MOSTLY SEPTAL PANNICULITIS

- **Erythema nodosum**
  - **Clinical**
    - Tender erythematosus nodules or plaques of anterior legs, usually bilateral, non-ulcerating, nonscarring.
    - Often reaction to 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 in early lesions, limited inflammation in old lesions.

- **Eosinophilic fasciitis and morphea profunda**
  - **Eosinophilic fasciitis (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 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 whipplei (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 perisepetal panniculitis with infiltrates of CD68+ S100+ CD1a- histiocytes with abundant pale sometimes vacuolated cytoplasm; emperipolesis 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 deficiency 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, and/or buttocks, with drainage of oily material; induced/aggravated by trauma or over-activity.
- Histopathology
  - Mostly lobular neutrophilic 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 mostly lymphocytic inflammation > lymphohistiocytic panniculitis involving 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 with 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-PD1 agents (pembrolizumab, nivolumab) and anti-CTLA4 medication (ipilimumab)
- Mostly neutrophilic, eosinophilic, and/or granulomatous/sarcoidal mostly lobular panniculitis or erythema nodosum-like mostly septal panniculitis.

Eosinophilic panniculitis (reaction pattern)
- Eosinophils may be prominent component of lobular or septal panniculitis in various settings, including arthropod bite reaction, injection site (local drug reaction), infection/infestation, factitial panniculitis, and 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) and external trauma.
  - Any anatomic site, depending on etiology, but often buttocks, arms, thighs
  - Migration of material (e.g. ruptured silicone breast implant or liquid silicone) may result in panniculitis at a distant site.
- Histopathology
  - Neutrophilic and/or granulomatous mostly lobular panniculitis, variable hemorrhage, fibrosis.
  - Swiss cheese-like pattern (variably 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, refractile urate crystals.
Granulomatous panniculitis (reaction pattern)
- Mostly septal
  - Erythema nodosum most common.
- Mostly lobular
  - Infection, factitial/traumatic, injection-site reaction.
  - Subcutaneous involvement alone or as component of a usually dermal granulomatous disorder, such as granuloma annulare, necrobiotic xanthogranuloma, rheumatoid nodule, sarcoid.

Infection-associated 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 +/- ulceration, duration depends 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, and fibrosis.

Localized lipoatrophy
- Clinical
  - Solitary/few lesions; lipoatrophic panniculitis of childhood often annular
  - Idiopathic, injection-site reaction, post trauma, or rarely a manifestation of autoimmune connective tissue disease.
- Histopathology
  - Absent or decreased fat with or without lymphohistiocytic inflammation.
  - “Involutional lipoatrophy” pattern
    - Small fat lobules composed of small lipocytes with multiple capillary-size small vessels.
  - Lipoatrophic panniculitis of childhood
    - Mostly lobular lymphohistiocytic inflammation; may resemble subcutaneous panniculitis-like T-cell lymphoma.
- **Lupus panniculitis (LEP)**
  - **Clinical**
    - Subcutaneous nodules and/or lipoatrophy mainly of proximal sites, particularly shoulders, arms, thighs, buttocks, with or without associated cutaneous or systemic lupus erythematosus.
  - **Histopathology**
    - Mostly lobular panniculitis; hyaline necrosis and lymphoid nodules often with germinal centers are 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 rapidly advancing extensive woody induration, in severely ill often premature or low birth weight neonate, onset within days of birth, usually fatal.
    - **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 deficiency panniculitis, early erythema nodosum, systemic drug-induced panniculitis, factitial/traumatic panniculitis, injection site reactions, infection-associated panniculitis, pancreatic panniculitis, and Sweet’s syndrome.

- **Pancreatic panniculitis**
  - **Clinical**
    - Subcutaneous nodules, often with ulceration, usually of legs but also may involve arms, thighs, or 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
  - Mostly lobular mainly 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), and karyorrhexis.
- Cytotoxic immunophenotype
  - CD3+ CD8+ TIA1+, granzyme B+, beta F1+ (TCR α/β)
  - CD4- CD56- EBV-
  - Rimming of adipocytes by Ki-67 positive atypical 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.