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PANNICULITIS
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MOSTLY SEPTAL PANNICULITIS

- **Erythema nodosum**
  - Clinical
    - Tender erythematous nodules or plaques of anterior legs, usually bilateral, non-ulcerating, non-scarring
    - Reaction – most often a drug, sarcoid, or inflammatory bowel disease in adults; streptococcal infection in children; association may not be identifiable
  - Histopathology
    - Mostly septal granulomatous panniculitis without necrosis, Miescher’s radial granulomas, septal widening
    - Neutrophilic inflammation and hemorrhage in early lesions, limited inflammation in old lesions

- **Eosinophilic fasciitis and morphea profunda**
  - Eosinophilic fascitis (EF)
    - Sudden onset, often after vigorous exercise or trauma, also a manifestation of chronic graft-versus-host disease
    - Woody induration, sometimes with restricted range of motion; “Groove” due to retraction of the subcutaneous tissue along superficial veins
    - Sparing of digits (versus scleroderma)
    - Peripheral blood eosinophilia and hypergammaglobulinemia
  - Morphea profunda/deep morphea
    - Distinguished from EF mainly by clinical features
  - Histopathology
    - Hyaline sclerosis and widening of subcutaneous fat septa and fascia
    - Lymphoplasmacytic inflammation mostly septal, sometimes lobular; involvement also of fascia, muscle; variable eosinophil infiltrate

- **Whipple’s disease**
  - Clinical
    - Rare multisystem chronic infection with Tropheryma whippiei (gram-positive rod-shaped bacillus): arthralgias, arthritis, fever, weight loss, diarrhea, malabsorption and malnutrition-related skin abnormalities
    - Erythema nodosum–like subcutaneous nodules before or after start of antibiotic therapy, mainly of lower extremities
  - Histopathology
    - Mostly septal panniculitis with lymphocytes, neutrophils, foamy histiocytes; organisms identified as PAS-positive diastase-resistant intracytoplasmic granules in histiocytes, by PCR and/or immunohistochemistry
H syndrome

- Clinical
  - Autosomal recessive
  - Symmetrical hyperpigmentation of inner thighs, indurated patches with hypertrichosis of abdomen and lower extremities, hearing loss, flexion contractures of digits, short stature, diabetes mellitus, lymphadenopathy
- Histopathology
  - Mostly septal and periseptal panniculitis with infiltrates of CD68+ S100+ CD1a- histiocytes with abundant pale sometimes vacuolated cytoplasm; emperipolosis of lymphocytes, plasma cells, and neutrophils; scattered lymphocytes or lymphoid aggregates, and plasma cells; septal fibrosis and widening; features in common with Rosai-Dorfman disease

MOSTLY LOBULAR PANNICULITIS: DIAGNOSES AND REACTION PATTERNS

Apha-1-anti-trypsin panniculitis

- Clinical
  - Most often in patients with ZZ phenotype and very low serum alpha-1-antitrypsin levels; also MZ, MS, and rarely SZ or SS phenotypes
  - Female > male; onset 3rd – 6th decade of life
  - Ulcerating erythematous plaques and nodules of thighs, hips, buttocks, with drainage of oily material; induced/aggravated by trauma or over-activity
- Histopathology
  - Neutrophilic mostly lobular panniculitis with lobular and perilobular fat necrosis; early lesions show septal neutrophilic inflammation (“splaying” of collagen); also neutrophilic inflammation and necrosis of deep dermis

Cold panniculitis

- Clinical
  - Infants > children >> adults (likely due to differences in fat composition)
  - Cheek or chin of infants, thighs of adults especially women wearing tight-fitting clothes while cycling or horseback riding
  - Reported under terms reflecting etiology, including popsicle panniculitis of cheeks and equestrian panniculitis of lateral thighs
  - Erythematous then violaceous indurated nodule or plaque
- Histopathology
  - Perivascular dermal inflammation > lymphohistiocytic panniculitis with inflammation of dermal-subcutaneous junction and superficial fat

Cytophagic panniculitis

- Clinical
  - Most often lymphoma with systemic hemophagocytic syndrome including fever, pancytopenia, hepatomegaly, coagulopathy, EBV infection
- Histopathology
  - Lobular atypical lymphocytic infiltrate
  - Cytophagic (“bean-bag”) histiocytes
Drug-induced panniculitis (reaction to systemically administered drug)
- Implicated drugs include apomorphine, BRAF inhibitors (vemurafenib, dabrafenib), tyrosine kinase inhibitors (imatinib, nilotinib), anti-PD agents (pembroluzimab, nivolumab) and anti-CTLA4 medication (ipilimumab)
- Histopathology of mostly neutrophilic, eosinophilic, and/or granulomatous/sarcoidal mostly lobular panniculitis or erythema nodosum-like mostly septal panniculitis

Eosinophilic panniculitis (reaction pattern)
- Eosinophils may be a prominent part of lobular or septal panniculitis in various settings, including arthropod bite reaction, injection site (local drug) reactions, infection and infestation, factitial panniculitis, or Wells’ syndrome
- Eosinophils may be a variable, usually minor component of the infiltrate in erythema nodosum, eosinophilic fasciitis, morphea profunda, lupus panniculitis, and other types of panniculitis

Erythema induratum
- Clinical
  - Nodules often with ulceration, typically of posterior legs; association with tuberculosis, uncommonly other disorders e.g. Crohn’s disease
- Histopathology
  - Necrotizing vasculitis with mostly lobular panniculitis; necrosis at center of fat lobules; neutrophilic or granulomatous inflammation, depending on lesion duration

Factitial, traumatic, injection-site panniculitis
- Clinical
  - High index of clinical and histopathological suspicion needed for diagnosis
  - Etiologies include injected drugs or cosmetic fillers (prescribed or illicit), external trauma
  - Any anatomic site, depending on etiology, but often buttocks, arms, thighs
  - Migration of material (e.g. ruptured silicone breast implant) may result in panniculitis at a distant site
- Histopathology
  - Neutrophilic and/or granulomatous mostly lobular panniculitis, variable hemorrhage, fibrosis
  - Swiss cheese-like pattern (variously sized pseudocysts or “holes”), foamy histiocytes, and multinucleated giant cells
  - Polarizable or non-polarizable foreign material may be identified

Gouty panniculitis
- Clinical
  - Ulcerating nodules or plaques, typically of legs, with drainage of monosodium urate crystals; arthritis
- Histopathology
  - Lobular fat necrosis, lymphohistiocytic inflammation including granulomas with multinucleated giant cells, amphophilic refractile needle-shaped urate crystals
Granulomatous panniculitis (reaction pattern)
- Mostly septal
  - Erythema nodosum
- Mostly lobular
  - Infection
  - Traumatic, factitial, injection-site reaction
  - Subcutaneous involvement alone or as component of a usually dermal granulomatous disorder, such as granuloma annulare, necrobiosis xanthogranuloma, rheumatoid nodule, sarcoid

Infection-induced panniculitis
- Clinical
  - Infection should be in differential diagnosis when evaluating most cases of panniculitis, particularly in immunosuppressed patients
  - Acute erythematous nodules or plaques, chronic lesions with/without ulceration, duration depending on causative organism and host reaction; any anatomic site
- Histopathology
  - Suppurative, granulomatous, and/or pauci-inflammatory
  - Fungal, mycobacterial, or bacterial etiology; organisms identified by histochemical stains and/or tissue culture

Lipodermatosclerosis
- Clinical
  - Most often in women, average age 60 years, with venous insufficiency
  - Circumferential hyperpigmentation and sclerosis of lower legs and ankles, with inverted bottle-like configuration – mainly clinical diagnosis
- Histopathology
  - Stasis changes of superficial dermis
  - Lipomembranous panniculitis pattern characteristic but not specific for lipodermatosclerosis: lobular fat necrosis, “frosty” pseudo-microcysts, foamy histiocytes, fibrosis; pseudoxanthoma elasticum-like septal elastic fibers

Localized lipoatrophy
- Clinical
  - Solitary or few lesions; lipoatrophic panniculitis of childhood often annular
  - Idiopathic, injection-site reaction, response to unidentified trauma, or less often a manifestation of autoimmune connective tissue disease
- Histopathology
  - Absent or decreased fat with or without lymphohistiocytic inflammation
  - “Involutional lipoatrophy” pattern characterized by small fat lobules composed of small lipocytes with multiple capillary-size small vessels
  - Lipoatrophic panniculitis of childhood with mostly lobular lymphohistiocytic inflammation; may resemble pediatric subcutaneous panniculitis-like T-cell lymphoma
**Lupus panniculitis (LEP)**
- Clinical
  - Panniculitis with or without associated cutaneous or systemic LE
  - Subcutaneous nodules and/or lipoatrophy mainly of proximal sites, particularly shoulders, arms, thighs, buttocks
- Histopathology
  - Mostly lobular panniculitis; hyaline necrosis and lymphoid nodules often with germinal centers are the two key features; also lymphocyte karyorrhexis, plasma cells, extravascular calcification
  - Differential diagnosis with subcutaneous panniculitis-like T-cell lymphoma may be problematic particularly when lymphocytic infiltrate is diffuse: plasma cells, nodules of B-cells in addition to T-cells, low Ki-67 expression favor LEP

**Neonatal panniculitis**
- Sclerema neonatorum
  - Clinical
    - Rarely observed condition of severely ill often premature or low birth weight neonates, onset within days of birth, usually fatal
    - Rapidly advancing extensive woody induration, first of buttocks and thighs
  - Histopathology
    - Radial arrays of needle-shaped lipid crystals in adipocytes, minimal or no inflammation
- Subcutaneous fat necrosis of newborn
  - Clinical
    - Indurated plaques or nodules of cheeks, buttocks, thighs, back, or extremities in full-term infants, due to perinatal complications
  - Histopathology
    - Lobular lymphohistiocytic inflammation with multinucleated giant cells and lipophagic histiocytes, fat necrosis, radial arrays of needle-shaped lipid crystals in adipocytes

**Neutrophilic panniculitis** (reaction pattern)
- Neutrophils may be the dominant cellular infiltrate in various settings, including alpha-1-antitrypsin panniculitis, early phase of erythema nodosum, systemic drug-induced panniculitis, factitial/traumatic panniculitis, injection site reactions, infection-induced panniculitis, pancreatic panniculitis, and subcutaneous Sweet’s syndrome

**Pancreatic panniculitis**
- Clinical
  - Subcutaneous nodules, often with ulceration, usually of legs but also may involve arms, thighs, trunk; may be presenting sign of pancreatic carcinoma or pancreatitis or occur later in the course of pancreatic disease
- Histopathology
  - Basophilic fat necrosis, saponification, “ghost-like” lipocytes, neutrophilic and granulomatous inflammation
- **Postirradiation pseudosclerodermatous panniculitis**
  - **Clinical**
    - Indurated plaque involving site of radiation, months to years after completion of therapy, most often for breast cancer
  - **Histopathology**
    - Lobular panniculitis with lipophagic granulomas, lymphocytes and plasma cells; septal fibrosis and widening with “radiation fibroblasts” – pattern distinct from post-radiation morphea

- **Post-steroid panniculitis**
  - **Clinical**
    - Mainly in children, following withdrawal of high-dose systemic steroids, typically involves face but also trunk or extremities
  - **Histopathology**
    - Mixed mostly lymphohistiocytic inflammation with multinucleated giant cells; radial arrays of needle-shaped lipid crystals in adipocytes

- **Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)**
  - **Clinical**
    - ~1% of cutaneous lymphomas
    - Multiple subcutaneous nodules or plaques of extremities and/or trunk
    - Fever, fatigue, lymphadenopathy, splenomegaly, hepatomegaly; hemophagocytic syndrome in some patients
  - **Histopathology**
    - Diffuse lobular infiltration of atypical small to medium size lymphocytes, adipocyte “rimming” (characteristic but not specific feature), karyorrhexis
  - **Cytotoxic immunophenotype**
    - CD3+ CD8+ TIA1+, granzyme B+, beta F1+ (TCR α/β)
    - CD4- CD56- EBV-
    - Rimming of adipocytes by Ki-67 positive lymphocytes
  - γ/δ T-cell lymphoma, extranodal T/NK-cell lymphoma, and other T-cell and B-cell lymphomas may involve subcutis but are not classified under the term SPTCL