Panniculitis

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Conflicts of Interest

• Chairman Scientific Advisory Board – Caliber I.D. Inc.
• Member Scientific Advisory Board – MELA Sciences Inc.
• Consultant – Novartis
• Consultant – Alnylam

Disorders of the Subcutis

• Septal
• Lobular
• Mixed
• Inflammatory (N/G/L)
• Pauci-inflammatory
Septal Panniculitis

- Erythema nodosum
- Necrobiosis lipoidica
- Morphea profundus

Erythema Nodosum

Clinical Features

- Young adults
- Nodular or plaque like lesions
  - Anterior aspect of lower legs (common)
  - Arms or abdomen (occurs occasionally)
- Clinical course
  - Initially erythematous, painful area
  - Evolves into nodule or plaque
  - Lasts 10 days to 8 weeks
  - Fever, malaise, arthralgias (variable s/s)

Causation

- Systemic diseases: CTD, Behcet’s, Sweet’s, sarcoidosis, etc.
- Drugs: Numerous drugs have been associated: penicillin, sulfa, Cipro, isotretinoin, etc.
- 30% idiopathic or of unknown cause.
Erythema nodosum:
Well Developed Lesion

- Septal fibrosis
- Septal chronic inflammation
  - Lymphocytes
  - Frank Vasculitis may not be present
  - Granulomatous changes
    - Small granulomatous aggregates of histiocytes
    - Miescher’s radial granuloma
    - Multinucleated giant cells
**Erythema nodosum:**

*Morphologic Clues to underlying etiology*

- Well formed sarcoidal granulomas: sarcoidosis and underlying low grade B cell malignancy
- Extravascular neutrophilia with abscess formation: bacterial infection (STrep) and Crohn’s disease
- Tissue eosinophilia: drug based etiology and Hodgkin lymphoma, distant fungal disease (intrapulmonary)
**CHRONIC ERYTHEMA NODOSUM**

*Clinical Features*

- Also referred to as nodular subacute migratory panniculitis
- Duration: months to years
- Associated conditions:
  - Sarcoidosis
  - Inflammatory bowel disease
  - Chronic rheumatoid disease
- Lesions
  - Less painful than classic erythema nodosum
  - Solitary and indurated

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**CHRONIC ERYTHEMA NODOSUM**

- Subcutaneous Tissue Septa
  - Thickened (widened)
  - Prominent lymphohistiocytic infiltrate
  - Occasionally find well formed granulomata with extension into lobules
    - Sarcoidosis and Crohn’s disease
Lobular Panniculitis

Cell Rich Inflammatory

Versus

Cell Poor

Classification of Cell Rich Panniculitis

- Neutrophil Dominant
- Mixed neutrophilic and granulomatous (erythema induratum, IBD, RA, hepatitis C)
- Lymphocyte Dominant (Lupus profundus, atypical lymphocytic lobular panniculitis, panniculitic T cell lymphoma)

Neutrophilic panniculitis

- Infective neutrophilic panniculitis
- Non-infective neutrophilic panniculitis
Neutrophilic panniculitis
Infective

- Usually reflects hematogenous dissemination

- Angioinvasive fungus (mucor) is the commonest pathogen although bacterial pathogens (staphylococcus and listeria)

- Caveat: Infectious panniculitis, however, in the setting of immunosuppression may be cell poor!
Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis

Illustrated Case
66 year old woman with a history of AML

Paraneoplastic Subcutaneous Sweet’s Syndrome
**Neutrophilic panniculitis**

*Noninfective*

- Causes:
  - Rheumatoid arthritis
  - Behcet’s disease
  - Inflammatory Bowel Disease
  - Hepatitis C
  - Subcutaneous Sweet’s syndrome as a manifestation of an underlying hematologic dyscrasia

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**Alpha 1 Antitrypsin Deficiency**

- Draining nodules on trunk, buttocks and proximal extremities
- Other protease inhibitor deficiency such as emphysema, hepatitis and angioedema,
- Necrotizing neutrophilic and lobular panniculitis
Eosinophilic Panniculitis

- Clinical lesion
  - Isolated nodule
  - May resemble EN
- Seen in a variety of disorders
  - Hypersensitivity reaction to drugs
  - HES i.e. myeloid or clonal T cell disorder
  - Reaction to infections/infestations
    - Parasites, Metazoal agents, Nematoad Gnastostoma spingerus
Erythema Induratum/Nodular Vasculitis
Clinical Features

• Predilection for the lower extremities/calf
  • Can involve shins: rarely involve buttocks, arms

• Lesions
  • May present as isolated deep nodules
    • May form plaques
    • Chronic forms may ulcerate
  • May present as multiple subcutaneous nodules
    • Occur in corps
    • May persist, form plaques and ulcerate
    • Nodules may resolve and then recur

Erythema induratum/nodular vasculitis
Etiology - Diverse

• Infections
  • Mycobacterial infection
  • Hepatitis C infection
  • Delayed hypersensitivity or Arthus type III reaction
  • Type of id reaction to non-viable components of the cell wall of M. tuberculosis
  • PCR studies show that as many as 80% of patients with erythema induratum are positive for mycobacterial DNA
Erythema induratum/nodular vasculitis
Histopathology

- Lobular or septolobular panniculitis
- Fully developed lesions
  - Vasculitis with a granulomatous infiltrate affecting both arteries and veins of varying caliber
    - Inflammation: neutrophilic, lymphocytic and/or granulomatous
    - Lymphocytic vasculopathy: Endothelial swelling and necrosis
    - Thrombosis, endothelial cell obliteration, ischemic necrosis
  - Lobules with granulomatous inflammation and necrosis (fibrinoid or coagulative fat necrosis)
  - Septum with inflammation, granulomata and necrosis
  - May show dermal inflammation and ulceration
Lupus Profundus

Lupus Panniculitis

Clinical

• Subcutaneous nodules or indurated plaques
  • May develop painful, large ulcers
  • Proximal extremities, trunk, lower back
• Chronic and recurrent disorder
• Associated conditions
  • Lupus erythematosus (systemic and discoid)
    • 1-3% of patients with LE
  • No lupus subtype or autoimmune disease
    • About 50% of cases

Histopathology

• Lobular panniculitis
  • Lymphocytic infiltrate
    • Plasma cells, eosinophils (variable findings)
  • Lymphocytic hyalining vasculitis with onion skin-like change (occasionally)
  • Lymphoid follicules
    • 20-50% of the cases
  • Lipophages, membranocystic change, calcification (variable findings)
  • Septa with hyalinizing fibrosis extending into lobules
    • Variable myxoid change
• Epidermis and dermis
  • 50% demonstrate the changes of lupus erythematous
Subcutaneous Panniculitis-like T Cell Lymphoma

- **Definition:**
  - Primary cytotoxic T-cell lymphoma involving the fat, comprising atypical lymphoid cells of varying size, representing less than 1% of all lymphoma

- Extracutaneous dissemination is rare
- The main sequela which ultimately leads to patient demise is hemophagocytic syndrome due to cytokine driven activation of histiocytes (phagocyte activating factor).
- Hallmarks of HPS: pancytopenia, fever, hepatosplenomegaly
- Although the natural course is aggressive reasonable success has been achieved with combination chemotherapy
Rimming by lymphocytes of individual fat cells.
Significant fat necrosis

A Thrombogenic Vasculopathy

SCUL
Subcutaneous Panniculitis like T Cell Lymphoma

Phenotypic profile:
- The cells have a mature T-cell phenotype
- The cells are usually CD8 granzyme TIA positive except when they are of the gamma delta subtype whereby the cells are negative for CD4 and CD8.
- Loss of pan T cell marker expression for both CD5 and CD7 is highly characteristic.
- Intermediate to high proliferation index
- T cell clonality studies are usually positive
- The cells may be of the gamma delta subtype in 25% of cases; the remainder are derived from T cells of the alpha beta subtype
CCL5 expression in Gamma/Delta T-cell lymphoma localized to the subcutis. A, B (case 1); C, D (case 7); A, C (H&E); B, D (CCL5). There is extensive and intense positivity of the neoplastic cells for CCL5. E, F (case 1), CCL5. Prominent granular cytoplasmic staining of CCL5 is seen in necrotic cells. Bars represent 50 μm.

Pauci-inflammatory Lobular Panniculitides

Lipodystrophy
Lipodermatosclerosis
Pancreatic fat necrosis
Traumatic Fat Necrosis
Factitial/lipid infection
Calciphylaxis
THE LIPODYSTROPHIES
Clinical Features

- Lipodystrophy: atrophy of the subcutaneous fat
  - Primary (idiopathic)
    - Total, partial or localized
  - Secondary (acquired)
    - Associated systemic disorders
      - Diabetes
      - Other endocrinopathies
    - Associated with prior Panniculitides
      - Lupus Panniculitis
      - Connective tissue panniculitis
    - Subcutaneous morphea
      - Total, partial or localized

- Total lipodystrophy
  - Effects the entire skin
  - Congenital or acquired
    - Acquired variant: associated with metabolic disorders

- Partial lipodystrophy
  - Symmetrical loss of facial fat
    - Unilateral variants occur
  - Atrophy of fat progresses to involve the upper trunk and arms
THE LIPODYSTROPHIES
Clinical Features

• Acquired partial lipodistrophy has 2 forms
  • 1) Atrophy of facial fat with or without atrophy of fat of the arms and legs
  • 2) Concomitant increase in (hypertrophy) of fat of the lower part of the body (buttocks, legs)

• Associated conditions
  • Recurrent infections
  • Endocrinopathies
  • Glomerulonephritis
  • HIV disease
    • Protease inhibitor therapy
    • Reverse transcriptase inhibitors

THE LIPODYSTROPHIES
Histopathology

• Early lesions
  • May begin as mild lobular panniculitis

• Established lesions
  • Atrophy of the subcutaneous fat (all cases)
  • Decrease in fat, small fat cells, septa with hyaline or myxoid connective tissue and many capillaries (some cases)
  • Occasionally perivenular lymphoid aggregates
    • Look for associated causes of secondary lipodistrophy
      • Lupus panniculitis, morphea, connective tissue diseases
    • Look for residual evidence of the primary disease
Lipodermatosclerosis
Clinical Features

• Clinical findings
  • Lower extremities
  • Early lesions: inflamed, indurated plaques
  • Stasis changes, mottled hyperpigmentation
  • Progressive hardening of the skin (sclerosis)
  • Champagne-glass deformity (severe form)

• Pathophysiology
  • Ischemia reflecting either venous insufficiency or arterial ischemia
Lipodermatosclerosis

Histopathology

- **Cardinal Hallmarks:**
  - Stasis changes in the dermis characterized by hemosiderin deposition, reactive angioendotheliomatosis, and fibrosis VERSUS Thrombotic microangiopathy with secondary fibrosis (etiology dependent)
  - Subcutis: lipomembranous fat necrosis and variable fibrosis and atrophy
Etiologic Considerations

- Lipodermatosclerosis is in essence a form of ischemic panniculitis
- Hence etiologies include:
  - Stasis
  - Defects in anticoagulation: Factor V Leiden
  - Primary antiphospholipid antibody syndrome

Extrinsic Causes of Panniculitis

Factitial panniculitis
- Secondary to injections of various substances
  - Pharmacologic agents, milk, oils, paraffin, toxic agents
- Histopathology
  - Mixed septal and lobular
  - Foreign body giant cells (polarized light examination) with engulfment of lipid by macrophages (dermis frequently involved)
  - Paraffin induced (sclerosing lipogranuloma) type
    - Swiss cheese appearance (fatty degeneration and formation of cystic spaces surrounded by foreign body giant cells)
    - Lipophages
    - Septa with hyaline fibrous tissue

Fat necrosis
Traumatic Fat necrosis

- Secondary to external injury/trauma
- Histopathology
  - Early stage
    - Small cystic spaces
    - A few neutrophils
  - Later stages
    - Microcysts, lipomembranous change, lipid-laden histiocytes
    - Fibrosis
    - Encapsulated fat necrosis
Subcutaneous Fat Necrosis of the Newborn: Histopathology

**Lobular panniculitis**
- Focal fat necrosis
- Fat cysts
- Adipocytes with intracytoplasmic clefts and radiating strands of residual eosinophilic cytoplasm
  - "Dissolved fat crystals" intracytoplasmic spaces (formalin)
  - "Fat crystals" identifiable in frozen section
  - Intracytoplasmic triglyceride deposits
- Inflammatory infiltrate
  - Lymphocytes, histiocytes, foreign body giant cells, a few eosinophils
Pancreatic Panniculitis
Pancreatic Panniculitis

Clinical Findings

- Subcutaneous nodules or indurated plaques
  - Extremities, usually lower, most common
  - Thighs, buttocks, lower trunk
  - May be painful or asymptomatic
  - Lesional ulceration associated with granular oily exudate

- Associated conditions
  - Acute Pancreatitis
  - Pancreatic carcinoma (acinic cell carcinoma)
  - Circulating lipase or amylase localize to the adipocytes of the lower extremity causing saponification
  - Polyserositis, arthritis, eosinophilia, leukemoid reaction

Hemorrhagic Pancreatitis and Fat Necrosis

- Extensive necrosis has caused loss of the normal lobular surface markings of the pancreas
- Chalky white surface represents saponification chelation of ca with fatty acids liberated by pancreatic enzymes
- Hemorrhage caused by digestion of vessel walls by pancreatic enzymes

Physical exam
Pancreatic Panniculitis
Histopathology

• Lobular panniculitis centered on the septum
• Early lesions
  • "Enzymatic fat necrosis": ghost-like cytoplasmic outlines
• Later lesions
  • Breakdown and liquefaction of fat cells
    • Basophilic: calcium deposits, hemorrhage, inflammation
  • Fibrosis
  • Fat necrosis, enzymatic
    • Ghost-like outlines
  • Pale basophilic cytoplasmic hue (calcium salts)
  • Inflammatory infiltrate
    • Neutrophils, lymphocytes, giant cells, lipophages
Calciphylaxis

Clinical

- Ulcerated plaques
  - Often bilateral, symmetrical, especially when on extremities
  - Truncal lesions, predominantly abdominal
- Ulceration,
  - sharply demarcated
  - often painful
- Associated conditions
  - Hyperparathyroidism, primary or secondary
  - Secondary hyperparathyroidism associated with renal failure
- Mortality
  - 20% if lesion peripheral (extremities)
  - 60-80% if lesion central (truncal)
Vascular changes can be heterogeneous. Endoluminal calcification to small vessel thrombosis without calcium.
Diagnosis

- Organizing endoluminal thrombotic calific microangiopathy affecting small arteries, venules and capillaries.
- The endoluminal fibro-occlusive calcific changes were largely localized to arteries while the pauci-inflammatory thrombotic changes affected capillaries and venules.
- Typical for Calciphylaxis.

Pathogenesis

- Although calciphylaxis is a form of vascular calcification, vascular calcification does not equal calciphylaxis.
- Monckeberg's medial calcific sclerosis is an innocuous form of dystrophic calcification affecting the media of small and medium arteries.
- Calciphylaxis vascular sensitization by PTH along with an external stimulus resulting in intimal calcification occurs.
- An underlying coagulopathy, most frequently related to occult protein C or S deficiency is found in some patients.

Calciphylaxis Pathogenesis

- Sensitization of endothelial cells by parathormone, critical.
- Underlying subclinical coagulopathy
  - Protein C deficiency
  - Protein S deficiency
Osteopontin Expression in Biopsies of Calciphylaxis, Magro et al

- Evaluated the expression of Osteopontin as a diagnostic marker and its role in lesional pathogenesis in 25 patients with Calciphylaxis.

- Lower extremities were the most commonly involved areas; however a truncal and genital distribution was also noted in 3 cases.

- Renal failure was present in at least 13 of 25 cases.
  - One patient had myeloproliferative disorder and one patient had advanced colon cancer.

- The dominant pathology was localized to the subcutaneous fat, characterized by mural calcification and luminal thrombosis affecting.
  - In 2 cases, a subcutaneous thrombogenic vasculopathy without calcification was noted.

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