Review of Granulomatous, Metabolic and Depositional Disorders
Granuloma Annulare

- Benign
- Asymptomatic
- Self-limited granulomatous disease of the dermis
- Five common Variations
  - Localized
  - Generalized
  - Subcutaneous
  - Perforating
  - Patch

http://www.aocd.org/?page=GranulomaAnnulare
Granuloma Annulare

- Etiology/Pathogenesis - Unknown
  - Thought to be a delayed type hypersensitivity reaction
  - $T_H^-1$ Response causing degradation of collagen
  - May be induced by
    - trauma
    - sun exposure
    - TB skin testing
    - vaccinations
    - viral infections
    - herpes zoster
    - genetic predisposition - HLA-B35 has had increased frequency in two studies
Granuloma Annulare - Localized

- Classic variant
- Skin colored, pink non scaly papules coalescing into annular or arciform plaques, moderately firm, ropelike border with central clearing. Most common locations on the distal extremities

http://www.aocd.org/?page=GranulomaAnnulare
Granuloma Annulare

- **Generalized**
  - 15% of cases
  - 10 or more lesions
  - 45% have lipid abnormalities
  - More chronic and relapsing course

- **Subcutaneous**
  - Most common form in children
  - Scalp and extremities
  - Painless

http://dermnetnz.org/dermal-infiltrative/granuloma-annulare.html
Granuloma Annulare

- Rare variants include – Perforating, Patch
- Histology
  - Palisading Granuloma with a necrobiotic foci in the dermis
  - **Mucin** present
  - lymphocytic infiltrate

http://www.dermpedia.org/case-type/9?page=65
Granuloma Annulare

- Associated Disorders
  - Diabetes Mellitus
    - The relationship between diabetes and GA is controversial
    - Earlier studies presented a relationship, more recent studies have failed to find the association previously reported
  - Autoimmune Thyroiditis
  - Hodgkin's and Non Hodgkin's Lymphoma
  - Hyperlipidemia and Hypercholesterolemia
  - HIV
  - Hep B and C
Treatments

- Often self-limited – 50% resolve within the first 2 years
- First Line – High potency topical or intralesional steroids
- Destructive
  - Cryotherapy: 25/31 patients had resolution with 1 treatment (10-60 sec)
  - Biopsy – controversial
- Lasers – PDL, CO₂, Excimer
Granuloma Annulare

- **Treatments**
  - **Oral antibiotics**
    - Doxycycline 100mg bid
    - Dapsone
  - **Antimalarials**
    - Hydroxychloroquine, Chloroquine
  - **Immunosuppressants**
    - Methotrexate, Cyclosporine, TNF-a
  - **Light Therapy**
    - NBUVB, PUVA, PDT
Granuloma Annulare

Take home points

- Benign – self limited in 50% of cases
- Delayed type hypersensitivity reaction – $T_H^{-1}$
- Localized form – most common
- Subcutaneous form – most common in children
- Can be associated with autoimmune thyroiditis
- Consider checking triglycerides in generalized GA
Clinical
- DM associated – 65% of patient’s have DM. Only found in 0.3% of DM patients
- Average age of 25 in patients with DM
- Non-DM associated in mid 40s
- Most commonly located on the anterior shins.
- Red, brown or violaceous papules. Progress to yellow, brown, atrophic telangiectatic plaques.
Pathogenesis

- Exact etiology remains unknown.
- One theory suggests that NL results from systemic microangiopathy associated with DM.
- May precede diabetes
Necrobiosis Lipoidica

- **Pathology**
  - **Histology** – Layers of granuloma in between pale degenerated collagen. Plasma cells, **no mucin**
Necrobiosis Lipoidica

- Treatment
  - First Line – High potency (Class I) topical steroids under occlusion
  - Intrallesional steroids – Use caution not to cause ulceration
  - Topical PUVA
  - Antimalarials – Hydroxychloroquine 200mg qd
  - Fumaric Acid Esters – Not approved by the FDA
  - Pentoxifylline
Necrobiosis Lipoidica

Take home points

- Only a small portion of patients with DMII (0.3%) will develop Necrobiosis Lipoidica
- Histology: Palisading Granuloma without mucin
- Located on anterior shins

Sarcoidosis

- Clinical - can affect multiple organs: Lungs most common
  - Skin manifestations occur in 17% of patients
  - Cutaneous manifestations are the initial presentations in 1/3 of patients
  - Multiple presentations exist
  - Macules, papules, nodules and plaques
    - red-brown, yellow-brown, violaceous, or hypopigmented
  - Erythema nodosum – most common non-specific cutaneous manifestation

http://escholarship.org/uc/item/3sh1s1qd/1b.jpg
Pathogenesis - Unknown

- Thought to involve genetically influenced dysregulation of the $T_h$-1 immune response to one or more extrinsic antigens
- May lead to over activation of inflammatory pathways and subsequent granuloma formation
- Case control study of 700 patients was unable to find any single etiologic agent.
Sarcoidosis

- Histopathology
  - Non-caseating granulomas
  - Aggregates of epithelioid histiocytes
  - Giant cells
  - Macrophages
  - Minimal lymphocytic infiltrate

http://dermaamin.com/site/histopathology-of-the-skin/71-s/2091-sarcoidosis-.html
Sarcoidosis

- **Histology**
  - Schaumann bodies
    - Basophilic laminated Inclusions in giant cells
  - Asteroid Bodies
    - Eosinophilic stellate inclusion bodies
Sarcoidosis

Variants

- Lupus Pernio – violaceous infiltration of the nose, cheeks or earlobes, often associated with a **chronic course**
  - Can cause scarring after resolution
  - Often associated with **upper respiratory tract disease**
Sarcoidosis

- Lofgren’s Syndrome
  - Triad
    - Erythema nodosum - Most common non-specific cutaneous finding, 25% of patients with sarcoidosis
    - bilateral hilar adenopathy
    - migrating polyarthritis

https://escholarship.org/uc/item/8rg7v6og/lofgren2.jpeg

http://www.hindawi.com/journals/crirh/2013/125251.fig.001.jpg
Sarcoidosis

- Heerfordt’s syndrome – Uveoparotid fever
  - Fever
  - parotid gland enlargement
  - anterior uveitis
  - facial nerve palsy

http://development.aao.org/publications/eyenet/200805/images/AMRdroo
n400.jpg
Darier-Roussy disease - Sarcoidal panniculitis
- painless subcutaneous mobile nodules without epidermal change.
Sarcoidosis

- Treatment – lack of high quality evidence to support efficacy
- Topicals - super potent steroids, mid potency for face.
- Intraliesional injections
- Systemic corticosteroids for severe disease
  - 20-40mg/kg/day with a slow taper
  - May add hydroxychloroquine 200-400mg/day or methotrexate 25mg/week, tapered to 5-15mg
Sarcoidosis

- minocycline – retrospective study of 27 patients, 14 had partial improvement while 6 had complete improvement on 1-6 months of minocycline

- Refractory treatments
  - Biologics - TNF – alphas – notably infliximab but data has been conflicting in larger studies
Sarcoidosis

- Take home points
  - Lesions that develop within a scar or tattoo should be ruled out for sarcoidosis
  - Erythema Nodosum – positive prognosis, associated with acute sarcoidosis
  - TH1 response to unknown antigen
Amyloidosis

- **Cutaneous**
  - Macular
  - Lichen
  - Nodular
  - Secondary

- **Systemic**
  - Primary systemic
  - Secondary systemic
  - Hemodialysis-associated
Amyloidosis

Macular

- Keratinocyte derived
- Hyperpigmented firm papules localized to the interscapular region
  - Asymptomatic or pruritic
  - Commonly associated with notalgia paresthetica

http://dermaamin.com/site/images/clinical-pic/m/macular-amyloidosis/macular-amyloidosis2.jpg
Lichen amyloidosis

- Keratinocyte derived
- Flat topped shiny papules
- Commonly over the shins
- Pruritic
- Seen in MEN 2A

[Image of lichen amyloidosis](http://dermaamin.com/site/images/clinical-pic/L/lichen-amyloidosis/lichen-amyloidosis10.jpg)
Amyloidosis

- Nodular
  - Single or multiple waxy nodules
    - Occasionally with purpura
  - AL – immunoglobulin light chains
    - Frequently Lambda light chains
  - Long term follow up needed for potential to progress to systemic
Amyloidosis

- **Systemic**
  - **Primary Systemic**
    - Pinch Purpura - ecchymosis and vessel fragility
    - **Macroglossia** – indentation of teeth
    - Shoulder pad sign - deposition around periarticular soft tissue
    - AL - light chain
    - May be associated with multiple myeloma

https://stanfordhealthcare.org/content/dam/SHC/conditions/blood-heart-circulation/images/alprimaryamyloidosis-photo-tongue.jpg
Amyloidosis

- Hemodialysis associated amyloidosis
  - Long term hemodialysis
  - Beta 2 microglobulin
  - Deposition in synovial membranes
    - Carpal Tunnel
- Senile Systemic amyloidosis
  - Late onset in elderly patients
  - ATTR - Transthyretin
Treatment

- **Macular**
  - Capsaicin
  - Topical steroids

- **Lichen**
  - Topical and intralesional steroids
  - NBUVB
  - CO2 laser
  - Retinoids

- **Nodular**
  - Excision or laser ablation
Scleromyxedema

- Clinical – Symmetric waxy firm papules, leonine facies, commonly involves the glabella with longitudinal furrowing
- Pathology
  - Associated with monoclonal gammopathy (debatable)
  - IgG lambda light chain
- Treatment – IVIG, Bortezomib, melphalan, thalidomide, stem cell transplant
Scleredema

- Clinical - Cutaneous brawny induration of the face, neck, scalp and upper extremities
- Three forms
  - Infection related – Streptococcal
  - Gammopathy related – Monoclonal gammopathy, IgG Kappa
  - Diabetes – IDDM
- Treatment – Phototherapy, cyclophosphamide, oral glucocorticoid, cyclosporine
Blisters, erosions and milia on sun exposed skin

Most common type of porphyria world wide
Porphyria Cutanea Tarda

- Defect – Uroporphyrinogen Decarboxylase
Porphyria Cutanea Tarda

- Triggers
  - Alcohol
  - HCV
  - Estrogen
  - Iron Overload
  - Hemochromatosis
- Labs: Total plasma porphyrins with reflex
  - Then stool, plasma and RBC fractionation
Porphyria Cutanea Tarda

- Treatment - Phlebotomy every 2 weeks, may combine with antimalarials
- Hydroxychloroquine: 100mg BIW
  - Takes on average 6.5 months to reach therapeutic levels with hydroxychloroquine and phlebotomy
  - Better compliance than phlebotomy
Erythropoietic Protoporphyria

- Most common porphyria in children
- Clinical – erythema, edema, crust, purpura and skin thickening
- Labs – Total erythrocyte protoporphyrin
  - Urine porphyrin levels normal
- Complications
  - Protoporphyrinic hepatopathy
  - Gallstones
Erythropoietic Protoporphyria

Treatment

- Broad Spectrum Sunscreen, Photo protective Clothing
- Avoidance of sunlight exposure from 11:00 AM – 3:00PM
- Beta-Carotene 30-90mg/day in children
- Cysteine supplements, 500mg bid
- Afamelanotide