and deep perivascular dermatitis”

  – COMMENT: The histological differential diagnosis is extensive and includes a viral/rickettsial infection, an infectious related exanthem, a drug eruption, gyrate erythemas, connective tissue disorder, and less likely lymphoma/leukemia cutis. Clinical correlation is recommended.
Case 2
A 65 year old male; clinical history r/o med vessel vasculitis, thromboembolic, infectious
Tissue culture: Fusarium sp
Ecthyma (Gangrenosum)- Like Lesions

• Severe variant of ecthyma present in 5% of immunosuppressed individuals
• Septicemia with *Pseudomonas aeruginosa*
• Erythematous macule or patch that becomes vesicular and develops into a gangrenous ulcer with an erythematous halo
• There are cases in the literature that have been reported in immunocompetent patients, not associated with septicemia and other bacterial or fungal microorganisms — ecthyma-like

• Histopathology
  – Necrosis of epidermis and dermis with hemorrhage into the dermis
  – Mixed inflammatory infiltrate surrounds infracted region
  – Vascular thrombosis present at the margins
Take home points

• Disease not limited to infection by Pseudomonas or immunocompromised as once thought
• Skin infection of various etiologies that leads to vasculitis and local skin necrosis
• Thus, the disease should be defined by clinical and histologic features not determined by the etiologic agent
Case 3
38 year old female with painful “bumps” at right abdomen

Courtesy of Dr. Sofia Chaudhry
The rest of the story...

- Using insulin pump
- Four weeks ago started on exenatide injections
Exenatide Panniculitis

• Exenatide is a glucagon-like peptide-1 receptor agonist that is administered once-weekly subcutaneously in a long-acting, formulation
  – Utilizes a PLG [poly(D,L-lactide-co-glycolide)] microsphere technology

• Causes a lobular or mixed lobular and septal panniculitis consisting of lymphocytes, histiocytes, and eosinophils

• Injected material, that appears as slightly retractile, rounded structures corresponding to the injected microspheres of PLG
  – Only occasionally found depending on the timeframe of biopsy as microspheres degrade
Take home points

• Don’t be afraid to use all the resources available to you

• Panniculitis with new foreign body with rather characteristic morphology and possibly staining pattern
Case 4
60 year old female; r/o calciphylaxis, nephrogenic system fibrosis, focal anasarca, other
Calciphylaxis

- Also known as calcific uremic arteriolopathy, calcifying panniculitis, uremic gangrene syndrome

- Lethal variant of metastatic calcification

- Incidence is 4.5 per 1 million / Prevalence in patients on hemodialysis is 4.1%

- Usually seen after the onset of end stage renal disease with secondary hyperparathyroidism
  - Hypercoagulable state
  - Obesity
  - Systemic steroids
• Pathogenesis:
  – Activation of the NF-KB pathway
  – Treatment: inhibitors of the RANKL-RANK-NF-KB pathway (bisphosphonates, recombinant osteoprotegerin)
  – Diagnosis based on wedge biopsy; current radiographic studies are limited in diagnosis

• Net-like pattern on plain radiographs (90% specific)

• Mortality rate 60-80% related to wound infection, sepsis and organ failure

• Surgical debridement is associated with improved survival

Histopathology

- Epidermal ulceration, focal dermal necrosis and vascular calcification
- Calcification involves small to medium vessels particularly in the subcutis
- *Perieccrine calcification
- Fibrin thrombi in smaller vessels
- Calcifying panniculitis
- Dermal angiomatosis
- * Von Kossa or Alizarin red for subtle calcification
- Rule out Mönckeberg's sclerosis
  - Elderly patients
  - Small amount of calcification in small vessels w/o thrombosis
Take home points

• Excisional biopsy (wedge) at a site where the edge of the necrotic eschar, the livedoid area, and the indurated skin can all be simultaneously captured to include subcutaneous tissue

• Special stain Von Kossa or Alizarin red for subtle calcification

• Perieccrine calcification is rare but highly specific
Cases 5 and 6
25 year old female with progressive hyperpigmented nodular plaques

Courtesy of Dr. Patricia Missall
40 year old female with discoloration/nodules on buttocks/hips following buttock augmentation with sesame oil

Courtesy of Dr. Hala Adil
A) Left low back  B) Left lateral thigh  C) Left anterior thigh
GMS negative
Fite negative
Lipogranuoloma

- Incidence is likely higher with improper technique and materials
- Described in the literature in the gluteal region, limbs, male and female breast, orbital region, abdomen and male genitalia
- Hotel/House parties (aka “pumping parties”)
  - Patient 5 injected Silicone and Hydrogel
  - Patient 6 injected Sesame oil
  - Muscle augmentation as an alternative or additive to intramuscular injections of steroids where it can cause muscle necrosis, fibrosis and atrophy

• **Adverse reactions**
  – related to the filler product itself
    • most injectable fillers are particulate or break down into particulates upon injection
    • size, shape, mechanical properties and surface chemistry of the particulates are known to influence their in vivo performance
      – Migration: smaller
      – Amount of inflammatory cytokines (TNF): phagocytosis
      – Surface chemistry: inflammatory response
      – Shape: angular forms lead to more foreign body response
  – procedural techniques
  – concentration of the product
  – presence of impurities
Pathophysiology

• CD4⁺ T-Cell activation by antigen presenting cells
  – Foreign body
  – Impurities & Adulterants
  – Microbial Contamination, Biofilm
  – Denatured host protein, Fibrinogen
  – Trauma

• Cytokine Release (TNF-α, IL-1, IL-6)
Amateur Silicone Injection Reported Adverse Events

• Immediate (seconds to hours)
  – Bleeding, Vessel Occlusion, Necrosis, Embolization, Sudden Death, Multiorgan System Failure, Acute pneumonitis, Alveolar Hemorrhage, Respiratory Failure

• Early (days to weeks)
  – Inflammatory nodules, Infection (bacterial, AFB), Migration, Angioedema, Lymphadenitis

• Late (months to years)
  – Granulomas
  – Recurrent Cellulitis
  – Morphea-like changes
  – Reactive Amyloidosis (28 years latent)
  – Auto-Inflammatory Syndrome Induced by Adjuvants
  – End organ Toxicity – Autoimmune Dz, Hypercalcemia due to granuloma

What is the cause of the late appearing reticular cutaneous pattern?

- Rare report of sesame oil injections causing vasculitis for which the authors postulated was secondary to an allergic reaction
- Migration of filler along septae in the SQ
- Mass effect
  - Diminished blood flow secondary to amount of substance injected or exuberant inflammatory response

Take home points

• Popularized dangerous trends can be sources for inflammatory dermatoses
• Pumping parties are a dangerous way to obtain curves
• Cutaneous reactions may occur at sites distant from injected sites as a result of migration of the filler substance
• There may also be a lapse of months to years prior to the development of a cutaneous reaction
• Reticular pattern can be a late manifestation
Thank you

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