Inflammatory Dermatopathology: A Case-based Update
Claudia I. Vidal, M.D., Ph.D.
Associate Professor of Dermatology and Pathology
Department of Dermatology
Saint Louis University School of Medicine

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Case 1

53 year old male with metastatic melanoma currently being treated with Nivolumab

Nivolumab
- Human IgG4 anti–programmed cell death 1 (PD-1) antibody
- Approved for the treatment of advanced melanoma, advanced non-small cell lung cancer, advanced renal cell carcinoma and classical Hodgkin lymphoma
- Works by activating the immune response against cancer cells
- Member of the novel class of drugs known as immune checkpoint inhibitors (ICIs)
  - Other similar agents include
    - Anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)
    - Anti–programmed death ligand 1 (PD-L1) inhibitors
Dermatologic Toxicity From Anti-PD-1 Therapy

- Occurs in 14-40% of patients
  - Less than that seen in patients treated with anti-CTLA-4 (47-68%)
- Classically manifests as a faintly erythematous and maculopapular rash, involving the trunk and extremities (head, palms, and soles are often spared), and may be pruritic
- Appears weeks to months following therapy and are not dose dependent
- Vitiligo is also common
  - Incidence between 8-25%
  - Has delayed appearance after several months of treatment
  - Seen exclusively in patients being treated for melanoma
- Other dermatologic adverse events include xerosis (5.3%), alopecia (2%), stomatitis (1.5%), urticaria (1.4%), photosensitivity (1.4%), hyperhidrosis (0.9%), skin exfoliation (0.7%)
- Case reports of exacerbation and new onset psoriasis, bullous pemphigoid, lupus, etc.
- Early studies suggest an association with cutaneous toxicity and positive outcome

Take home points

- ICI s can be added to the ever growing list of medications that induce a lichenoid drug reaction
- Mnemonic “HANG PIC”
  - HCTZ
  - Antimalarials / Allopurinol / Anti –TNF / Anti-CD20
  - Naproxen/NSAIDS
  - Gold
  - Penicillamine / Phenothiazine
  - ICI s (immune checkpoint inhibitors)
  - Captopril / ACEI / Ca Channel blockers

Case 2

4 month old infant; r/o viral, mast cell, LCH
Dx: Superficial and deep perivascular dermatitis

Syphilis
- Caused by spirochete *T. pallidum*

Additional photos

*Acquired*
1. Primary – painless 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)
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. pallium-specific IgM
- Early or late
  - Prematurity
  - Low birth weight
  - Rhinorrhea
  - Mucocutaneous lesions
    - Macular rash, vesiculobullous or scaling lesions predominantly on palms and soles
    - Condyloma lata

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

Take home points

- Syphilis is not new but rising
- 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 or bacterial infection, an infectious related exanthem, a drug eruption, gyrate erythemas, connective tissue disorder, and less likely lymphoma/leukemia cutis. Clinical correlation is recommended.
Case 3

A 65 year old male; clinical history r/o med vessel vasculitis, thromboembolic, infectious

Ecthyma Gangrenosum

- Generally accepted definition = Severe variant of ecthyma present in 5% of immunosuppressed individual and is 2/2 septicemia with Pseudomonas aeruginosa
- Erythematous macule or patch that becomes vesicular and develops into a gangrenous ulcer with an erythematous halo
- Histopathology
  - Necrosis of epidermis and dermis with hemorrhage into the dermis
  - Mixed inflammatory infiltrate surrounds infarcted region
  - Vascular thrombosis present at the margins
Ecstasy-like

• There are cases in the literature that have been reported in immunocompetent patients, not associated with septicemia and other bacterial or fungal microorganisms
• EG is not new but there is a call for acceptance of a broader definition of the disease

Take home points

• Disease not limited to infection by Pseudomonas or immunocompromised as once thought
• Skin infection of various etiologies can lead to vasculitis and local skin necrosis
• Thus, the disease should be defined by clinical and histologic features not determined by the etiologic agent

Case 4

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 5

60 year old female; r/o calciphylaxis, nephrogenic system fibrosis, focal anasarca, other

Courtesy of Dr. Emily Prodanovic
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
  - 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
- Intimal fibroblastic proliferation
- Microthrombi / Fibrin thrombi in smaller vessels
- Extracellular soft tissue calcification / Calcifying panniculitis
- *Perieccrine calcification
- * 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

- Perieccrine calcification is rare but highly specific
- Special stain Von Kossa or Alizarin red for subtle calcification
- 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

Cases 6 and 7

25 year old female with progressive hyperpigmented nodular plaques
40 year old female with discoloration/nodules on buttocks/hips following buttock augmentation with sesame oil

A) Left back  B) Left lateral thigh  C) Left anterior thigh
**Amateur Silicone Injection Reported Adverse Events**

- **Immediate (seconds to hours)**
  - Bleeding, Vessel Occlusion, Necrosis, Embolization, Sudden Death, Multorgan System Failure, Acute pneumonitis, Alveolar Hemorrhage, Respiratory Failure
- **Early (days to weeks)**
  - Inflammatory nodules, Injection (bacterial, AFB), Migration, Angioedema, Lymphadenitis
- **Late (months to years)**
  - Granulomas
  - Recurrent Cellulitis
  - Morphea-like changes
  - Reactive Amyloidosis (28 years latent)
  - AutoInflammatory Syndrome Induced by Adjuvants
  - End organ Toxicity – Autoimmune Di, hypercalcemia due to granuloma

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**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

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cvidal1@slu.edu

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