Panniculitis Made Simple

Alina G. Bridges, D.O.
Assistant Professor
Program Director, Dermatopathology Fellowship
Department of Dermatology, Division of Dermatopathology and Cutaneous Immunopathology
Mayo Clinic, Rochester, MN
Panniculitis Made Simple

Goals of this Lecture

• Describe primary and secondary forms of panniculitis
• Use clinical and pathologic correlation effectively in the diagnosis of panniculitis
• Review the treatment of various panniculitides, which is determined by establishing the underlying cause
Definitions
Adipose Tissue

Adipocytes
(white adipose cells)
Inflammatory infiltrate in the subcutaneous fat

- Inflammatory disorder of the skin - **Panniculitis**
  - Primary panniculitis
  - Secondary panniculitis
- Infection
- Neoplasm
- Crystal Deposition Disease associated with Panniculitis
Panniculitis

• Clinically, in all forms of panniculitis, lesions may present as subcutaneous indurated nodules

• Most often on the lower extremities, but the torso, buttocks, arms & head and neck area can be the primary site of inflammation
Are there distinguishing clinical features?

• Age, gender, anatomic site of lesions, duration, course

• Background – precipitating factors, immunosuppression, metabolic/other systemic disorder, trauma/injection

• Morphology – ulcers, drainage, atrophy, sclerosis, scars
What is the best diagnostic approach to panniculitis?

- Incisional or excisional biopsy is the optimal procedure
  - Double punch method may be considered
Panniculitis

Mixed

Septal

Lobular
Primary Panniculitis

Septal

Without vasculitis

Erythema nodosum

Acute

Subacute to chronic nodular migratory panniculitis
Erythema Nodosum

• One of the more common inflammatory causes of panniculitis
• Young adult women
• Tender erythematous nodules on the shin
• Systemic symptoms
  – Fever, malaise, arthralgias
  – Headache; ocular, and GI complaints
Erythema Nodosum

Etiology

• **Reactive Process**
  – Idiopathic - 30%
  – Infection:
    • Streptococcal (in children this is by far the most common precipitant)
    • URI, Coccidiomycosis, Yersinia

• **Drug**
  • OCP, estrogens, sulfonamides, penicillin, bromide, iodide, Echinacea

• **Sarcoidosis**
  • May present with fever, cough, joint pains, hilar adenopathy
    – Lofgren syndrome

• **IBD**: Crohn > UC

• **Behcet syndrome**

• **Malignancy**
Chronic Erythema Nodosum

• AKA EN migrans, or subacute nodular migratory panniculitis of Vilanova and Piñol

• Distinguished from acute EN by:
  – Rare
  – Older women
  – Unilateral or asymmetrical if bilateral
  – Painless or less tender than acute EN lesions
  – Not associated with systemic symptoms except arthralgias
  – Not associated with underlying diseases
  – Begin as a single lesion that tends to resolve, but migrates centrifugally, forming annular plaques or subcutaneous nodules with central clearing
  – Prolonged course of months to years
EN Pathology

• Septal panniculitis without vasculitis
  – Septal fibrosis and edema
  – Neutrophils (early) or lymphocytes and other mononuclear cells (later), or a mixture
  – In older lesions, histiocytes and multinucleate giant cells may predominate

• Meischer microgranulomas
  – Small collections of macrophages within septa or at septal-lobular interface

• In chronic EN, septal fibrosis and septal granulomas composed of epithelioid histiocytes are seen
Erythema Nodosum

• Course
  – Lasts a few days to weeks and slowly resolves

• Management
  – Identify the trigger
  – Treatment of underlying dz
  – Bed rest
  – Leg elevation
  – NSAID (avoid in IBD --> flare)
  – Potassium iodide (300mg TID solution in juice)
  – Colchicine (esp. if have Behcet)
Primary Panniculitis

Septal

With vasculitis

Thrombophlebitis

Cutaneous PAN
Cutaneous Polyarteritis Nodosum (C-PAN)

- **Tender** erythematous nodules on the lower extremities in the setting of livedo reticularis
- **Ulceration** possible
- **Treatment**
  - NSAIDs
  - Systemic steroids
  - No treatment (resolves spontaneously)
Primary Panniculitis

Lobular

With vasculitis

Nodular vasculitis/erythema induratum
Erythema Induratum/Nodular Vasculitis

• Clinical and pathologic features are identical
• Differ only by the presence of tuberculosis as a precipitating factor in erythema induratum
Erythema Induratum/Nodular Vasculitis

- Delayed type hypersensitivity reaction
  - Get PPD, quant, CXR
    - To TB
      - Associated with +PPD, + PCR of the affected tissue (in 50–70%), active TB, & occ. responds to anti-TB meds
    - Some cases have no assn with TB
  - Other causes: Nocardia, PTU
Erythema Induratum/Nodular Vasculitis

- Not common
- Tender, SQ nodules on the calves of middle-aged women
- Bilateral and less red and tender than EN
- Often ulcerate, drain oily liquid
- Heal with atrophic scars
- Recur over years
Nodular Vasculitis: Pathology

• Lobular panniculitis with lymphocytes and histiocytes arranged in well-formed granulomas
• Fat necrosis (caseous, coagulative in 50%) within the lobules
• Small to medium-size vessel vasculitis at the periphery of the lobules
Nodular Vasculitis
Treatment

- Treat underlying cause:
  - Anti-mycobacterial Abx
  - Discontinue PTU
- Corticosteroids
- NSAIDs
- Potassium Iodide

- Tetracycline
- Mycophenolate mofetil
- Bed rest
- Leg elevation
- Avoid smoking
Primary Panniculitis

Mixed

Lipodermatosclerosis
Lipodermatosclerosis
Liposclerotic panniculitis, Sclerosing Panniculitis

- Commonly seen
- Medial legs, ankle
- Females in 40s
- Venous insufficiency
- Venous stasis dermatitis
- Obesity common
- Acute phase: progressively erythematous, “woody”, tender indurated plaques
  - Easily mistaken for cellulitis
- Chronic phase: atrophy of SQ tissue resulting in inverted champagne bottle deformity
Lipodermatosclerosis
Lipodermatosclerosis: Pathology

• Changes of stasis dermatitis in superficial dermis

• Septal panniculitis
  – Dermal and SQ fibrosis

• Lobular panniculitis
  – Lipophagic fat necrosis
  – Cystic fat degeneration
  – Lipomembranous change (frost on the windowpane)
Lipodermatosclerosis
Treatment and Prognosis

• Chronic and difficult to treat
• Treat venous insufficiency
  – Compression hose (20-30 mm Hg)
  – Elevation
  – Danazol, an anabolic steroid (fibrinolytic)
Primary Panniculitis

Lobular

Without vasculitis

A1ATdef

Pancreatic

With needle-shaped clefts

Sclerema neonatorum

Subcutaneous fat necrosis of newborn

Post steroid panniculitis

Physical

Drug

Cold, Foreign body/Factitial, Trauma
\(\alpha1\)-Antitrypsin Deficiency Panniculitis

- Inherited disorder (gene SERPINA1) characterized by low serum \(\alpha\)-1 antitrypsin levels
  - 120 different alleles divided into M, S, Z
  - PiMM - normal phenotype in 90% of population
  - PiZZ - associated with severe deficiency with emphysema, liver cirrhosis
  - PiZZ or PiSZ phenotypes more prone to panniculitis

- ↓ \(\alpha1\)-Antitrypsin activity and ↓ liver-derived serine protease inhibitor (A1AT inhibits trypsin, collagenase, elastase)
  - Tissue damage from uninhibited complement cascade and inflammatory cell activity, coagulation abnormalities
α-1 Antitrypsin Deficiency Panniculitis

• Recurrent, *tender*, erythematous plaques and nodules on the trunk, buttocks & proximal extremities that *ulcerate* & liquefy with abscess formation & drainage of oily brown liquid

• During the 3rd & 4th decades

• Men=women

• May be precipitated by *pathergy* (trauma)
Alpha 1 Antitrypsin Deficiency
Panniculitis

4-5 cm erythematous, fibrinoid-based, hemorrhagic ulcer in the right groin/suprapubic area

Irregular violaceous non-blanching plaques on the forearm
α1-Antitrypsin Deficiency
Panniculitis Pathology

- Infiltrate involving the lobules early by neutrophils, then lymphocytes, and histiocytes
- Followed by lobular liquefactive fat necrosis
- DDX: Infection, neutrophilic dermatosis
α1-Antitrypsin Deficiency Panniculitis Treatment

• α1-antitrypsin infusion (60 mg/kg/week) x 3-7 weeks → Best optimal serum level >50mg/ml
• Avoid alcohol
• Dapsone
• Doxycycline

• Plasma exchange
• Liver transplant
• Systemic steroids may exacerbate the panniculitis
• Gene Therapy
Primary Panniculitis

Lobular

Without vasculitis

A1ATdef

Pancreatic

With needle-shaped clefts

Sclerema neonatorum

Subcutaneous fat necrosis of newborn

Post steroid panniculitis

Physical

Cold, Foreign body/Factual, Trauma

Drug
Pancreatic Panniculitis

- 2% of pts with pancreatic disorders
  - Pancreatitis—skin resolves
  - Pancreatic carcinoma—skin persists
    - Acinar (84%) > Islet cell
- 40% of cases, the skin lesions are the 1st symptom of the underlying pancreatic dz
- More common in men
- ↑Lipase has clear relationship with panniculitis
Pancreatic Panniculitis

- **Painful**, erythematous & edematous SQ nodules on **pretibial** area, knees and ankles
- **Ulcerate** and drain oily brown substance
- May have visceral fat necrosis (omentum, peritoneum) --> Abd pain
- SQ nodules may occur 1-7 months before pancreatic disease
- **Schmidt's Triad**: SQ nodules, polyarthritis, eosinophilia --> poor prognosis
Pancreatic Panniculitis Pathology

- Neutrophilic lobular infiltrate admixed with lymphocytes, histiocytes, foam cells, & FBGC
- Surrounding fat necrosis with “ghost-like” adipocytes that have intracytoplasmic fine, basophilic granular material (calcification)
Pancreatic Panniculitis Treatment and Prognosis

• Compression & elevation
• Treat underlying disease
• Octreotide – inhibits pancreatic enzyme production
• Clear with resolution of pancreatitis
• In carcinoma, more chronic
Primary Panniculitis

Lobular

Without vasculitis

A1ATdef

Pancreatic

With needle-shaped clefts

Sclerema neonatorum

Subcutaneous fat necrosis of newborn

Post steroid panniculitis

Physical

Drug

Cold, Foreign body/Factitial, Trauma
Sclerema Neonatorum

- Rare now, due to use of thermally controlled incubators
- Affects seriously ill, low birth weight and premature neonates within first week of life
  - Unable to maintain body T or have experienced profound hypothermia
- Higher amount of saturated fats in adipose tissue that solidify more rapidly at low temperatures
- High mortality rate --> sepsis
Sclerema Neonatorum

- 1st few days of life, skin begins to harden, usually initially on the buttocks or lower extremities
- Rapidly spreads to involve the whole body
- Spares palms, soles, and genitalia
- Skin becomes wax-like, dry, cold, rigid
- Limited mobility
- Visceral fat may also be involved
Sclerema Neonatorum

• Pathology:
  – Lobular panniculitis with no fat necrosis
  – No inflammation
  – Needle-shaped clefts in enlarged lipocytes (sites of dissolved triglyceride crystals)
  – Thickened fibrous septa

• Treatment and prognosis:
  – Treat underlying disease
  – Poor prognosis; but if survive will have normal skin
Subcutaneous Fat Necrosis of the Newborn

- Seen in first few weeks in healthy neonates
- Etiology:
  - Obstetric trauma (CS), hypothermia, hypoglycemia, hypoxia
- Clinical:
  - Localized, indurated, erythematous/violaceous nodules and plaques
  - Cheeks, back, buttocks, thighs
  - Resolves in months without scarring
  - Associated with hypercalcemia (1-4 months after) & thrombocytopenia
Subcutaneous Fat Necrosis of the Newborn

• Pathology:
  – Lobular panniculitis
  – Fat necrosis with a dense chronic inflammatory infiltrate
  – Needle-shaped clefts (crystal rosettes) in lipocytes and giant cells

• Treatment and prognosis:
  – Supportive care
  – Systemic steroids in severe inflammation
  – Monitor Ca++ and platelets
  – Excellent prognosis with spontaneous resolution
Post-Steroid Panniculitis

• Occurs during rapid corticosteroid withdrawal in patients treated acutely with high doses of systemic corticosteroids
  – Substantial weight gain has usually occurred during the corticosteroid therapy.

• Firm subcutaneous nodules begin to appear within a month of tapering the corticosteroids

• Areas of abundant subcutaneous fat are favored—the cheeks, trunk, and proximal extremities
Post-Steroid Panniculitis

• Pathology:
  – Similar to subcutaneous fat necrosis of newborn
  – Patchy lobular panniculitis
  – Needle-shaped clefts in adipocytes

• Treatment and prognosis:
  – None, resolves

Figure 1. Multiple firm tender, erythematous subcutaneous nodules on the neck.
Primary Panniculitis

Lobular

Without vasculitis

A1ATdef

Pancreatic

With needle-shaped clefts

Sclerema neonatorum

Subcutaneous fat necrosis of newborn

Post steroid panniculitis

Physical

Drug

Cold, Foreign body/Factitial, Trauma
Physical Panniculitis: Cold

- Popsicle panniculitis: infants, cheeks and chin
- Equestrian panniculitis: thigh
- **Tender** erythematous SQ nodules on exposed surfaces (face, buttocks, lateral thighs) often in winter
- Do not ulcerate
Cold Panniculitis Pathology

- Marked edema in papillary dermis
- Lobular panniculitis
- Necrosis of adipocytes
- Mixed infiltrate with neutrophils, lymphocytes, histiocytes
Traumatic Panniculitis

• Clinical:
  – SQ nodules and plaques +/- erythema
  – Lipoatrophia semicircularis: anterolateral thighs of people who knock them against desk
  – Traumatic fat necrosis of the breast: obese women
  – Mobile encapsulated lipoma: end stage of TP

• Pathology:
  – Lobular panniculitis w/o vasculitis
  – Cystic spaces of fat necrosis surrounded by fibrosis, hemorrhage and inflammation
Physical Panniculitis

- Factitial, foreign body sclerosing lipogranuloma, paraffinoma, silicone granuloma
  - Talwin injection
  - Other injectable substances: milk, feces, Vit K
  - Sclerosing lipogranuloma of the male genitalia: Injection of oily material
  - Grease gun granuloma: verrucous nodules on dorsal hands
Factitial Panniculitis

- Indurated subcutaneous nodules that may undergo liquefaction, ulcerate & discharge pus or thick oil fluid
- Healing leaves depressed scars
- An unusual shape, site, or distribution of lesions
- Path: Necrotizing lobular panniculitis with cystic fat necrosis (swiss cheese appearance) and no vasculitis
- Polarization, EM may be helpful
Talwin injection
Primary Panniculitis

Lobular

Without vasculitis

A1ATdef

Pancreatic

With needle-shaped clefts

Sclerema neonatorum

Subcutaneous fat necrosis of newborn

Post steroid panniculitis

Physical

Cold, Foreign body/Factitial, Trauma

Drug
BRAF Inhibitor Panniculitis

- Tender erythematous subcutaneous nodules on legs, arms and trunk
- Associated with arthralgias
- 3 days to 7 months after starting therapy
- Interface dermatitis and lobular neutrophilic panniculitis

- Treatment
  - NSAIDs
  - Prednisone
Secondary panniculitis

Lobular or mixed

CTD

Subcutaneous Sweet syndrome

LE, DM
Lupus Panniculitis

- Chronic cutaneous form of LE
- Occurs in 2% of patients with SLE (+ANA)
- 70% of patients also have DLE (+DIF)
- DLE + panniculitis = lupus profundus
- Multiple painful, firm, indurated nodules
- Overlying skin may be involved with alopecia, erythema, or atrophy
- Ulceration with subsequent depressed scar formation (lipoatrophy) & calcification may occur
- Typically on the face, buttocks, or proximal extremities of women
Lupus Panniculitis Pathology

- Lobular panniculitis w/o vasculitis
- May extend into the septa
- Dense lobular lymphocytic infiltrate with histiocytes and plasma cells
- Hyaline necrosis of fat lobules
- Mucinous edema, lipomembranous change and calcification
- Identical to panniculitis seen in dermatomyositis
Lupus Panniculitis Treatment and Prognosis

• Treatment:
  – Rest
  – Avoid trauma
  – Photoprotection
  – Antimalarials
  – Mycophenolate mofetil
  – Intraleisional steroids
  – Systemic steroids
  – Dapsone
  – Thalidomide
  – Cyclophosphamide

• Prognosis:
  – Chronic recurrent course
Secondary panniculitis

Lobular or mixed

CTD

LE, DM

Subcutaneous Sweet syndrome
Subcutaneous Sweet Syndrome

• Classic lesions & tender, erythematous SQ nodules on arms, legs, and buttocks
• Fever, joint pain, leukocytosis, ↑ESR
• Pathology
  – Lobular neutrophilic panniculitis
  – Admixed with lymphocytes and histiocytes
  – No vasculitis
• Treatment – Steroids, steroid sparing agents, adalimumab
Panniculitis of Morphea/Scleroderma

- Indurated plaques
- Trunk and extremities
- SubQ involvement can occur in:
  - Generalized or linear morphea
  - Scleroderma
  - Morphea profunda
  - Pansclerotic morphea of childhood: generalized
  - Eosinophilic fasciitis → limbs
Morphea Pathology

- Thickened eosinophilic sclerosis of dermal collagen extending to the septae
- Eccrine glands located within the dermis rather than at dermal-subcutaneous jxn because the SC fat has been replaced by collagen
- Perivascular, periadnexal and septal lymphoplasmacytic inflammation
Panniculitis of Morphea

- Treatment
  - IL or oral steroids
  - Antimalarials
  - MTX
  - Phototherapy
  - Extracorporeal photopheresis
  - Penicillamine
  - Imatinib (tyrosine kinase inhibitor) for pansclerotic morphea
  - Response is poor
Secondary panniculitis

Septal

Morphea, scleroderma, Fasciitis, eosinophilic

Palisading granulomatous dermatitis

Subcutaneous GA

NLD

Sarcoidosis – Darier Roussy

RN

IBD

Cutaneous Crohn disease
Necrobiosis Lipoidica

- Typically involves the anterior legs
- Symmetrical
- Multiple lesions not uncommon
- Plaques with telangiectasia, central depression with yellowish hue
- Ulceration possible
- Women > > men
- Diabetes in 10 to 25 %
Secondary panniculitis

Septal

Morphea, scleroderma, Fasciitis, eosinophilic

Palisading granulomatous dermatitis

Subcutaneous GA

NLD

Sarcoidosis

RN

Cutaneous Crohn disease

IBD
Cutaneous Crohn Disease

- Most often seen in well-established cases of bowel disease
- Does not run a parallel course in the skin
- More often seen in colorectal disease
- Cutaneous lesions may not be contiguous with bowel lesions, occurring at distant sites, face and lower extremities
- No gender predilection
- Approximately half have genital lesions
Cutaneous Crohn Disease

- Nongenital Crohn Disease:
  - Ulcerative plaques, nodules, pustules, abscesses, fissures, fistulas, and sinus tracts

Nodule with suppuration
Cutaneous Crohn Disease
Pathology

- Sarcoidal noncaseating granuloma
- Surrounded by lymphoplasmacytic inflammation
Cutaneous Crohn Disease
Pathology

• Necrobiotic granuloma
  – May resemble necrobiosis or granuloma annulare
  – Must be differentiated from infection
Inflammatory infiltrate in the subcutaneous fat

- Inflammatory disorder of the skin
  - Primary panniculitis
  - Secondary panniculitis
- Infection – Bacterial, Deep Fungal, Mycobacterial
- Neoplasm
- Crystal Deposition Disease associated with Panniculitis
Infectious Panniculitis

- Mostly seen in immunocompromised patients
- Bacteria & fungi involved (Staph aureus, Strep pyogenes, Pseudomonas spp, Klebsiella spp, Norcardia spp, typical and atypical Mycobacterium, Candida spp, Fusarium spp, Histoplasma, Cryptococcus, Actinomyces israeli, Sporothrix schenckii, Aspergillus fumigatus, Alternaria & Chromomycosis)
- Acute & granulomatous lobular inflammation
• 47 yo F w/ right calf pain X weeks, s/p kidney transplant – rule out calciphylaxis
• Fascial and subcutaneous edema
• Myositis vs muscle infarction vs other
• ? Evolving compartment syndrome
Inflammatory infiltrate in the subcutaneous fat

- Inflammatory disorder of the skin
  - Primary panniculitis
  - Secondary panniculitis
- Infection – Bacterial, Deep Fungal, Mycobacterial
- Neoplasm – DLBCL leg type, SPLTCL
- Crystal Deposition Disease associated with Panniculitis
Subcutaneous Panniculitis-like T-cell Lymphoma

- Subcutaneous nodules
- Clues to suspecting are
  - Lesions persist for months
  - Without spontaneous involution
  - Continued progression of lesions
  - Constitutional symptoms
  - No identifiable cause
Subcutaneous Panniculitis-like T-cell Lymphoma
Subcutaneous Panniculitis-like T-cell Lymphoma
Inflammatory infiltrate in the subcutaneous fat

- Inflammatory disorder of the skin
  - Primary panniculitis
  - Secondary panniculitis
- Infection – Bacterial, Deep Fungal, Mycobacterial
- Neoplasm
- Crystal Deposition Disease associated with Panniculitis
Crystal Deposition Disease associated with Panniculitis

- Calciphylaxis → Calcium in small vessels of subQ

- Hyperuricemia → Sodium urate crystals in subQ

- Oxalosis →
  - Primary (AR): Alanine-glyoxylate aminotransferase or D-Glycerate dehydrogenase
  - Secondary: CRF or long term hemodialysis
Gout Panniculitis
Cutaneous Oxalosis
Calciphylaxis

- Clinically, the lesions present as panniculitis or vasculitis
  - Bullae, ulcers, or livedo reticularis can be present
- Painful, increasing violaceous, subcutaneous, firm variably necrotic, ulcerated nodules
Calciphylaxis Pathology

- Occlusive vasculopathy in the dermis
- Necrotizing lobular fat necrosis with panniculat vascular thrombosis
- Extravascular calcification in the panniculus
  - Intravascular calcification not uncommon
Soft tissue X-ray

- Net-like pattern of calcification
- 90% specificity
‘One of the worst ways to die’
Clinical Pearls

• Calciphylaxis is multifactorial, progressive painful and usually fatal

• The prognosis is dismal (median survival of 10 mos.)
  – 1-year survival: 46%
  – 2-year survival: 20%

• Potential complications of gangrene, sepsis, & multisystem organ failure contribute to overall mortality of > 60%
Clinical Pearls

• Under-recognized syndrome
  – Occurs in 4% of hemodialysis patients
  – Non uremic cases
    • Associated with warfarin therapy, CTD, hematologic malignancies, diabetes, primary hyperthyroidism, vitamin D deficiency, protein C and S deficiency, factor V Leiden deficiency, Crohn Disease, and liver disease

• No clearly effective treatments
### Calciphylaxis Treatment Strategies

<table>
<thead>
<tr>
<th>Correct calcium-phosphate balance</th>
<th>Improve tissue perfusion &amp; oxygenation</th>
<th>Wound Care Debridement</th>
<th>Pain control Palliative care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium thiosulfate</td>
<td>TPA</td>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Hyperbaric oxygen</td>
<td>Whirlpool</td>
<td></td>
</tr>
<tr>
<td>Low calcium dialysate</td>
<td>Avoid warfarin for anticoagulation</td>
<td>Maggot</td>
<td></td>
</tr>
</tbody>
</table>

- **Multidisciplinary approach**
- **Mechanism - Thrombotic tissue ischemia; Must address the clot & prevent more**
Panniculitis Made Simple

- Good clinical input is key to understanding the pathology
- Careful selection of biopsy site and a deep specimen containing abundant fat obtained by incisional or excisional biopsy is important for success in diagnosis
- Special stains, immunohistochemistry, molecular testing and evaluation for systemic disorders may need to be obtained
- Treatment is determined by establishing the underlying cause
Thank you!

Bridges.Alina@mayo.edu
Comments/questions?