Cutaneous Deposition Diseases - Part 2
Cutaneous Deposition Disorders

Group of unrelated conditions characterized by the presence of endogenous or exogenous substances within the dermis or subcutis
Endogenous Cutaneous Deposition Disorders

- Lipoid Proteinosis
- Porphyria
- Amyloidosis
- Colloid Milium
Lipoid Proteinosis
Hyalinosis Cutis et Mucosae

Urbach-Wiethe Disease
Lipoid Proteinosis

- Autosomal Recessive
- ECM-1: Extracellular Matrix Protein 1
- South Africa
- Hyaline-like material deposited in skin, mucous membranes, brain, and viscera
- Cause is unknown
Lipoid Proteinosis: Pathogenesis

- **Hyaline-like material:**
  - deposited in blood vessel walls and free in the papillary dermis
  - deposits consist of 2 substances:
    - True hyaline of fibroblast origin
    - Reduplicated basement membranes
Lipoid Proteinosis:
Presentation

- Hoarse cry at birth / infancy
- Hoarseness throughout life
Lipoid Proteinosis: Clinical Features

- Skin lesions appear during the first two years of life as 2 overlapping stages
- **Stage 1: Inflammatory**
  - Lasts through teens
  - Vesiculobullous and crusted erosions of the skin, mouth and throat
  - Resolve with atrophic, ice-pick scars on face
Lipoid Proteinosis: Clinical Features

- **Stage 2: Infiltrative**
  - Deposits increase in the dermis
  - Thick, yellow, waxy skin
  - Papules/plaques/nodules on face, extremities
  - Verrucous nodules on elbows, knees, hands
  - Generalized hyperkeratosis/infiltration may occur
Lipoid Proteinosis: Clinical Features

- **Eyes:**
  - Moniliform blepharosis (beaded papules) on the palpebral margins

- **Lips:**
  - Pebbling of lip mucosa

- **Tongue:**
  - Infiltration of frenulum, fixed to the mouth floor
  - Firm and woody
Lipoid Proteinosis: Clinical Features

- Bilateral, intracranial, sickle-shaped calcifications in the temporal lobe
- Seizures, memory loss, rage attacks
Lipoid Proteinosis:
Clinical Features

- Patchy or diffuse alopecia
- Hypo- or aplasia of teeth
- Multiple organ systems may be affected but rarely result in significant clinical symptoms
Lipoid Proteinosis:
Clinical Course

- Stable or slowly progressive
- Normal life span
- Slightly increased infant mortality rates due to respiratory complications
- Adults are at risk for laryngeal obstruction and may require tracheostomy
Lipoid Proteinosis: Differential Diagnosis

- Xanthomatosis
- Amyloidosis
- Colloid milium
- Papular mucinosis
- Myxedema
Lipoid Proteinosis: laboratory findings

- There are no consistent lab abnormalities
- ESR, serum lipids, calcium, bone marrow biopsies, and chromosomal studies are either inconsistent or inadequately studied
Lipoid Proteinosis: Histology
Figura 2: PAS 100X - superficial dermis with deposition of a PAS-positive and diastase-resistant substance
Figura 3: 
PAS 400X - Depósito de material ao redor de glândula écrina

Figure 3: 
PAS 400X - material deposited around the eccrine gland
Lipoid Proteinosis: Histology

- Early: pale pink hyaline-like thickening of the papillary dermal capillaries
- Later: hyperkeratosis, papillomatosis, and a thick dermis with diffuse bundles of pink hyaline oriented perpendicularly to the DEJ
- Hyaline mantles surround or replace eccrine glands
Lipoid Proteinosis: Staining Pattern

- The hyaline is PAS positive, diastase resistant:
  - indicating neutral mucopolysaccharides
- Alcian Blue and Hyaluronidase:
  - reveal hyaluronic acid
Lipoid Proteinosis: Treatment

- No known cure
- All therapy is based on anecdotal reports
  - Oral DMSO
  - Dermabrasion
  - Surgical resection of vocal cord plaques
- Supportive treatment (anticonvulsants)
Porphyria
The Porphyrias

- A group of inherited or acquired disorders resulting from excessive production of porphyrins or their precursors during heme synthesis
- The synthesis of heme occurs primarily in the liver and bone marrow
Porphyria Classification

- **Erythropoietic**
  - Congenital Erythropoietic Porphyria (CEP)

- **Hepatic**
  - Porphyria Cutanea Tarda (PCT)
  - Acute Intermittent Porphyria (AIP)
  - Variegate Porphyria (VP)
  - Hereditary Coproporphyria (HCP)

- **Erythrohepatic**
  - Hepatoerythropoietic Porphyria (HEP)
  - Erythropoietic protoporphyria (EPP)
Pathogenesis

- Enzyme defects in the heme synthetic pathway result in elevated intermediates called *porphyrinogens*.

- Porphyrinogens are oxidized to photosensitizing *porphyrins*.

- Porphyrins absorb radiation in the *Soret Band* (400-410 nm).
Pathogenesis

1. Porphyrins become excited/unstable
2. Transfer energy to oxygen
3. Oxygen free radicals are created
4. Free radicals transfer energy to cells and DNA
5. Tissue damage: skin, liver, and RBC
Porphyria Histology
Congenital Erythropoietic Porphyria: Gunther’s Disease
Congenital Erythropoietic Porphyria

- Mom comes into office with pink diapers
- Baby cries and screams when outside
- Baby has red teeth
Congenital Erythropoietic Porphyria

- Autosomal Recessive
- Uroporphyrinogen III Cosynthetase
- Very rare: < 200 case reports
Congenital Erythropoietic Porphyria

- Presents in early childhood (birth-5 years)

**Early:**
- Immediate photosensitivity with burning, edema, erythema and blistering after UV exposure

**Late:**
- Mutilating, deforming scars of nose, ears, fingers
- Scarring alopecia, dyspigmentation, sclerodermoid changes
Congenital Erythropoietic Porphyria

- Hypertrichosis w/ lanugo hair over face/neck/extra.
- Photophobia, ectropion, corneal scars, blindness
- Erythrodontia
- Hemolytic anemia
- Splenomegaly
- “wherewolves”
Congenital Erythropoietic Porphyria
Congenital Erythropoietic Porphyria

- **Uroporphyrinogen III Cosynthetase**
- Uroporphyrin and coproporphyrin accumulate in urine, feces, plasma, RBC, bone
- Uroporphyrin I in erythrocytes leads to **hemolysis**
- Hemolysis turns the urine pink (**stains diapers**)
CEP: Labs

- CBC: Hemolytic anemia (schistocytes)
- Urine, RBC, Plasma: Uroporphyrin
- Stool: Coproporphyrin
CEP: Management

- Photoprotection (even bili lights!)
- Transfusions
- Beta-carotene
- Splenectomy
- Hydroxyurea: suppress BM heme synthesis
- Bone Marrow Transplant
- If detected early...normal life span
CEP successfully treated with BMT
Hepatic Porphyrias

- Acute Intermittent Porphyria
- Variegate Porphyria
- Hereditary Coproporphyria
- Porphyria Cutanea Tarda
Porphyria Cutanea Tarda

- Most common porphyria
  - Autosomal Dominant (Familial)
  - Acquired
- Uroporphyrinogen decarboxylase
  - Familial: deficient in RBC and hepatocytes
  - Sporadic: deficient in hepatocytes only
Porphyria Cutanea Tarda

- All acquired forms are precipitated by an inducer
- Inducers:
  - Alcohol, estrogen, hepatic tumors
  - Iron, Hemodialysis
  - HCV, HBV, HIV
- Inducers may unmask familial cases
- C282Y gene: predisposes to HC and PCT
Porphyria Cutanea Tarda

- **Homozygous inherited form:**
  - Hepatoerythropoietic Porphyria (HEP)
  - erythrocyte *and* hepatic enzymes are deficient
Porphyria Cutanea Tarda

- Presents in 3rd – 4th decade
- Familial cases may present earlier
- Uroporphyrins in skin lead to photosensitization after absorbing light energy in the Soret Band (400-410 nm)
PCT: Clinical Features

- Delayed photosensitivity with bullae, erosions, fragility
- Facial hypertrichosis, hyperpigmentation
- Scars, milia, sclerodermoid plaques
- Subcutaneous calcification
- Alopecia
- Liver hemosiderosis
- Diabetes mellitus
PCT Labs

- Urine: Uro > Copro
- Feces: Isocopro
- RBC: Normal
- Urine porphyrins fluoresce w/ Wood’s lamp
- DDx: Variegate Porphyria
  - Compare urine Uro:Copro ratio
  - PCT= 8:1; VP=1:1 or Copro > Uro
PCT: Management

- Identify the etiology
- Photoprotection
- Phlebotomy: 500ml BIW to Hbg 11/ Hct 35
  - Clinical response lags behind biochemical response
- Plaquetil 100-200mg BIW
  - Rx until urine uroporphyrin < 100micrograms/24hr
- Chloroquine-solubilizes porphyrins for excretion
- Lifestyle modification
Pseudoporphyrinia

• Mimics PCT (clinical and histo), except:
  • No hypertrichosis or hyperpigmentation
  • No sclerodermoid changes
  • No porphyrin abnormality

• Triggers:
  • Hemodialysis
  • Drugs (naprosyn, furosemide, HCTZ, TCN, nalidixic acid, dapsone, pyridoxine)
  • UVA (tanning beds)
Pseudoporphyria Treatment

- Discontinue offending drugs
- Photoprotection
- Hemodialysis- associated cases:
  - difficult to treat
  - monitor over time for true PCT
Acute Attack Porphyrias
VP; AIP; HCP
Variegate Porphyria

- Autosomal Dominant
- South Africans of Dutch ancestry
- Protoporphyrinogen Oxidase
- Skin identical to PCT
- Onset of symptoms after puberty
- Neurovisceral attacks as adults
Acute Neurovisceral Attacks

- Induced by exposure to environmental stressors
  - Drugs (barbiturates, estrogen, griseo, sulfa)
  - Starvation / hypoglycemia
  - Hormonal fluctuations (menses, pregnancy)
  - Infections / fever

- Mechanism:
  - Deranged heme metabolism leads to neural dysfunction
  - Heme precursors ALA, PBG toxic to neural tissues
Acute Neurovisceral Attacks

• GI:
  • Colicky abdominal pain, n/v, constipation

• CNS:
  • peripheral neuropathy w/ pain/weakness/paralysis
  • seizures, psychosis, coma

• CVS:
  • tachycardia, hypertension

• Death
Variegate Porphyria: Labs

- Plasma porphyrin fluorescence spectrum: 627 nm is diagnostic:
- Increased urinary ALA, PBG during attacks
- Urine: Copro ≥ Uro (opposite of PCT)
- Feces: Proto > Copro
Management of Attacks

- Glucose loading
- Hematin infusions (neg. feedback to ALA)
- Analgesia
- Supportive Care
- Avoid triggers
- Prognosis: neuro damage/death from attacks
Acute Intermittent Porphyria

- Autosomal Dominant
- Porphobilinogen deaminase
- No skin findings
- Presents after puberty with attacks
- *Enzyme defect alone is insufficient for phenotypic expression: triggers are necessary*
Acute Intermittent Porphyria

- Diagnosis is a challenge
  - Multiple doctors, multiple exploratory laps
- Elevated urinary ALA, PBG during and between attacks
- RBC enzyme assay can confirm (false negs)
- Hyponatremia 2\(^{nd}\) to ADH secretion
- Urine is port-wine colored
AIP: Port-wine urine
Acute Intermittent Porphyria

- **Prognosis:**
  - Permanent neurologic damage can occur
  - Excellent prognosis with early diagnosis, avoidance of triggers
Hereditary Coproporphyrinia

- Autosomal Dominant
- Coproporphyrinogen oxidase
- Presents in 3rd-4th decade
- Acute attacks mimic AIP and VP
  - same triggers
- Skin (30%): similar to PCT, VP
- Neurologic sx more common than skin
Hereditary Coproporphyria

- Elevated urinary ALA, PBG during attacks
- Stool, urine: Copro
  - vs. AIP: “Ain’t in Poop”
PCT-like skin plus acute attacks: think HCP, VP
Summary: Acute Attack Porphyrias

- **AIP**: no skin findings
- **VP and HCP**: skin mimics PCT
  - Differentiate with porphyrin profiles
- **Stool**:
  - VP = Proto
  - HCP = Copro
- **Urine**:
  - AIP = ALA, PBG during and between attacks
  - VP, HCP = Copro, ALA, PBG during attacks only
  - Pink-red: VP, HCP during attacks
  - Port-wine: AIP during and between attacks
Erythrohepatic Porphyrias

- Hepatoerythropoietic Porphyria
- Erythropoietic Protoporphyria
Hepatoerythropoietic Porphyria

- **Uroporphyrinogen Decarboxylase**
  - Autosomal Recessive
  - Homozygous defect (2 mutant copies)
  - PCT: 1 mutant copy

- **Presents in infancy (by age 2)**
  - Similar to mild Gunther’s (CEP)
  - Severe photosensitivity, bullae and erosions
  - Dark urine at birth
  - Photosensitivity diminishes with age
Hepatoerythropoietic Porphyria

- **Late clinical findings:**
  - Sclerodermoid plaques and hypertrichosis
  - Mutilating scars in acral areas
  - Acral osteolysis (short digits)
  - Scarring alopecia, ectropion
  - Erythrodontia

- **Hemolytic Anemia**
- **Splenomegaly**
HEP: Labs

- **Urine**: Uroporphyrin
- **Feces**: Coprophyrin
- **RBC**: Protoporphyrin
  - vs. CEP: Uro
- Hemolytic Anemia
HEP: Management

- Avoidance, avoidance, avoidance
- **DO NOT** phlebotomize (anemic!)
Erythropoietic Protoporphyria

- Autosomal Dominant
- Ferrochelatase

- Presents in early childhood (avg. is 4)
- Immediate photosensitivity with burning, erythema and edema (*rare vesicles*)
  - “I don’t want to go out”
Erythropoietic Protoporphyria

- **Late:**
  - Waxy thickened scars over nose, face, hands creates **pebbling** of the skin
  - Elliptical scars on face, perioral area
Easily Produces Pebbly Fingers
Erythropoietic Protoporphyria

- Mild anemia
- Protoporphyrin Cholelithiasis
- Mild liver disease: jaundice
  - Rarely leads to cirrhosis, hepatic failure

DDx:
- hydroa vacciniforme, PMLE, solar urticaria, other mild porphyrias
Erythropoietic Protoporphyria

- RBC, plasma, feces: Protoporphyrin
- **NOT** in urine
  - Protoporphyrin are insoluble in water
  - *ain’t in pee pee*
EPP: Management

- Photoprotection/Avoidance
- **Beta-carotene**: 80mg bid - radical scavenger
- Transfusions
- Hematin
- Cholecystectomy
- Liver transplant
Porphyria Pearls

- **Congenital Erythropoietic Porphyria**
  - *Carrot Eating Prevent Usual Terrible Complications*
    - Uroporphyrinogen III Cosynthetase

- **Porphyria Cutanea Tarda**
  - *People Can Tell U Drink Constantly*
    - Uroporphyrinogen Decarboxylase

- **Variegate Porphyria**
  - *Veld People aPpear Pretty Odd*
    - Protoporphyrinogen Oxidase
Porphyria Pearls

• Acute Intermittent Porphyria
  • An Insane Prussian Peed Blue Dye
    • PBG Deaminase

• Hereditary Coproporphyria
  • Hairy Crazy People Can Pee Orange
    • Coproporphyrin oxidase

• Hepatoerythropoietic Porphyria
  • His Early Presentation gives U Da Clue
    • Uroporphyrinogen Decarboxylase
Porphyria Pearls

- Erythropoietic Protoporphyria
  - Easily Produces Pebbly Fingers
    - Ferrochelatase