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-inflamatory
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

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
  - Behçet's disease
  - Inflammatory Bowel Disease
  - Hepatitis C
  - Subcutaneous Sweet's syndrome as a manifestation of an underlying hematologic dyscrasia

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 hyalinizing vasculitis with onion skin-like change (occasionally)
  • Lymphoid follicles
    • 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 erythematosus
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.

Subcutaneous nodules
Characteristically Involving the extremities And trunk
The main symptoms May be those related To the nodules

- 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
**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.
Subcutaneous T cell Lymphoma

CD8

Granzyme

Ki67
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
  Fat necrosis

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
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

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

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 calific 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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