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)
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
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
  • 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!

• Non-infective neutrophilic panniculitis
  • Causes:
    • Rheumatoid arthritis
    • Behcet’s disease
    • Inflammatory Bowel Disease
    • Alpha 1 antitrypsin deficiency
    • Hepatitis C
    • Panniculitic Bacterid
    • Subcutaneous Sweet’s syndrome as a manifestation of an underlying hematologic dyscrasia

Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis

Background: Lobular panniculitic neutrophilic dermatoses encompass layers of panniculitis, necrotizing lobular, panniculitis, erythematous inflammation and subcutaneous fat. Both conditions, while usually panniculitis includes lobular neutrophilic dermatoses are described in this paper. Panniculitis is a rare condition that may cause a range of symptoms and have a variety of causes.

Methods: We describe 9 cases of acute panniculitis due to neutrophilic dermatosis that presented as an acute onset of neutrophilic dermatosis.

Results: Four males and five females had a mean age of twelve years. All cases were characterized by extensive lesions. The predominant clinical findings included tender nodules, with or without surrounding erythema, and ulceration. Microscopically, there was a neutrophilic infiltrate with perivascular and subcutaneous fat. A distinctive histopathological feature was the presence of neutrophilic lobular panniculitis, with a mononuclear infiltrate. The patients were treated with systemic corticosteroids, antibiotics, and antithrombotic agents. No recurrence was noted.

Subheading: Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis

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Illustrated Case

66 year old woman with a history of AML

Paraneoplastic Subcutaneous Sweet’s Syndrome

Sweet's syndrome in the setting of CD34-positive acute myelogenous leukemia treated with granulocyte colony stimulating factor: evidence for a clonal neutrophilic dermatosis

Background: Sweet’s syndrome in the setting of hematologic disorders can be complicated due to paraneoplastic-associated disease, especially in leukemias, and it may be a rare manifestation. This case highlights the diagnostic challenges and management options.

Materials and Methods: The case presents a patient with CD34+ acute myelogenous leukemia (AML) treated with granulocyte colony stimulating factor (G-CSF). Histological examination revealed neutrophilic infiltration, mimicking Sweet’s syndrome. Immunohistochemistry confirmed the presence of myeloid cells consistent with AML.

Results: The patient responded well to granulocyte colony stimulating factor (G-CSF) therapy, with resolution of skin lesions and improvement in hematologic parameters. Long-term follow-up showed a complete remission of both leukemia and dermatologic manifestations.

Conclusion: The case underscores the importance of a comprehensive approach to the diagnosis and management of Sweet’s syndrome in patients with hematologic disorders, emphasizing the role of hematopoietic cell transplantation in achieving long-term remission.

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Sweet's syndrome in the setting of CD34-positive acute myelogenous leukemia treated with granulocyte colony stimulating factor: evidence for a clonal neutrophilic dermatosis

In the undigested lanes for both the bone marrow and buccal mucosa, 2 distinct alleles are present. The Hepa II digested lane in the bone marrow specimen shows preferential protection of 1 allele whereas the negative buccal mucosa shows equal protection of both alleles; the findings are consistent with a clonal population in the bone marrow.

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. tuberculosum
  - PCR studies show that as many as 80% of patients with erythema induratum are positive for mycobacterial DNA

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

Lupus Panniculitis

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

Lupus profoundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia
- Tender erythematous nodules and plaques
- α/β: CD4+/CD8+, CD56-/phenotype
- Systemic symptoms frequent
  - Weight loss, fever, fatigue
  - Variable hemophagocytic syndrome
- Lymphocytic lobular panniculitis with fat necrosis
- 5-year survival > 80%
- Precursor lesion: atypical lymphocytic lobular panniculitis
Atypical Lymphocytic Lobular Panniculitis
Preneoplastic waxing and waning Phase of SFTCL

Weber Christian Disease
- Classic case: recurrent lower extremity nodules, with fever, arthritis and malaise
- Relapsing febrile nonsuppurative nodular panniculitis
- Lobular panniculitis
- Varied histologic pictures temporally associated with the time course of the lesion: neutrophils, mononuclear cells, lipophages, ringed granulomas and fibrosis
- Probably varied etiologies and some original cases represent SCTCL and alpha 1 antitrypsin deficiency

Pauci-inflammatory Lobular Panniculitides
- Lipodystrophy
- Lipodermatosclerosis
- Pancreatic fat necrosis
- Traumatic Fat Necrosis
- Factitial/lipid infection
- Calcinosis

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
Lipoatrophy

Clinical Features

• 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

Acquired partial lipodystrophy 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 lipodystrophy
      • 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

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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
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 calcific 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 = 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.

- Osteopontin expression was confined to the subcutis, most striking in calcified vessels but also apparent in vessels without calcification.
- Calciphylaxis represented a unique calcific thrombogenic vasculopathy not limited to renal failure.
- Ectopic osteopontin expression may define a critical and initial event in the calciphylaxis pathogenesis. Therapeutic agents designed to reduce osteopontin expression may be of value in its treatment.

Osteopontin expression was confined to the subcutis, most striking in calcified vessels but also apparent in vessels without calcification.
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