The Mucinoses
General Information

- “A group of disorders in which an abnormal amount of mucin accumulates in the skin”
- Pathogenesis of all is unknown
General Information

- Associations
  - Paraproteinemia (scleromyxedema, scleredema)
  - Diabetes (scleredema)
  - Thyroid disease (pretibial myxedema, myxedema)
  - Connective tissue disease (LE, DM).
Goals

- Goal: To review, and characterize disorders characterized by abnormal dermal mucin, usually **Hyaluronic Acid**.
- *-The mucopolysaccharidoses are primarily characterized by a deposition of dermatan sulfate or heparan sulfate.
General Information - Mucin

- What is mucin?
  - Component of the dermal extracellular matrix
  - Produced by fibroblasts
  - Jelly-like amorphous material made of glycosaminoglycans

- What are glycosaminoglycans?
  - Complex carbohydrates composed of repeating polysaccharides
  - Hyaluronic Acid, Dermatan sulfate, chondroitin sulfate
  - Capable of absorbing 1000 times their own weight in water
General Information - Mucin

- Why does it accumulate in the skin?
  - Overall, we don’t know
- Possible Mechanism: promotion of upregulation of mucin production
  - Immunoglobulins and/or cytokines?
    - Evidence for: Increased serum immunoglobulin levels and circulating autoantibodies found in some cutaneous mucinoses
    - Evidence against: The serum of these patients stimulates mucin production in vitro even after the removal of IgG
  - An unknown serum factor?
- Possible Mechanism: reduction in normal catabolic degradation of mucin
Histology - Mucin

- H&E – Mucin stains blue between collagen bundles, or appears as widened collagen bundles
- Confirmational stains – alcian blue, colloidal iron, toluidine blue
- PAS (-) and often hyaluronidase-sensitive
- Fixation in alcohol may improve detection
- Monoclonal antibodies available to detect heparin sulfate
General Information - Classification

- Two major groups:
  - Primary - mucin deposition is the major histologic feature and results in clinically distinct lesions
    - Degenerative-inflammatory forms (which may be dermal or follicular based on where the mucin is located)
    - Hamartomatous-neoplastic
  - Secondary - mucin is only an associated finding
Primary Degenerative-Inflammatory Mucinoses: General Information

• Clinically – lichenoid papules, nodules, and/or plaques
• May have a variable degree of fibrosis
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema

• Terminology:
  • Synonyms: Lichen myxedematosus, papular mucinosis (often all three terms used synonymously in the literature)
  • Most patients reported to have Lichen myxedematosus or papular mucinosis without indication of subtype, in fact have scleromyxedema
Primary Degenerative-Inflammatory Mucinoses:
Scleromyxedema - History

- 1906 - First described by Dubreuilh and in 1908 by Reitman
- 1953 – Montgomery and Underwood – distinguished it from scleroderma and generalized myxedema
- 1954 – Gottron coins the name scleromyxedema
- 1963 – Associated with a monoclonal gammopathy
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – General Information

- **Epidemiology:**
  - Uncommon, only 114 cases reported (Rongioletti)
  - Middle aged adults
  - No sex predilection
- **Associated with monoclonal gammopathy – significance is a matter of debate**
- **Associated with many systemic disorders**
- **Fatal outcome reported with increased frequency**
- **Must distinguish from local variants where the skin only is involved**
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema - Pathogenesis

- **Unknown**
- **Immunoglobulin driven?**
  - Evidence for:
    - Scleromyxedema serum enhances fibroblast proliferation in vitro
  - Evidence against:
    - Paraprotein levels do not correlate with extend or progression of disease.
    - However, immunoglobulin purified from the paraprotein containing serum unable to stimulate fibroblast proliferation...

- **Which suggests a pathogenic circulating factor**
  - Additionally – clinical remission following stem cell transplantation points to the bone marrow as a source of this circulating factor

- **Finally – it has developed following intradermal injections of hyaluronic gel – Could it be a human adjuvant disease?**
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema - Clinically

- Widespread, symmetric eruption
- Numerous 2-3 mm firm, waxy papules
- Closely spaced
- Commonly linear

Location:
- Hands, forearms, face, neck, upper trunk and thighs.
- Glabella typically involved (deep longitudinal furrowing)
- Mucous membranes and scalp are not involved

Progression:
- Plaques become erythematous and infiltrated
- Surrounding skin stiffens-can get sclerodactyly, and decreased mobility of mouth and joints
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema - Clinically

- Nearby skin is shiny and indurated, resembling scleroderma
  - ****-PIP with elevated rim and central depression—“doughnut sign”
- Nearby skin also with erythema, edema, and brownish discoloration
- Assoc symptoms: itching is not rare
- Nails: Always absent: cuticular telangiectasias and calcinosis
MUCIN IS NOT FOUND EVERYWHERE!

Musculoskeletal –
- Slight to severe proximal muscle weakness in 27% of patients, which can be associated with elevated muscle enzymes and inflammatory EMG findings
- Joints 10.5% - arthralgia, migratory arthritis, seronegative polyarthritis, occasional mucin deposition.
- Carpal tunnel syndrome - 9.6%

CNS disturbances (15%) and peripheral neuropathy
- May come before, during or after cutaneous manifestations
- At least 10 cases of coma – preceded by dysarthria, flu-like illness and weakness – if you see this, admit immediately for close observation
- CT – normal
- Autopsy shows no mucin in brain

Lungs – dyspnea 16.7%, restrictive or obstructive lung involvement

GI - Dysphagia and nasal regurgitation – 31.6% of patients
- XRay – show esophageal aperistalsis
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Clinically – Other Organ System Findings

- **Kidneys**
  - Scleroderma-like renal disease
  - Mucin deposition in perivascular connective tissue and in Bowman’s capsule

- **Cardiovascular** - Hypertension, atherosclerosis, and myocardial infarction

- **Eyes**
  - Eyelids may be thickened
  - Ectropion and lagophthalmos may occur
  - Cornea may be involved

- **Raynaud's** – 8.8%, Sclerodactyly, acrosteolysis, association with other rheumatologic diseases described
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Histology

- First will notice: Slight superficial perivascular lymphoplasmocytic infiltrate
- Epidermis normal or thinned due to the pressure of underlying mucin and fibrosis
- Follicles may be atrophic
- **But need to look for the “triad:”**
  - 1) diffuse deposit of mucin in upper and mid reticular dermis
  - 2) Increased collagen deposition
  - 3) Marked proliferation of irregularly arranged fibroblasts
- May see fragmented and decreased elastic fibers
- Pannicular septa never involved in scleromyxedema (contrast to NSF)
- Mucin may fill the walls of myocardial blood vessels as well as the interstitium of the kidney, pancreas, adrenal glands and nerves
Fig. 46.4 Histopathology of *scleromyxedema*. Typical triad of fibrosis, proliferation of irregularly arranged fibroblasts, and interstitial deposits of mucin in the upper and mid reticular dermis.

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Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Associations

- Paraproteinemia (83.2%) - usually IgG with λ light chains
  - Few with κ light chains (FITZ???)
  - Biclonal IgG and IgA paraproteinemia or polyclonal hypergammaglobulinemia reported
- Mild plasmacytosis in bone marrow, but only progresses to multiple myeloma in 10% of cases
- Other cancers: Hodgkin’s and non-Hodgkin's lymphoma, Waldenström’s macroglobulinemia, leukemia described, especially after chemotherapy
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Differential Diagnosis

- Scleroderma and scleredema – neither has papules
- NSF – lack facial involvement and paraproteinemia. Fat is involved on path, not in scleromyxedema.
- Localized variants (to follow)
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Treatment

- Overall is disappointing
- Attempted treatments - all have produced some improvement
  - topical and intralesional hyaluronidase; corticotrophin; topical, intralesional and systemic corticosteroids; PUVA; Grenz ray and electron beam therapy; retinoids; plasmapheresis; extracorporeal photochemotherapy; dermabrasion; and pical dimethyl sulfoxide
- Chemotherapy – aimed at plasma cell dyscrasia
  - Low dose melphalan (monthly courses) – show some improvement, but 30% of deaths due to hematologic malignancies and septic complications.
  - Often given In combination with thalidomide and corticosteroids –
  - Same regimen used to treat elderly patients and those with comorbidities with multiple myeloma
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Treatment

- GCSF- beneficial in one patient with associated idiopathic neutrapenia
- Cyclosporine, IFN alpha (improved one case, worsened another).
- Stem cell transplantation
- Case reports of spontaneous improvement and resolution, even after 15 years, therefore limit toxic medications to disfigured, disabled, or ill patients
Primary Degenerative-Inflammatory Mucinoses:
Localized Lichen Myxedematosus – General Information

- Synonyms: Papular Mucinosis
- No evidence of:
  - Sclerotic features
  - Paraproteinemia
  - Systemic involvement
  - Thyroid disease
- All subsets are very rare
- Many texts do not distinguish between the localized variants.
Primary Degenerative-Inflammatory Mucinoses: Localized Lichen Myxedematosus – Clinically

- **Description:**
  - Small, firm, waxy papules
  - May become nodules or confluent into plaques
- **Location:**
  - Confined to few sites
  - Usually upper and lower limbs and trunk
Primary Degenerative-Inflammatory Mucinoses: Localized Lichen Myxedematosus – Histologic

- Mucin deposition
- Less characteristic than scleromyxedema (no triad)
- Variable fibroblast proliferation
- Fibrosis is not marked, may even be absent
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Subtypes - Discrete Papular LM

- Prevalence probably underestimated (only 8 reported cases)
- Clinical:
  - Description:
    - Firm, smooth, waxy or flesh-colored papules (not solely nodules). 2-5 mm in diameter, numbering from a few to hundreds.
    - May be erythematous or yellowish
    - Isolated, or confluent into nodules and/or plaques
    - Affected skin not indurated
  - Location:
    - Limbs and trunk in symmetric distribution
    - Face spared
    - Not solely on hands
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Subtypes - Discrete Papular LM

- **Histology:**
  - Upper and mid dermis with edema and a diffuse or focal mucinous deposit.
  - Epidermis uninvolved.
  - Fibroblast proliferation is variable, but neither collagen deposition nor sclerosis

- **Treatment/Natural History:**
  - Lesions progress slowly without systemic symptoms
  - Rarely resolve spontaneously
  - Progression to scleromyxedema has never been proven
Fig. 46.7A Histopathology of localized lichen myxedematosus – discrete papular type. A Mucin deposits (blue) splay collagen bundles in the dermis, but there is only slight fibroblast proliferation and no sclerosis (H&E). B Mucin accumulation within the dermis is made obvious by an Alcian blue stain (pH 2.5).
Fig. 46.7B Histopathology of localized lichen myxedematosus – discrete papular type. A Mucin deposits (blue) splay collagen bundles in the dermis, but there is only slight fibroblast proliferation and no sclerosis (H&E). B Mucin accumulation within the dermis is made obvious by an Alcian blue stain (pH 2.5).

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Primary Degenerative-Inflammatory Mucinoses:
Localized LM – Subtypes - Acral Persistent Papular Mucinosis

- 20 case reports
- $W>M$
- Described by Rongioletti, who wrote the article

Clinical:
- Description: multiple ivory to flesh-colored papules
- Location: ONLY ON THE BACKS OF THE HANDS, EXTENSOR WRISTS, and occasionally the distal forearms
Primary Degenerative-Inflammatory Mucinoses:
Localized LM – Subtypes - Acral Persistent Papular Mucinosis

- **Histology:**
  - Mucin in the upper reticular dermis, mostly focally, sparing the subepidermal zone
  - Normal fibroblasts in number

- **Treatment/Natural History:**
  - Lesions persist and may increase slowly without systemic involvement.
  - Overall, good prognosis, without spontaneous resolution
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Subtypes - Papular Mucinosis Of Infancy

- Synonym: cutaneous mucinosis of infancy
- 5 cases reported
- May be an overlap with a mucinous nevus
- Clinical:
  - Description: firm, opalescent papules
  - Location: upper arms, especially the elbows, and the trunk
- Histology:
  - Superficial lymphocytic infiltrate
  - Mucin stored focally in the superficial dermis (looks as though it may be “encased” in epidermis)
  - Normal fibroblasts numbers
- Treatment/Natural History:
  - No systemic involvement
  - No spontaneous resolution
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Subtypes - Pure Nodular LM

- **Synonym:** Atypical Tuberous Myxedema of Jadassohn-Dosseker
- **Clinical:**
  - Description: multiple nodules on with mild or absent papular eruption
  - Location: limbs and trunk
- **Histology:** Mucin in reticular dermis
- **Treatment/Natural History:**
  - No therapy required
  - Topical corticosteroids may be of some benefit
  - One report of HIV patient with complete resolution after isotretinoin treatment
  - Spontaneous resolution reported as well
Primary Degenerative-Inflammatory Mucinoses:
Localized LM – Subtypes - Atypical Forms

- Localized with scleromyxedema-like symptoms without skin sclerosis or paraproteinemia
- Rarely localized LM associated with monoclonal gammopathy
- HIV related localized lichen myxedematosus – 14 cases, none had visceral involvement
- Toxic syndrome related localized lichen myxedematosus –
  - Toxic oil syndrome (ingestion to rapeseed oil in Spain)
  - L-tryptophan associated eosinophilia-myalgia syndrome
  - Share clinical features including constitutional symptoms, peripheral eosinophilia, hyperpigmentation, and a sclerodermoid appearance
  - Lesions resolve after exposure to substance is ceased, slowly
- Hep C related localized lichen myxedematosus – reported in Japan
Mucinoses:  
Localized LM – Subtypes - Self-Healing  
Papular Mucinosis

- Was felt to be a subtype of localized lichen myxedematosus, usually found in children
- **Again, no paraproteinemia or thyroid dysfunction**
- Resolve spontaneously over a few weeks to many months (up to 8)
- No sequelae
- Clinically:
  - **Description:**
    - Acute eruption of papules in linear infiltrated plaques
    - May have subcutaneous nodules on the face and periarticular regions with periorbital swelling.
  - **Location**
    - Face, neck, scalp, abdomen, and thighs.
- May be associated with systemic findings (fever arthralgias, weakness).
- May be associated with nephroblastoma (1 report), or carpal tunnel syndrome.
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Subtypes - Self-Healing Papular Mucinosis

- **Histology:**
  - Mild perivascular infiltrate
  - Mucin diffusely in upper and mid dermis
  - Slight increase in fibroblast numbers
  - Mucin also found in periarticular nodes of juvenile type

- **Treatment/Natural History:**
  - Lesions resolve spontaneously or after biopsy
  - Diagnosis made by the spontaneous resolution of lesions.
Primary Degenerative-Inflammatory Mucinoses: Localized LM – Differential Diagnosis

- Biopsy for Histology to rule out:
  - GA
  - Lichen amyloid
  - Lichen planus
  - Other lichenoid eruptions
- Must differentiate from scleromyxedema
Primary Degenerative-Inflammatory Mucinoses: Scleredema – General Information

- **Synonyms**: Scleredema adultorum of Buschke, Scleredema diabeticorum
- **History**:  
  - 1876 - Described by Pitford (Buschke erroneously credited for first description in 1902)  
  - 1970 – Relationship to DM established  
- **Affects all races**
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Pathogenesis

- Diabetes
  - Proposed mechanisms:
    - Irreversible glycosylation of collagen and resistance to degradation by collagenase leading to an accumulation of Type I collagen
    - Excess stimulation by insulin, microvascular damage, hypoxia may increase synthesis of collagen and mucin
  - ? – Streptococcal infection, lymphatic injury, paraproteinemia
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Subtypes

- **Clinical:** 3 forms or with/without DM
- In general, skin changes felt better than seen.
- **Type 1:**
  - Middle aged women and children
  - Preceded by fever, malaise and an infection
  - Cervicofacial skin **suddenly** hardens, extending to trunk and upper limbs.
  - Face is expressionless, opening of mouth and swallowing are difficult
  - Resolves in a few months to 2 years
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Subtypes

- **Type 2:**
  - Same as the first with more subtle onset
  - No preceding illness
  - Persists for years
  - More frequently associated with a monoclonal gammopathy

- **Type 3**
  - Obese middle aged men with DM
  - Subtle onset
  - Persistent involvement
  - Involves posterior neck and back
  - *Peau d’orange*
  - Has proved fatal in one case with internal involvement
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Associations

- Can have systemic involvement
- Associated with hyperparathyroidism, RA, Sjogren’s syndrome, malignant insulinoma, multiple myeloma, gall bladder carcinoma, HIV infection
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Histology

- First notice: sparse perivascular lymphocytic infiltrate
- Marked thickening of reticular dermis, extending below sweat gland coils
- Large collagen bundles separated by clear spaces (mucin) – variable, may need multiple biopsies to diagnose
- Dermis appears “fenestrated”
- No increase in fibroblast numbers
- Reduced number of elastic fibers
- Mucin also accumulates in skeletal muscle and heart
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Differential Diagnosis

- Scleroderma - scleredema lacks acral involvement, Raynaud’s and telangiectasias
- Scleromyxedema – scleredema lacks papules; histologically it lacks fibroblast hyperplasia
- Cellulitis - often misdiagnosed by non-dermatologists due to the erythema
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Outcome/Treatment

- Little morbidity except for limitation of movement
- Control of hyperglycemia does not influence the skin
- Treatment is unnecessary if associated with infection
- If associated with monoclonal gammopathy or diabetes, regression is uncommon
  - Attempted treatments with some reported success - PUVA, cyclophosphamide pulse therapy plus oral corticosteroids, cyclosporine, factor XIII infusion, electron beam therapy
  - Attempted treatments without reported success – systemic and intralesional corticosteroids, intralesional hyaluronidase, methotrexate, antibiotics, penicillamine
- Limit aggressive therapy to individuals with disabling disease or systemic manifestations
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema

- Localized (pretibial) myxedema
- Synonym – thyroid dermopathy
- Usually due to Graves
- Epidemiology of Graves Disease
  - Onset usually in 20’s-30’s
- Pretibial myxedema
  - a sign of Graves (along with goiter, exophthalmus, *thyroid acropachy*, and thyroid stimulating immunoglobulins that recognized the thyroid-stimulating hormone receptor)
  - Found in 1-5% of Graves patients, but in up to 25% of those with exophthalmus
  - May occur in Hashimoto’s, following treatment of Graves, and even in euthyroid patients
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema - Pathogenesis

- Due to mucin deposition
- A serum factor (non related to thyroid stimulating immunoglobulins) may incite fibroblasts to make mucin
- Fibroblasts from the dermis of the lower extremities more sensitive to this factor than other areas of the body
- An insulin-like growth factor, trauma, and lymphatic obstruction may also play a role
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema - Clinically

**Description:**
- Cutaneous induration of the shins
- Skin colored, purple-brown, or yellowish
- Waxy indurated nodules or plaques
- Often painful and pruritic
- *Peau d’orange* appearance
- Hypertrichosis and hyperhidrosis confined to pretibial shins
- Can present as a diffuse, nonpitting edema evolving into elephantiasis

**Location:**
- Anteriolateral aspect of lower legs and feet
- Rarely, but may, affect the face, shoulders, upper extremities, lower abdomen, scars or donor graft sites
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema - Histology

- Perivascular and periadnexal lymphocytic infiltrate
- Hyperkeratosis, papillomatosis, and hyperplasia of epidermis
- Mast cells present as well as large, stellate fibroblasts
- Large quantities of mucin in the reticular dermis, often showing a grenz zone of collagen
  - Collagen bundles appear widened
  - Mucin stains with Alcian blue, colloidal iron, or toluidine blue
  - Dermis appears thickened
  - Reduced elastic fibers
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema

- Differential Diagnosis:
  - LSC, Hypertrophic LP, Lymphedema, elephantiasis,
  - All lack mucin deposition on pathology, and not seen in setting of thyroid disease
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Pretibial Myxedema - Treatment/Natural History

- Morbidity is usually minimal
- Entrapment of peroneal nerves by mucinous connective tissue may cause foot drop or faulty dorsiflexion
- Treating hyperthyroidism does not improve the cutaneous lesions;
- Lesions often occur after hyperthyroid treatment begun

Treatment

- Topical corticosteroids under occlusion and Intralesional Kenalog
  - May lead to improvement and cause relief, symptomatically
- Skin grafting often followed by relapses
- Some benefit - plasmapheresis, gradient pneumatic compression, octreotide
- May clear spontaneously (mean 3.5 years)
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- A manifestation of severe hypothyroidism (compare to pretibial myxedema which is usually hyperthyroidism)

- **Pathogenesis:**
  - Mucin deposited in the dermis
  - Due to a quantitative or functional deficiency of thyroxine.
  - Impaired degradation rather than increased synthesis suggested as the cause

- May be Congenital (cretinism), Juvenile, or Adult onset
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- Congenital (cretinism):
  - 1/5000 neonates
  - Dwarfism, mental retardation, somnolence, constipation, feeding problems, poor muscle tone, persistent jaundice, respiratory problems.
  - 1/3 of infants have no symptoms.
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- Juvenile –
  - Develops in a previously euthyroid child.
  - Short stature, abnormal physical and mental development (poor school performance), retardation of sexual maturity.
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- Adult onset –
  - Most common form of the disease.
  - Women 40-60 years old.
  - Usually due to Hashimoto’s, therapy of Graves, or rarely pituitary or hypothalamic failure.
  - Initial symptoms include mental and physical sluggishness, weight gain, constipation, leg cramps, loss of appetite, cold intolerance
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema - Clinically

- **General:**
  - Pale, cold, waxy and dry skin
  - Absence of sweating – May lead to ichthyosis or eczema craquelé
  - Purpura of the extremities
  - Delayed wound healing
  - Xanthomas

- **Face:**
  - Puffy periorbital tissues, tongue, lips, hands, genitals
  - Broad nose
  - Face has a dull expression.

- **Yellowish discoloration of palms and soles due to carotenemia**
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema - Clinically

- Hair and nails:
  - Dry and brittle
  - Diffuse patchy non-scarring alopecia
  - Hypertrichosis on shoulders and back
  - Alopecia of the lateral 1/3 of the eyebrow
- Blue telangiectatic fingertips
- Clavicular pad (diagnostic in cretinism)
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- **Systemic findings:**
  - Cardiomegaly
  - Megacolon or bowel obstruction
  - Psychiatric symptoms mimicking Alzheimer’s disease
  - Serositis
  - Carpal tunnel syndrome
  - Seventh nerve palsy
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema - Histology

- Skin looks nearly normal on H&E
- Mucin deposition, perivascular and perifollicular
- Splay collagen bundles extending into subcutaneous fat and nerves
- Normal number of fibroblasts
- Reduced elastic fibers
Primary Degenerative-Inflammatory Mucinoses: With Altered Thyroid Function – Generalized Myxedema

- **Workup**
  - Low levels of T₄, high TSH in primary, low TSH in secondary (does not usually occur in secondary)

- **Treatment/Natural History:**
  - Measure T₄ and TSH 3-6 days after development (part of newborn screen)
  - Begin treatment by three months old.
  - Symptoms subside with thyroxine administration, but recur if it is discontinued
  - If untreated, can die of myxedema coma
Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosis

- Synonyms: Plaques-like cutaneous mucinosis, midline mucinosis, reticulated erythematous mucinosis syndrome
- A rare, persistent, photoaggravated, rash
- Now grouped with LE tumidus
- Plaques-like cutaneous mucinosis is probably a different clinical presentation of the same syndrome

History:
- 1960 – described by Perry
- 1974 – name coined by Steigleder and colleagues

Epidemiology:
- Middle aged women, but also in men and children
- Seen worldwide
Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosis

- **Pathogenesis:**
  - Sunlight may be causal or a promoting factor
  - Fibroblasts exhibit an abnormal response to stimulation by IL-1β

- **Clinical:**
  - **Description:**
    - Pink to red macules and papules
    - Merge into reticulated and annular patterns or plaque-like lesions.
    - May be pruritic
  - **Location:**
    - Mid back or chest
    - May spread to abdomen

- Not associated with systemic disease or laboratory abnormalities
Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosis

- **Histology:**
  - Normal epidermis
  - Perivascular and perifollicular (at times) T-cell infiltrate
  - Small amounts of interstitial mucin in upper dermis
  - Vascular dilation
  - Tubuloreticular inclusion in endothelial cells and pericytes
    - Also seen with viral infections and high levels of interferon and within cells in lupus erythematosus

- **Differential Diagnosis:** Discoid LE, Seb derm, TV (should both have scale)
Perivascular lymphocytes

Paleness due to mucin
Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosis - Treatment/Natural History

- Worsened by sun exposure, but also has been reported to be beneficial.
  - Broad spectrum sunscreens
  - Reports of clearance with UVA1
  - Phototests can sometimes reproduce lesions
- Antimalarials will clear lesions in 2-6 weeks
- Variable response to topical and systemic corticosteroids, tacrolimus, tetracycline, UVB, cyclosporine
Primary Degenerative-Inflammatory Mucinoses: Cutaneous Lupus Mucinosis

- **Synonyms**: Papulonodular mucinosis in lupus erythematosus, papular and nodular mucinosis of Gold
- **Occurs in 1.5% of patients with LE**
- **Clinical**:
  - **Description**:
    - Asymptomatic, skin-colored to reddish 0.5-2 cm papules and nodules
    - Rarely merge into large plaques
    - May have central depression and pigmentation
  - **Location**: back, V of chest, upper extremities
- **May antedate or begin at the same time as cutaneous LE**
Primary Degenerative-Inflammatory Mucinoses: Cutaneous Lupus Mucinosis

- **Histology:**
  - Slight to moderately dense perivascular lymphocytic infiltrate
  - Large amounts of mucin in upper and mid dermis, sometimes involving the fat
  - Epidermal changes of LE absent

- **Natural History:**
  - Clinical course related to underlying disease activity
  - 75% or patients with LE have systemic involvement, usually renal and articular
  - Some only have CCLE or SCLE
  - Only occasionally reported to worsen after sun exposure

- **Treatment**
  - The same as for LE – sunscreens, corticosteroids, antimalarials
  - IL Kenalog useful in reducing large nodules or plaques
Primary Degenerative-Inflammatory Mucinoses: Cutaneous Focal Mucinosis

- Epidemiology: only in adults
- Clinical:
  - Description: asymptomatic, skin colored papule or nodule, less than 1 cm
  - Location: anywhere on the body, including oral cavity
- Assoc symptoms: rarely linked to thyroid disorders
- Definitive Diagnosis is made by histology alone
Primary Degenerative-Inflammatory Mucinoses: Cutaneous Focal Mucinosis

• **Histology:**
  - Mucin in the upper and mid dermis
  - Fat is spared
  - Clift-like spaces, but no cysts seen
  - Vimentin (+), spindle-shaped fibroblasts
  - Minor population dermal dendrocytes that are partially Factor XIIIa (+) and partially CD34 (+)
  - Absent elastic and reticulum fibers
  - Normal capillary number

• **Differential diagnosis –**
  - (Angio)myxomas - true benign neoplasms and can recur after excision
Primary Degenerative-Inflammatory Mucinoses: Miscellaneous Mucinosis

- Neuropathia mucinosa cutanea – described once
- Atypical tuberous myxedema (Jadassohn-Dosseker) – variant of nodular lichen myxedematosus
- Perifollicular mucinosis and eccrine mucinosis – described in an HIV (+) patient, a histologic epiphenomenon. Represents a “muciparous” reactive tendency in HIV
- Familial forms described
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis - Follicular Mucinosis

- Synonyms – Alopecia mucinosis, mucinosis follicularis, Pinkus’ follicular mucinosis-benign primary form
- Uncommon, inflammatory disorder
- Primary follicular mucinosis is an idiopathic benign form, not linked to lymphoma
- Described in 1957 by Pinkus
- Predilection for children and adults in 20’s and 30’s
- Pathogenesis: ???
  - Proposed etiologies: follicular keratinocyte mucin deposition in follicles
  - Cell-mediated immune mechanisms
    - Including a reaction to *Staphylococcus aureus*
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis – Follicular Mucinosis - Clinical

- **Description**: acute or subacute eruption
  - One to several pink plaques or grouped follicular papules
  - Sometimes with scale
  - Associated with alopecia
  - Nodules, annular plaques, folliculitis, follicular spines and acneiform eruptions described
- **Location**: limited to the face and scalp
- *** - A second form characterized by a generalized distribution, larger and more numerous plaques, a chronic course and older population is likely secondary follicular mucinosis associated with atopic dermatitis or CTCL
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis - Follicular Mucinosis - Histology

- Perifollicular infiltrate of lymphocytes, eosinophils and histiocytes
- Mucin in the follicular epithelium and sebaceous gland causing keratinocytes to disconnect
- Advanced cases – follicles are converted into cystic spaces filled with mucin, inflammatory cells, and altered keratinocytes
Fig. 46.13C Follicular mucinosis. A Several pink plaques on the face of a young girl. B Grouped follicular papules on the leg of an older adult in association with erythematous plaques. Note the associated alopecia. The hemorrhagic crust is the site of a previous biopsy. C Histology of follicular mucinosis. Mucin deposition (blue–gray) within the follicular epithelium.

(Courtesy of Thomas Horn MD.)
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis - Follicular Mucinosis

• **Differential Diagnosis:** MF-related alopecia mucinosis
  - Difficult to differentiate.
  - No single reliable criteria
  - Benign features –
    - Solitary plaque
    - Young age
    - Limited number of lesions
    - Located only on head and neck
    - Spontaneous resolution
    - Lack of atypical lymphocytes on path

• **Treatment/Natural History:**
  - No specific treatment
  - Most resolve in 2-4 months
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis - Urticaria-Like Follicular Mucinosis

- Very rare
- Occurs in middle aged men

**Clinical:**

- **Description:**
  - Purpuric urticarial plaques and papules
  - Erythematous, “seborrheic” background
  - As lesions resolve, red macules persist for weeks

- **Location:**
  - Head and neck
  - Hair bearing areas involved, but neither follicular plugging or alopecia seen
Primary Degenerative-Inflammatory Mucinoses: Primary Follicular Mucinosis - Urticaria-Like Follicular Mucinosis

- No associated systemic disease

- **Histology:**
  - Lymphocytes, eosinophils around vessels in the upper dermis
  - Mucin-filled cystic spaces in hair follicles

- **Treatment/Natural History:**
  - Waxes and wanes irregularly over months to 15 years
  - Inconsistent response to sunlight, but beneficial in a small amount of cases
  - Good prognosis
  - Antimalarials and dapsone reported as effective
Primary Hamartomatous-Neoplastic Mucinosis

- Primary Hamartomatous-Neoplastic Mucinosis – mucin found in many tumors, but in only two is mucin a distinctive feature
  - Mucinous Nevus
  - (Angio)myxoma
Primary Hamartomatous-Neoplastic Mucinosis- Mucinous Nevus

- Benign hamartoma
- Congenital or acquired
- Clinical: Plaque with a unilateral linear nevoid pattern

Histology:
- Epidermis can be normal, but can be acanthotic with elongated rete ridges and hyperkeratosis
- May resemble an epidermal nevus (points to a combined hamartoma – features of a epidermal nevus and connective nevus of proteoglycan type)
- Diffuse mucin in the upper dermis
- Collagen and elastic fibers absent in these areas
Primary Hamartomatous-Neoplastic Mucinosis - (Angio)myxoma

- Terms angiomyxoma and myxoma synonyms
- Benign, acquired neoplasm
- Can be solitary or multiple
- May be a manifestation of Carney complex (cutaneous myxomas, cardiac myoma, numerous lentigines, multiple blue nevi, endocrine overactivity)
Primary Hamartomatous-Neoplastic Mucinosis - (Angio)myxoma

- **Histology:**
  - Lobulated lesion in the dermis
  - Mucinous matrix
  - Variably shaped fibroblasts, mast cells, few collagen and reticulin fibers
  - Bizarre multinucleated cells and regular mitotic figures
  - Prominent dilated capillaries typical
  - Epithelium – may have keratinous cysts or epithelial strands with trichoblastic features entrapped within the lesion

- **Differential diagnosis** – Cutaneous focal mucinosis – myxomas are true benign neoplasms and can recur after excision