Cutaneous Deposition Diseases
Cutaneous Deposition Disorders

- Group of unrelated conditions characterized by the presence of endogenous or exogenous substances within the dermis or subcutis
- Our focus: endogenous depositions
Endogenous Cutaneous Deposition Disorders

- Amyloidosis
- Lipoid Proteinosis
- Colloid Milium
- Porphyrias
Learning Objectives

- Amyloidosis and Lipoid Proteinosis
  - Pathogenesis
  - Clinical presentation
  - Diagnosis
  - Histopathology
  - Treatment
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Amyloidosis

- Term coined by a German botanist to describe the cellulose-like substance of plants
- Extracellular deposition of *any of a group of unrelated proteins*
- Distorts tissue architecture and function
Amyloid Ultrastructure

- **Light Microscopy**
  - eosinophilic, amorphous substance
  - Congo Red stain with polarized light: apple-green birefringence

- **Electron Microscopy**
  - 7.5-10nm wide linear, nonbranching tubular fibrils loosely arranged in a meshwork
  - fibrils are composed of several filaments arranged in a β-pleated sheet configuration
Amyloid: H&E
Congo Red H&E

Congo Red under Polarized Light
Amyloid: EM
Amyloid EM
(Beta-2 Microglobulin)
Amyloidosis Classification

- The clinical type of amyloidosis depends on the amyloid fibril protein and the pathogenic mechanism of deposition

- Amyloidosis can present with either systemic or localized deposits
Amyloidosis Classification

- **Systemic**
  - *Primary*
  - *Myeloma-Associated*
  - Secondary/Reactive
  - Heredofamilial
  - Hemodialysis-Related

- **Local Cutaneous**
  - *Primary*
  - Nodular
  - Macular
  - Lichenoid
  - Secondary
  - Incidental
Pathogenesis
(what is amyloid??)

- Amyloid deposits contain a nonfibrillar protein called *Amyloid-P*
- Amyloid-P is identical to Serum Amyloid P (SAP), a normal circulating plasma globulin
- SAP is an integral constituent of the microfibrillar sheath of normal elastic fibers
- SAP is related to C-Reactive Protein and is an elastase inhibitor
Pathogenesis

- **SAP** and the *beta-pleated sheet* configuration protect amyloid deposits from degradation and phagocytosis

- Thus, the progressive and irreversible course of amyloidosis
Pathogenesis: Systemic Amyloidosis
Primary and Myeloma-Associated Amyloidosis

- Immunoglobulin light chains (lambda) are the precursors to the amyloid fibril protein, designated as **Amyloid L (AL)**

- The light chains are derived from serum immunoglobulins originating from a **clonal plasma cell dyscrasia**

- The plasma cell dyscrasia is occult in the primary form or overt in myeloma
Secondary Systemic Amyloidosis

- Serum Amyloid A (SAA) is the precursor to the amyloid fibril protein, designated Amyloid A (AA)
- SAA is a high density lipoprotein and an acute-phase reactant in healthy patients
- Elevated SAA in amyloidosis is linked to chronic inflammation with persistent activation of the acute phase response
Diseases Associated with Secondary Amyloidosis

- Infectious
- Autoimmune
- Malignant
- Miscellaneous
- Chronic Cutaneous Diseases
**Associated Condition**

- Monoclonal Gammopathy
  - Monoclonal Proliferation of Ig-Secreting Plasma Cells / B Cells
    - Soluble Precursor
      - Insoluble Fibrils

**Multiple Myeloma**

- Monoclonal Ig Light Chains
  - AL Amyloid Deposition
    - Proteolysis
      - Proteolysis
        - SAP
          - SAP
            - GAG
              - GAG

**Chronic Inflammation**

- Macrophage Activation
  - IL-1 Secretion
    - Liver Cells
      - SAA
        - AA Amyloid Deposition
Pathogenesis: Heredofamilial Forms

- Familial Mediterranean Fever: AA Amyloid
  - Recurrent polyserositis and fever; MEFV gene

- Muckle-Wells Syndrome: AA Amyloid
  - Urticaria/Deafness/Amyloid

- Familial Nephropathic, Polyneuropathy, and Cardiac: Prealbumin (transthyretin)
Pathogenesis: Hemodialysis-Related Amyloidosis

- High levels of $\beta_2$-microglobulin
  - protein not cleared by certain HD membranes
- Limited deposition in articular structures
- Presents with Carpal Tunnel Syndrome
- Skin manifestations rare
  - finger “wrinkling”; truncal lichenoid lesions
Pathogenesis: Localized Cutaneous Amyloidosis
Pathogenesis: Nodular Amyloidosis

- AL Amyloid

- Cutaneous plasmacytoma locally produces Ig light chains as precursors to AL fibrils

- Local neoplastic (monoclonal) vs. reactive (polyclonal) deposition
Pathogenesis: Macular and Lichenoid Forms

- Degenerated or altered keratin
- *Fibrillar Body Theory*
  - Necrotic epidermal cells are transformed into amyloid by dermal macrophages and fibroblasts
- *Secretion Theory*
  - Amyloid precursors are secreted by disrupted basal cells and assembled at the DEJ
The exact characterization and pathogenesis of all forms of amyloidosis is not quite clear.
Summary: Classification/Fibrils

I. Systemic

1. Primary AL
2. Myeloma-Associated AL
3. Secondary AA
4. Heredofamilial
   a. Familial Med. Fever AA
   b. Muckle-Wells AA
   c. Nephropathic, neuro, cardio. Transthyretin
5. Hemodialysis Associated $\beta_2$- MG
II. Localized

1. Primary Cutaneous
   a. Nodular
   b. Macular
   c. Lichenoid

2. Secondary Cutaneous
   a. Tumors and PUVA
Amyloidosis: Clinical Features
Primary Systemic Amyloidosis

- Non-Cutaneous
  - Constitutional symptoms
    - Fatigue, weight loss, edema, dyspnea, syncope, paresthesias
  - Macroglossia
Systemic Amyloid: Macroglossia
Primary Systemic Amyloidosis

- Carpal Tunnel
- Sicca Syndrome
- Shoulder Pad Sign
- RA-like deposition in small joints
- GI bleed, peripheral neuropathy, cardiac sx
Primary Systemic Amyloidosis

- CHF and arrhythmia cause death in 40% of patients with systemic amyloidosis
Primary and Myeloma-Associated Amyloidosis

- Skin or mucous membrane lesions are seen in ~40% or less
- **Purpura** is most common
  - Amyloid deposition in vessel walls +/- coagulopathy from infiltration of liver
  - after minor trauma (**pinch purpura**)
  - Eyelids, axilla, umbilicus, anogenital
  - Facial purpura after Valsalva or proctoscopy
Primary and Myeloma-Associated Amyloidosis

- Less common cutaneous manifestations:
- Asymptomatic waxy, hemorrhagic papules, plaques and nodules in flexures, central face, retroauricular folds, and tongue
- Sclerodermatous infiltration
- Bullae
- Alopecia
- Cutis Laxa
Waxy, hemorrhagic periorbital papules of systemic amyloidosis
Bullous Amyloidosis
Clinical: Nodular Amyloidosis

- Rarest form of cutaneous amyloidosis
- Firm, waxy subcutaneous nodules on the face, extremities, trunk or genitalia
- May be atrophic, anetodermic, or bullous
- Female:male = 2:1
- Presents in the 6th or 7th decade
- Rare association with Sjogren’s Syndrome
Nodular Amyloid

- Think of Jodi’s patient
Nodular Amyloid
Clinical: Nodular Amyloidosis

- Less than 15% of localized nodular lesions will progress to systemic amyloidosis.

- If this occurs, investigate for a latent paraproteinemia and systemic disease.
Clinical: Lichen Amyloidosis

- Red-brown, pruritic, hyperkeratotic papules on the shins with spread to the dorsal feet and thighs
- Chinese ancestry most commonly affected
Lichen Amyloidosis
Clinical: Macular Amyloidosis

- Gray-brown pruritic papules/patches
  - upper back, trunk, or extremities
  - Notalgia Paresthetica commonly associated
- Central and South American, Asian, and Middle Eastern patients most common
- *Lichen and macular amyloid have not been reported to progress to systemic disease*
Macular Amyloid
Variants of Primary Localized Amyloidosis

- Periorbital hyperpigmentation
- Auricular Papules
- Whorled biphasic form in Blaschko’s Lines
  - Macular and lichenoid lesions in the same patient
Rare Variants of Primary Localized Amyloidosis

- Poikilodermatous Cutaneous Amyloid: PCA
  - focal or generalized
  - PCA Syndrome: AD disease with poikiloderma, lichenoid papules, photosensitivity, blistering, and short stature
- Familial- pruritic, swirled pigmentation on trunk or extremities beginning in childhood
Secondary Localized Amyloidosis

- Clinically insignificant microscopic deposits of amyloid as a secondary phenomenon associated with skin tumors
  - BCC, SCC, Seb K, DSAP
  - PUVA

- Mechanism analogous to lichen and macular forms (keratinocyte destruction)
Amyloidosis: Histology
Amyloid Stains

- **Congo Red**
  - apple-green birefringence under polarized light

- **Potassium Permanganate + Congo Red**
  - Secondary amyloid (AA) loses its staining with Congo Red after pretreatment with PP
  - Primary systemic, myeloma-associated, and localized amyloid deposits are resistant to PP
Amyloid H&E
Amyloid: Congo Red
Congo Red: H&E
Congo Red: Polarized Light
Amyloid Stains

- Periodic acid- Schiff (PAS)
- Methyl violet
- Crystal violet
- Cotton dyes: sirius red, pagoda red, dylon
- Fluorescent dyes: thioflavin-T, phorwhite BBU
- Antisera to fibril proteins is most sensitive
Amyloid: Thioflavin-T
Amyloid Electron Microscopy

- Formalin fixed tissue can be used for EM
- Amyloid deposits contain 6-10nm wide, straight, non-branching, non-anastomosing filaments arranged in a loose meshwork
Amyloid Electron Microscopy
Histology: Systemic Amyloidosis

- **H&E:**
  - dermal and subcutaneous pink, fissured, amorphous masses
  - deposits in vessel walls, fat, and surrounding eccrine glands and other mesenchymal tissues
  - Amyloid Rings: distinctive amyloid deposits around individual fat cells
  - No associated inflammation
Amyloidosis

Plasma cells

MNGC
Histology: Systemic Amyloidosis

• Biopsy of:
  • Clinically normal skin is positive in ~50% of primary systemic forms
  • Rectum is positive in 75% of primary systemic forms

• FNA of abdominal fat pad is most sensitive
  • 95% positive in primary and myeloma-associated
  • 65% positive in secondary forms
Histology:
Systemic Amyloidosis

- Although skin is grossly uninvolved in secondary systemic amyloidosis, amyloid deposits in the deep dermis around adnexae, blood vessels, and fat cells are seen in 50%.

- Distinguish AA from AL amyloid with:
  - Indirect IF with anti-amyloid A antiserum
  - Potassium permanganate reaction
Histology:
Localized Amyloidosis

- **Nodular Amyloid**
- Atrophic epidermis overlies large amorphous masses extending from the dermis into the fat
- Deposits surround BV, adnexae, and fat cells
- *Inflammatory infiltrate with plasma cells, Russell bodies, and giant cells is present*
- Plasma cells lie at the periphery of amyloid
Amyloid encases blood vessels
Plasma cells and giant cells
Russell Bodies: plasma cells with vacuoles representing stored Ig
Histology: Localized Amyloidosis

- Lichen and Macular Amyloid
- Amyloid deposits in papillary dermis
- Pigment incontinence, hemorrhage, and hemosiderin in papillary dermis
- EM: amyloid composed of amyloid filaments, normal and degenerated tonofilaments, and lysosomes
- Monoclonal anti-keratin antibodies react with the deposits
Amyloidosis: Treatment
Treatment: Primary Systemic Amyloidosis

- **Cytotoxic chemotherapy**
  - Melphalan, prednisone, colchicine, penicillamine, azathioprine, vincristine, cyclophosphamide

- **Supportive Care**
  - Dialysis; cardiac and renal transplant

- **Bone Marrow Transplantation**

- **Dimethyl Sulfoxide (DMSO)**
  - Nontoxic antiinflammatory solvent may inhibit synthesis or promote degradation of amyloid
Treatment: Secondary
Systemic Amyloidosis

- Treatment of the underlying disorder may improve the secondary amyloid deposits

- Specific Therapies:
  - Juvenile RA: chlorambucil
  - Familial Med. Fever: colchicine
Treatment:
Localized Amyloidosis

- **Nodular Amyloid**
  - Excision; CO2 Laser; ED&C
  - Recurrences are expected

- **Lichen Amyloid**
  - Topical DMSO, dermabrasion, oral retinoids
  - Topical steroids and antipruritics are usually ineffective

- **Macular Amyloid**
  - UVB
Satisfactory treatment overall is lacking for all forms of amyloidosis