Granulomatous, Metabolic and Depositional Disease

LewisGale Montgomery Hospital
Blacksburg, Virginia

Gina Caputo, DO PGY-4
Jacqueline Fisher, DO PGY-4
Trent Gay, DO PGY-3
Christine Sickles, DO PGY-3
Nathan Miller, DO PGY-2
Robert Murgia, DO PGY-2
Disclosures

- No relevant financial relationships to disclose.
Non-Infectious Granulomas

- Sarcoidosis
- Granuloma annulare
- Necrobiosis lipoidica
- Necrobiotica xanthogranuloma
Sarcoidosis

- Multisystem granulomatous disease characterized by non-caseating granulomas involving lungs and lymph nodes, heart, skin, eyes, liver, kidneys, muscles, joints, and brain
- Unclear etiology, but related to increased activity of cell-mediated immune system
- Epidemiology
  - Bimodal age distribution in women (25-35 and 45-65)
  - Increased incidence in African Americans
Clinical Findings

- In 1/3 of pts; may be presenting symptom
- Non-scaly, skin-colored to red-brown papules and plaques, may develop within pre-existing scars or within sites of previous trauma, usually annular
- Distribution: symmetric face, lips, neck, upper trunk, extremities
- Less common presentations: hypopigmentation, subcutaneous nodules, acquired ichthyosis, alopecia and micropapular lesions, erythroderma, erythema multiforme, and verrucous plaques

Nail changes

- Clubbing, subungual hyperkeratosis, onycholysis
Variants of Sarcoidosis

- Darier-Roussey disease
  - Painless, firm, mobile subcutaneous nodules without epidermal changes. Also known as sarcoidal panniculitis

- Lupus pernio
  - Papulonodules and plaques in areas most affected by cold (nose, ears, cheeks). Associated with lung involvement (75%) and upper respiratory involvement (50%)

- Löfgren’s syndrome
  - Acute sarcoidosis; erythema nodosum, hilar adenopathy, fever, migrating polyarthritis, and acute iritis
Histology of Sarcoid

- Superficial and deep dermal epithelioid cell granulomas devoid of prominent infiltrates of lymphocytes or plasma cells
- 10% have fibrinoid deposition
- Multinucleated histiocytes (giant cells) may contain eosinophilic stellate inclusions (asteroid bodies) or rounded laminated basophilic inclusions (schaumann bodies)
- Non-caseating granulomas
Diagnosis of Sarcoidosis

- Diagnosis of exclusion
  - supporting clinical history and histologic evidence of non-caseating granulomas
- Radiologic findings
  - hilar/paratracheal LAD, pulmonary infiltrates
- PFTs
  - restrictive pattern
- Laboratory
  - ANA elevated in 30%
  - ACE elevated in 60%
  - Anemia, eosinophilia, lymphopenia, elevated ESR, hypercalcemia
Treatment of Sarcoidosis

- Topical or intralesional corticosteroids
- Systemic manifestations
  - oral prednisone for 4-6 weeks at 1mg/kg/day
- Cutaneous manifestations
  - hydroxychloroquine or chloroquine, MTX
Granuloma Annulare

- **Etiology**
  - Trauma, insect bite reactions, tuberculin skin testing, sun exposure, PUVA therapy and viral infections.

- **Clinical presentation**
  - Pink, violaceous, or flesh colored plaques composed of small papules forming arciform to annular plaques
  - Usually symmetrical and acral distribution
Types of Granuloma Annulare

- Localized GA
  - Pink to red non-scaly papules and plaques in annular formation
  - Located on the extremities

- Generalized
  - Small, skin-colored or pink-violet papules symmetrically distributed on trunk and extremities
  - Usually involves trunk and at least 1 extremity

- Subcutaneous GA
  - “Pseudorheumatoid nodules”
  - Painless, firm subcutaneous nodules
  - Most common in lower extremities
Types of Granuloma Annulare

- Perforating GA
  - Small, umbilicated papules with a central crust or hyperkeratotic core
  - May become pustular or ulcerated
- Patch GA
  - Patches of erythema on extremities and trunk
  - Usually symmetric and macular
- Annular elastolytic giant cell granuloma (AEGCG)
  - Photoinduced subtype of GA vs GA appearing on sun damaged skin
Diseases Associated with Granuloma Annulare

- DM
- Hyperlipidemia
- Thyroid disease
- Infectious agent
  - Possible connections with *Borrelia burgdorferi*
  - Tb related immune response that mimics GA
  - Chronic Hep B
  - Chronic Hep C
  - HIV
- Paraneoplastic syndrome
  - seen in solid-organ tumors, Hodgkin and non-Hodgkin lymphoma, leukemia
  - Presentation atypical; painful lesions on palms and soles
Histology of Granuloma Annulare

- Focal degradation of fibrin and elastin fibers with deposition of mucin
- Two patterns of granulomatous inflammation
  - palisading
  - interstitial
Treatment of Granuloma Annulare

- Spontaneous resolution occurs within 2 years in 50% of pts, but 40% recur
- Intralesional or topical corticosteroids
- PUVA
- Cryotherapy
- CO2 Laser treatment

- Systemic agents may be used in severe cases
  - Oral Niacinamide
  - Isotretinoin
  - Dapsone
  - Antimalarials: hydroxychloroquine, chloroquine
  - TNF-alpha inhibitors: infliximab and adalimumab
Necrobiosis lipoidica

- Clinical presentation
  - Yellow-brown, atrophic, telangiectatic plaques with an elevated violaceous rim, typically located in the pretibial region
  - Start as small, firm, red-brown papules → central epidermal atrophy
  - Multiple and bilateral
  - Rarely, SCC develops in lesions of NLD
- Diabetes association
  - 30-40% of NLD have DMI
Histology of Necrobiosis Lipoidica

- Layers of granulomatous inflammation in the dermis parallel to normal/atrophic epidermis, extending into subcutaneous fat without mucin deposition
- Palisaded and interstitial dermatitis with superficial or deep perivascular infiltrate
Treatment of Necrobiosis Lipoidica

- Treatment
  - High potency topical corticosteroid or intralesional injection into active border
  - ASA in combination with dipyridamole
  - Niacinamide

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Metabolic and Depositional Diseases

- Amyloidosis
  - Systemic
  - Cutaneous
- Mucinoses
  - Scleromyxedema
  - Scleredema
  - Reticular erythematous mucinosis
- Porphyria
- Familial hyperlipidemias
- Gout
- Pseudogout
Amyloidosis

- Several diseases sharing common feature of abnormal deposition of eosinophilic amyloid protein in various tissues
  - Amyloid properties: insoluble fibril protein aggregates with β-pleated sheet configuration

- 2 Categories
  - Cutaneous
  - Systemic
    - Associated with increased morbidity and mortality
Types of Cutaneous Amyloidosis

- Macular
- Lichen
- Nodular
- Secondary
Macular Amyloidosis

- **Keratinocyte** derived
- Presents with hyperpigmented small firm papules in rippled appearance coalescing into thin plaques
  - Located on interscapular region of the back
  - Asymptomatic or moderately pruritic
  - +/- notalgia paresthetica
- Treatment → Reduce friction, high-potency topical corticosteroid, topical capsaicin
- Seen in **MEN type 2A syndrome**
Lichen amyloidosis

- Keratinocyte derived
- Small flat-topped shiny papules, highly pruritic
- Located over shins
- Treatment → Reduce friction, high-potency topical corticosteroid +/- intralesional corticosteroid, phototherapy
Nodular amyloidosis

- AL (immunoglobulin light chains, typically λ)
- Single or multiple waxy nodules ± purpura on limbs/trunk
- May progress to systemic involvement (7% of cases)
- Treatment → excision or laser ablation
Secondary amyloidosis

- Keratinocyte derived
- Amyloid deposits seen both in benign and malignant cutaneous tumors
Histology of Amyloidosis

- Lichen/Macular amyloidosis → deposits of eosinophilic, homogenous and amorphous material in papillary dermis with melanin incontinence
- Nodular amyloidosis → waxy eosinophilic fissured nodules involving dermis
- Characteristic staining pattern → Apple-Green Birefringence under Polarized Light with Congo Red stain
- Other stains → Methyl violet, Crystal violet, Periodic acid-Schiff (PAS) positive (diastase resistant), Sirius red, Pagoda red 9, Scarlet red, and Thioflavin T
Types of Systemic Amyloidosis

- Primary systemic amyloidosis
- Secondary systemic amyloidosis
- Hemodialysis-associated amyloidosis
- Familial amyloidosis
- Senile systemic amyloidosis
Primary Systemic Amyloidosis

- Amyloid immunoglobulin light chain (AL)
- Associated with **underlying plasma cell dyscrasia**
- Cutaneous clinical presentation:
  - Up to 50% with macroglossia
  - Ecchymosis and ‘pinch’ purpura
  - Waxy nodules and plaques
  - **Bullous lesions** (especially hemorrhagic)
- Non-cutaneous clinical presentation:
  - Hoarseness, carpal tunnel syndrome, RA-like arthropathy, **shoulder pad sign**, cardiac arrhythmias, heart failure, restrictive cardiomyopathy
- **Abdominal fat pad aspiration** to confirm amyloid deposits and establish diagnosis in absence of cutaneous findings
Secondary Systemic Amyloidosis

- Amyloid deposition in organs due to underlying chronic inflammatory or infectious process
  - Rheumatoid arthritis, tuberculosis, chronic abscess, and periodic fever syndromes, etc.
- Non-immunoglobulin protein: amyloid associated (AA)
Hemodialysis-associated Amyloidosis

- Due to increased secretion of β2-microglobulin in patients with long-term hemodialysis
- Deposition of amyloid in synovial membranes
  - Results in carpal tunnel syndrome and spondyloarthropathy
Familial Amyloidosis

- Deposition of transthyretin-derived amyloid (ATTR) in peripheral and autonomic nervous system
  - Transthyretin transports thyroxine and retinol
  - Produced by the liver
- Slowly progressive disorder resulting in peripheral and autonomic neuropathy
- Treatment → Orthotopic liver transplantation
Senile Systemic Amyloidosis

- Late-onset disease seen in elderly patients
- Due to deposition of *Transthyretin-derived amyloid (ATTR)* fibrils in the heart
  - Causes CHF and cardiomyopathy
Mucinoses

- Heterogenous group of skin disorders involving abnormal accumulation of mucin
- Mucin
  - Mixture of acid glycosaminoglycans normally produced in small amounts by fibroblasts
  - Special stains for mucin include alcian blue, colloidal iron, and toluidine blue
- 4 Types
  - Scleromyxedema, Lichen myxedematous, Scleredema, Reticular erythematous mucinoses
Scleromyxedema

- Generalized symmetric eruption of several firm waxy papules accompanied by induration and thickening of the skin
  - Located on hands, forearms, face (‘leonine facies’), neck, thighs, and upper trunk
- Associated with IgG λ (lambda light chain) monoclonal gammopathy
- Poor prognosis
- Treatment → stem cell transplant, oral immunosuppresants (including thalidomide); monthly melphalan associated with increased mortality
Lichen Myxedematosus

- AKA: Papular mucinosis
- Localized form of scleromyxedema with small shiny papules on extensor extremities
- Does NOT progress to scleromyxedema
- Shows little tendency for spontaneous resolution
- Treatment → Observation or topical corticosteroids
Scleredema

- 3 Forms:
  - Infection-related → Streptococcal
    - Self limited induration of cervicofacial area with extension to proximal extremities and trunk in women and children
  - Gammopathy-related
    - Insidious onset and similar presentation to above due to monoclonal gammopathy
  - Diabetes-related
    - Progressive erythema and induration of neck and back in obese men with IDDM
- Treatment (for latter 2 types) → UV therapy, cyclophosphamide, oral glucocorticoid, or cyclosporine
Reticular erythematous mucinosis

- Erythematous macules and papules in a reticulated pattern on midline chest and back
- Possibly induced by UV light
- Treatment → oral antimalarials and sun protection
Porphyria

- Inherited or acquired disorders due to enzyme deficiency causing increased production of porphyrins during heme synthesis
- Porphyrins absorb light intensely in the Soret band (400-410nm)
  - Forms reactive oxygen species with subsequent damage to skin, liver, and/or erythrocytes
Porphyria Cutanea Tarda (PCT)

- **Triggers:**
  - Alcohol, Hepatitis C, Estrogen, Polychlorinated hydrocarbons, Iron overload, HIV

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyria Cutanea Tarda (PCT)</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Tense bullae, erosions, milia, scarring on sun-exposed skin; hypertrichosis, scleroderma-like changes, facial hyperpigmentation</td>
<td>Phlebotomy every 2 weeks, low-dose hydroxychloroquine</td>
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<tr>
<td>Type</td>
<td>Defect</td>
<td>Description</td>
<td>Treatment</td>
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<tr>
<td>Congenital Erythropoietic Porphyria (CEP)</td>
<td>Uroporphyrinogen III cosynthaase</td>
<td>Extreme photo-sensitivity</td>
<td>Avoid light</td>
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<td>Erythrodontia</td>
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<td>Red urine</td>
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<td>Hemolysis</td>
<td>Transfusions for anemia</td>
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<td>+/- bone marrow transplant and splenectomy</td>
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<tr>
<td>Erythropoietic Protoporphyria (EPP)</td>
<td>Ferrochelatase</td>
<td>Photosensitivity</td>
<td>Avoid light</td>
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<td></td>
<td></td>
<td>Gallstones</td>
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<td></td>
<td></td>
<td>Hepatic damage</td>
<td></td>
</tr>
<tr>
<td>Acute Intermittent Porphyria (AIP)</td>
<td>Porphobilinogen Deaminase</td>
<td>NO skin findings: Neurologic and psychiatric</td>
<td>Remove trigger (barbiturates, alcohol, etc.),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>findings</td>
<td>glucose loading, hematin infusion</td>
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<tr>
<td></td>
<td></td>
<td>Increase in abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Variegate Porphyria (VP)</td>
<td>Protoporphyrinogen Oxidase</td>
<td>Overlap btwn AIP and PCT</td>
<td>Same as AIP</td>
</tr>
<tr>
<td>Hereditary Coproporphyria</td>
<td>Coproporphyrinogen Oxidase</td>
<td>Mild version of AIP, may have PCT-like skin</td>
<td>Same as AIP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>findings</td>
<td></td>
</tr>
<tr>
<td>Hepatoerythropoietic Porphyria</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Overlap btwn. PCT and CEP</td>
<td>Photoprotection only</td>
</tr>
</tbody>
</table>
### Familial Hyperlipidemias

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Lipid Levels</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Familial LPL deficiency/hyper-chylomicronemia</td>
<td>↓ Lipoprotein lipase (LPL) or apoprotein CII defect</td>
<td>↑↑ TG (chylomicrons)</td>
<td>Eruptive xanthomas, acute pancreatitis, lipemia retinalis</td>
</tr>
<tr>
<td>Ila- Familial hyper-cholesterolemia/defective apo B100</td>
<td>LDL receptor defect</td>
<td>↑↑ Cholesterol (LDL)</td>
<td>Tendinous and tuberous xanthomas, Xanthelasma</td>
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<tr>
<td>Ilb- Familial combined hyper-cholesterolemia</td>
<td>LDL receptor defect</td>
<td>↑ Cholesterol, ↑ TG</td>
<td>Tendinous and tuberous xanthomas, Xanthelasma</td>
</tr>
<tr>
<td>III- Familial dysbetalipoproteinemia</td>
<td>Apoprotein E defect</td>
<td>↑ Cholesterol, ↑ TG</td>
<td>Xanthoma Striatum Palmare, tuberous xanthomas</td>
</tr>
<tr>
<td>IV- Familial hyper-triglyceridemia</td>
<td>↑ Production of VLDL</td>
<td>↑ TG</td>
<td>Eruptive xanthomas; assoc. w/ DM, obesity, alcoholism</td>
</tr>
<tr>
<td>V</td>
<td>Apolipoprotein C-II defect</td>
<td>↑↑ TG, ↑ Cholesterol</td>
<td>Eruptive xanthomas, acute pancreatitis</td>
</tr>
</tbody>
</table>
Types of Xanthomas

- Eruptive Xanthomas: Type I, IV, V
- Xanthelasma: Type II, III
- Xanthoma Striatum Palmar: Type III
Gout

- Recurrent attacks of acute inflammatory arthritis
- Due to hyperuricemia leading to deposition of needle-like monosodium urate crystals in skin and joints
- Presents with firm, skin-colored white-yellow papules or nodules (tophi) that may ulcerate and drain chalky material
- Negative birefringence under polarized light

Treatment
- Acute attacks: NSAIDs and Colchicine
- Prophylaxis: Colchicine, Allopurinol (over-producers of uric acid), or Probenicid (under excretion of uric acid)
Pseudogout

- Deposits of calcium pyrophosphate dihydrate crystals in joints
  - Crystals appear shorter than urate crystals and are rhomboidal in shape
- Weakly positive birefringence under polarized light
References


7. Photos courtesy of Dr. Gary White and Regional Dermatology; Jere Mammino DO; DermNet New Zealand. http://creativecommons.org/licenses/by-nc-nd/3.0/nz/; Mayo Foundation for Medical Education and Research; Dr. Jan R. Mekkes. Dermatoloog AMC Amsterdam, JAMA. Plastic Surgery Key: Disorders of the Subcutis; Atlas of Pathology