

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

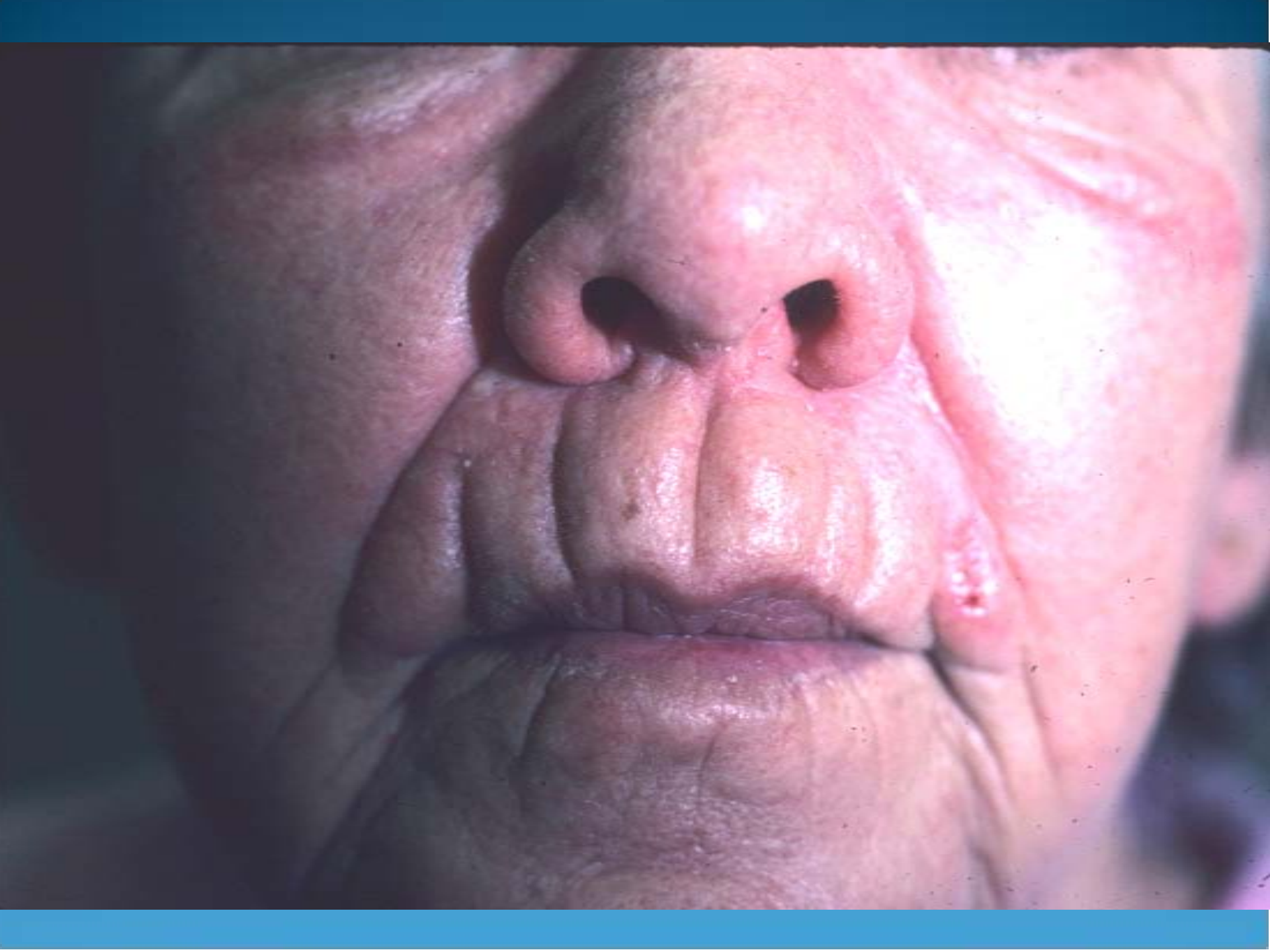
- Unknown
- Immunoglobulin driven?
 - Evidence for:
 - Scleromyxedema serum enhances fibroblast proliferation in vitro
 - Evidence against:
 - Paraprotein levels do not correlate with extent or progression of disease.
 - However, immunoglobulin purified from the paraprotein containing serum unable to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

















50-2

7

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







Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Clinically – Other Organ System Findings

- 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

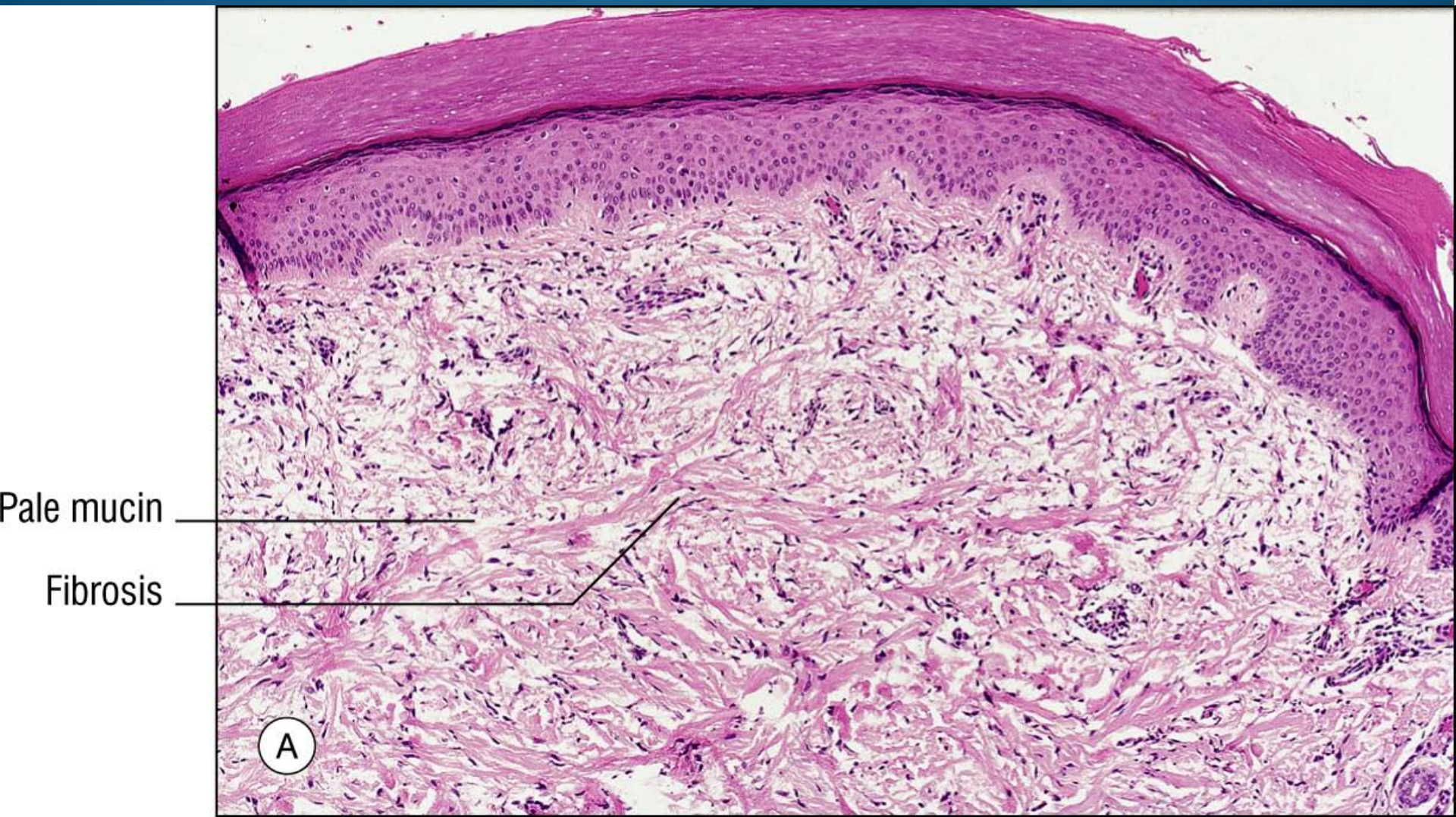
Primary Degenerative-Inflammatory Mucinoses: Scleromyxedema – Clinically – Other Organ System Findings

- 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, acroosteolysis, 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



© 2005 Elsevier Inc. Rapini, Practical Dermatopathology.

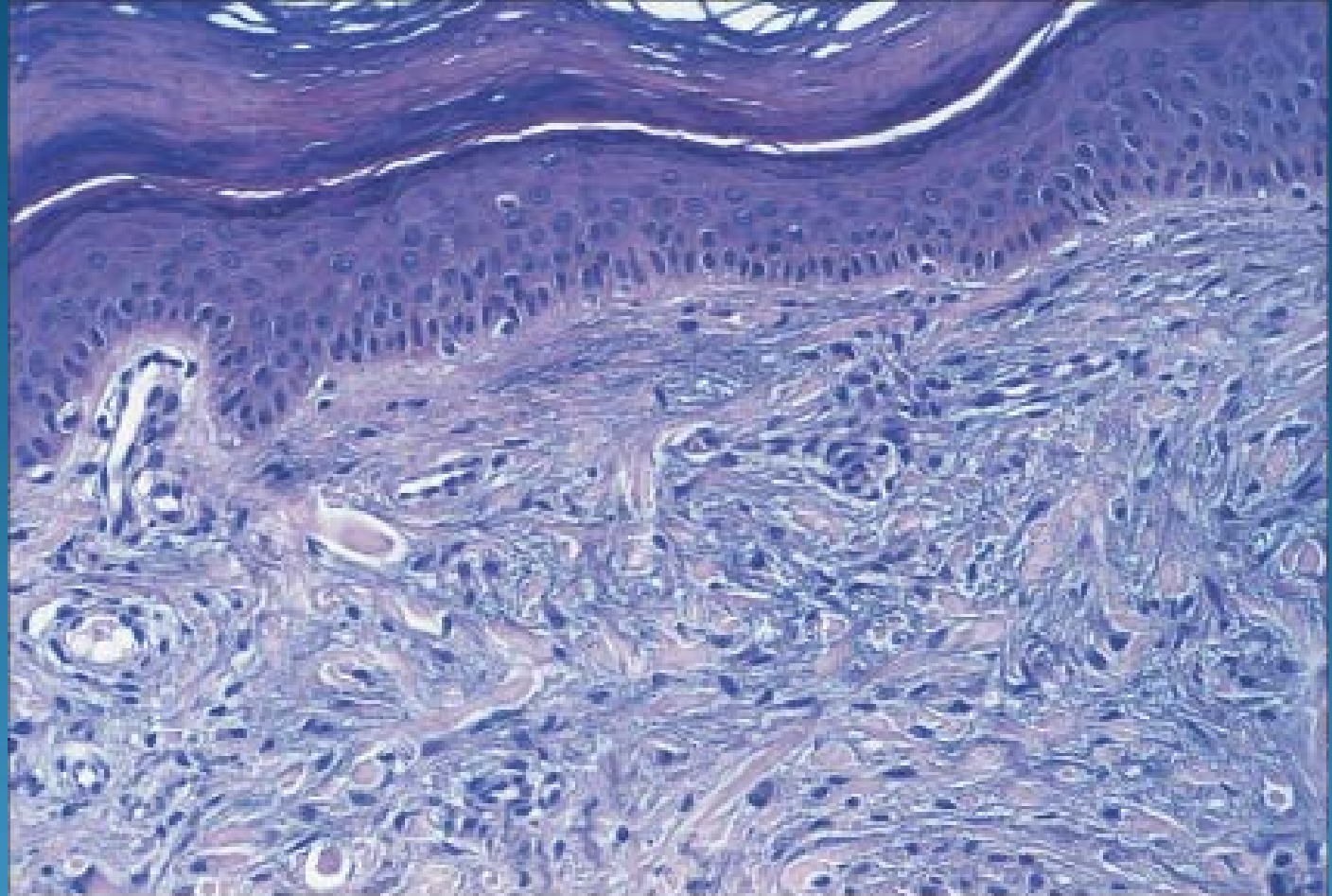


Fig. 46.4 Histopathology of scleromyxedema. Typical triad of fibrosis, proliferation of irregularly arranged fibroblasts, and interstitial deposits of mucin in the upper and mid reticular dermis.

© Copyright 2008 by Mosby, Inc., an affiliate of Elsevier Inc.

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 neutropenia
- 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

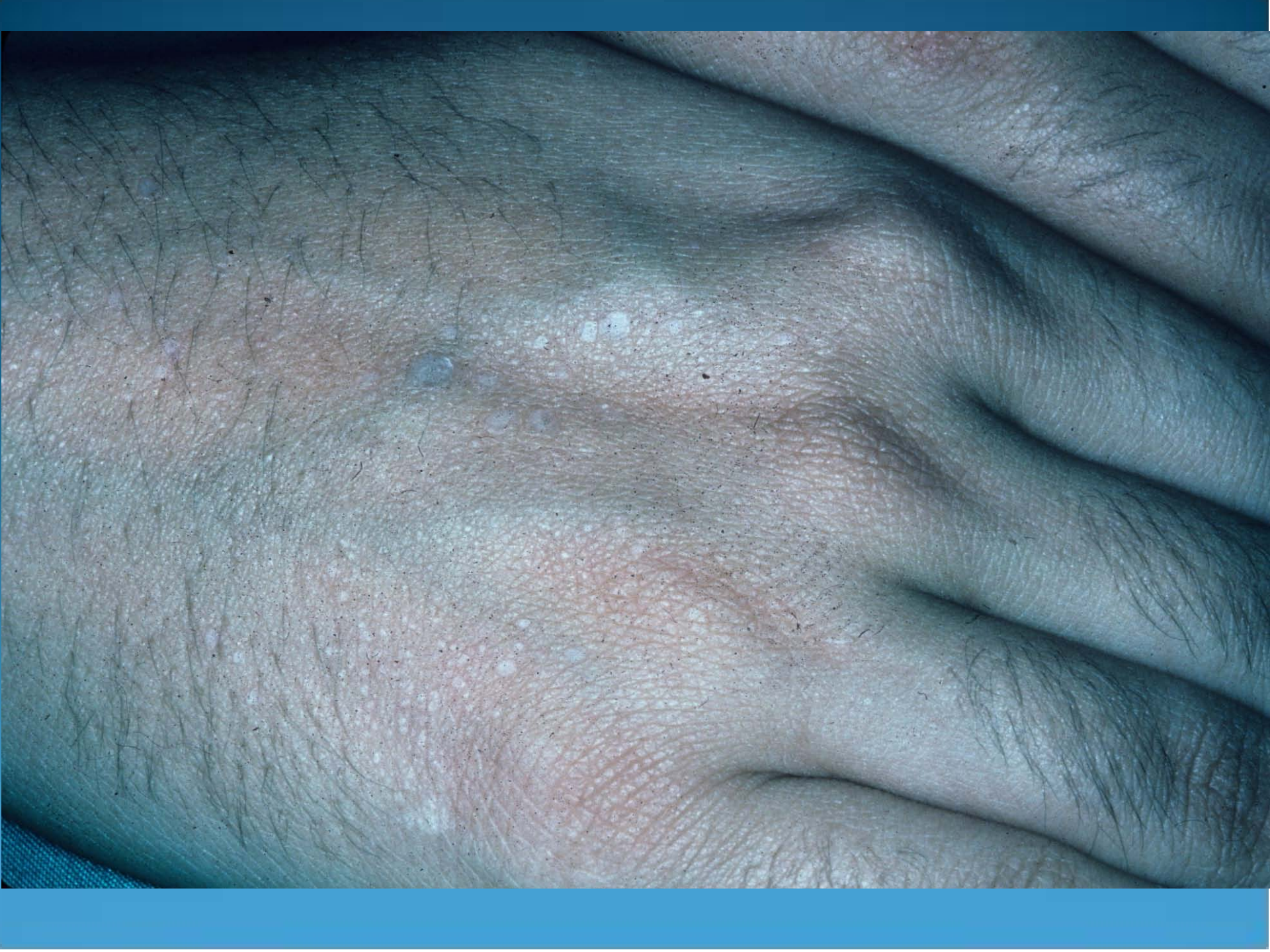
- Mucin deposition
- Less characteristic than scleromyxedema (no triad)
- Variable fibroblast proliferation
- Fibrosis is not marked, may even be absent

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

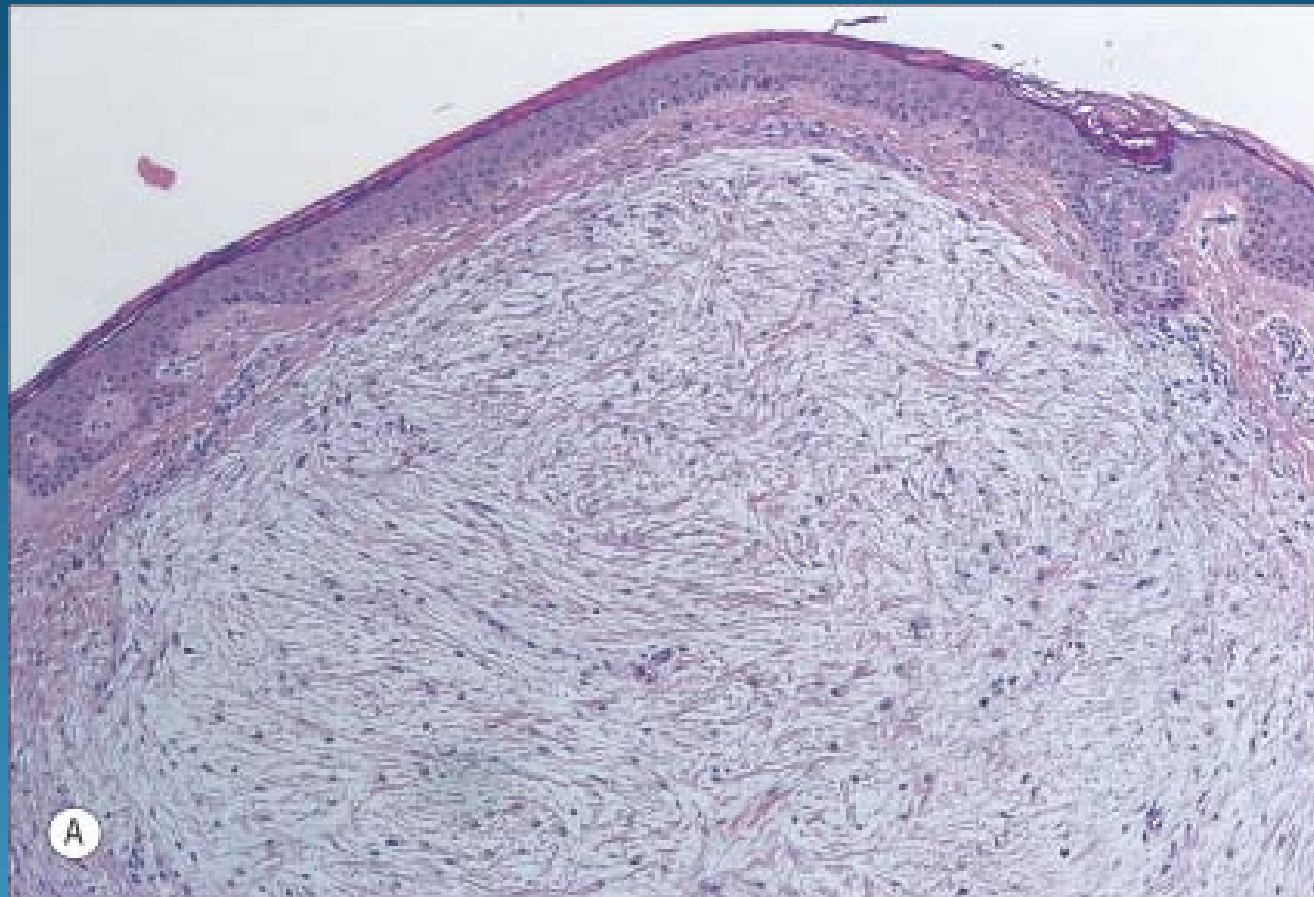


Fig. 46.7A Histopathology of localized lichen myxedematosus – discrete papular type. A Mucin deposits (blue) splay collagen bundles in the dermis, but there is only slight fibroblast proliferation and no sclerosis (H&E). **B** Mucin accumulation within the dermis is made obvious by an Alcian blue stain (pH 2.5).

© Copyright 2008 by Mosby, Inc., an affiliate of Elsevier Inc.

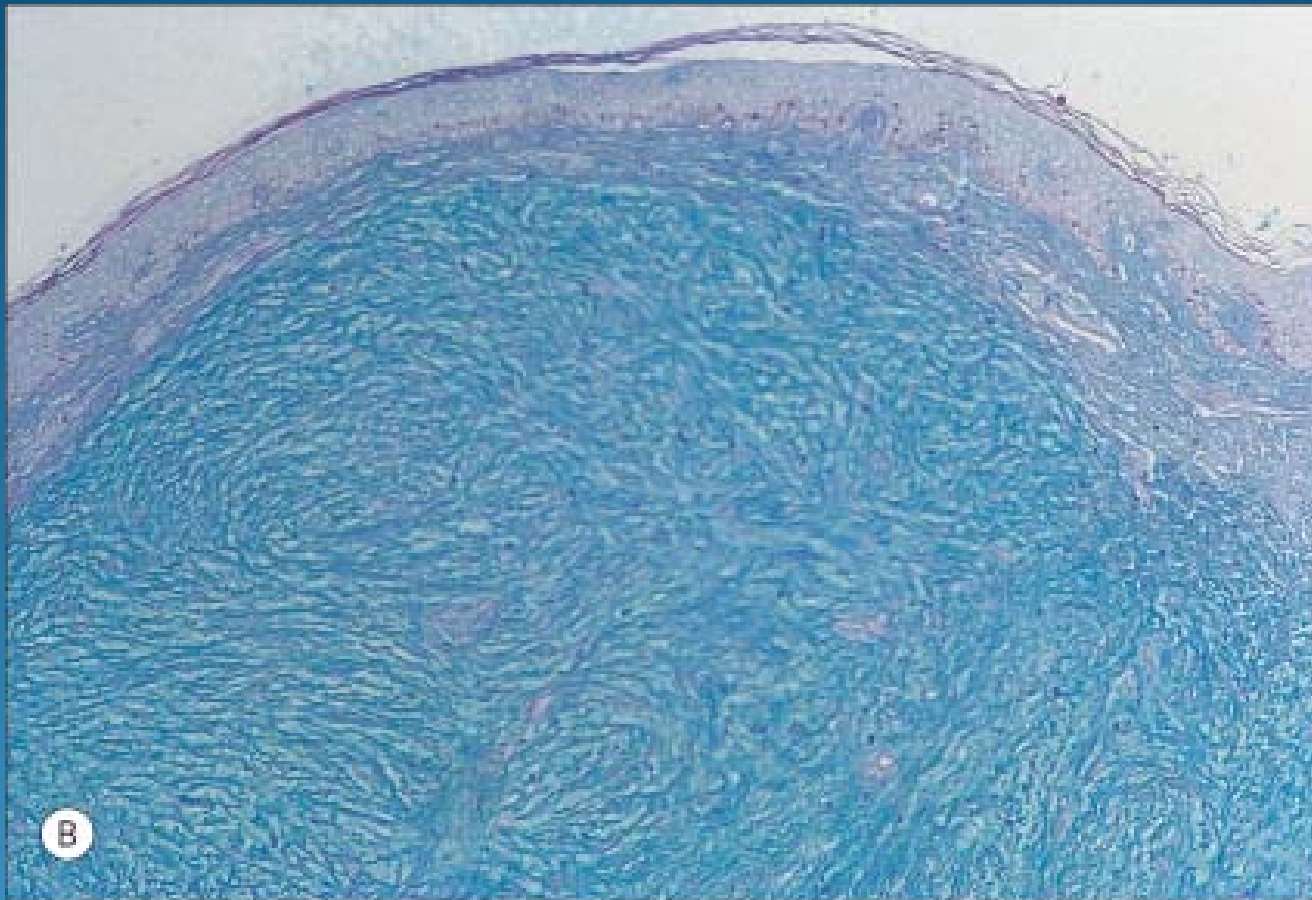


Fig. 46.7B Histopathology of localized lichen myxedematosus – discrete papular type. A Mucin deposits (blue) splay collagen bundles in the dermis, but there is only slight fibroblast proliferation and no sclerosis (H&E). **B** Mucin accumulation within the dermis is made obvious by an Alcian blue stain (pH 2.5).

© Copyright 2008 by Mosby, Inc., an affiliate of Elsevier Inc.

Primary Degenerative-Inflammatory Mucinoses:

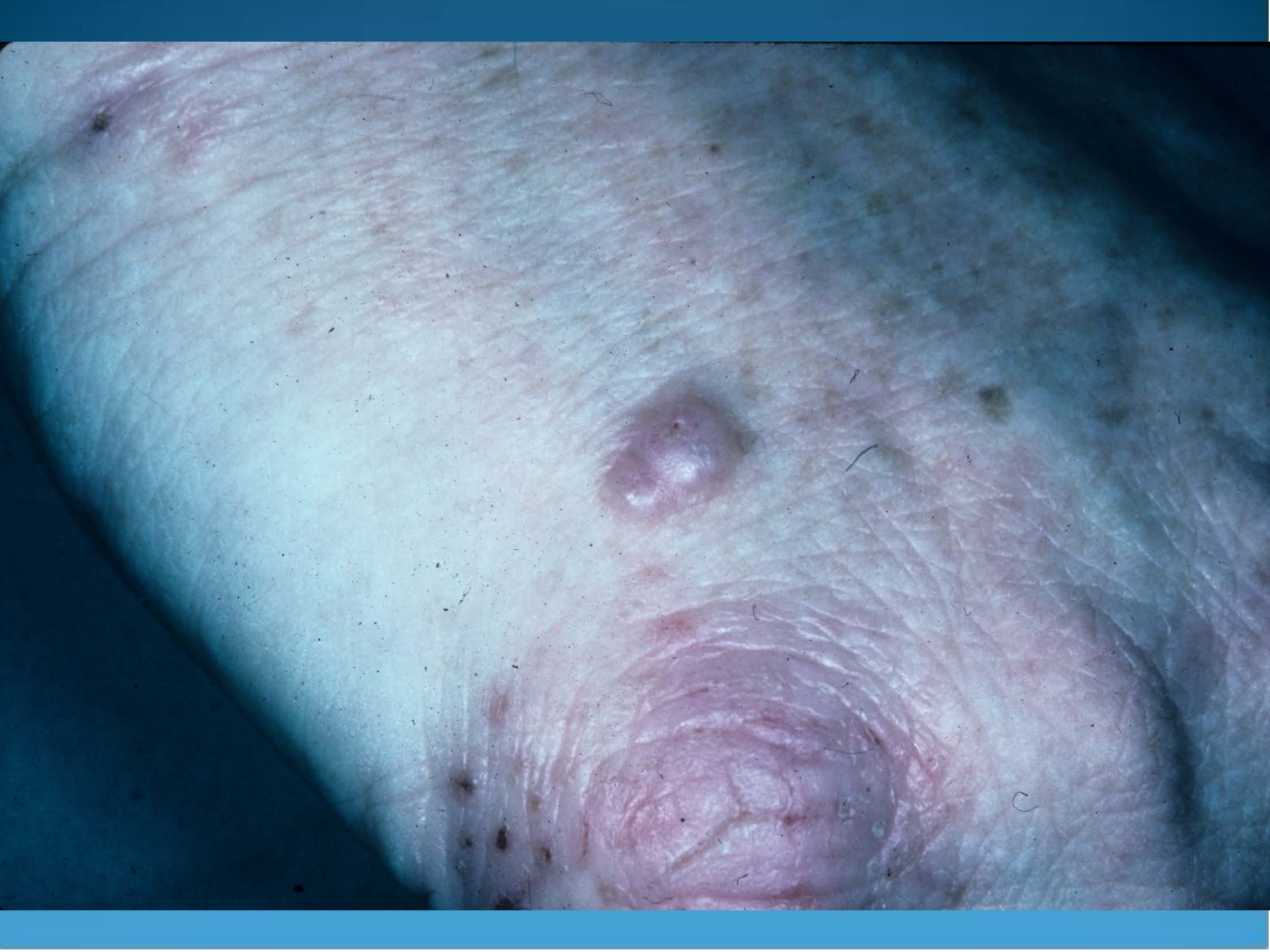
Localized LM – Subtypes - Acral Persistent Papular Mucinosis

- 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:

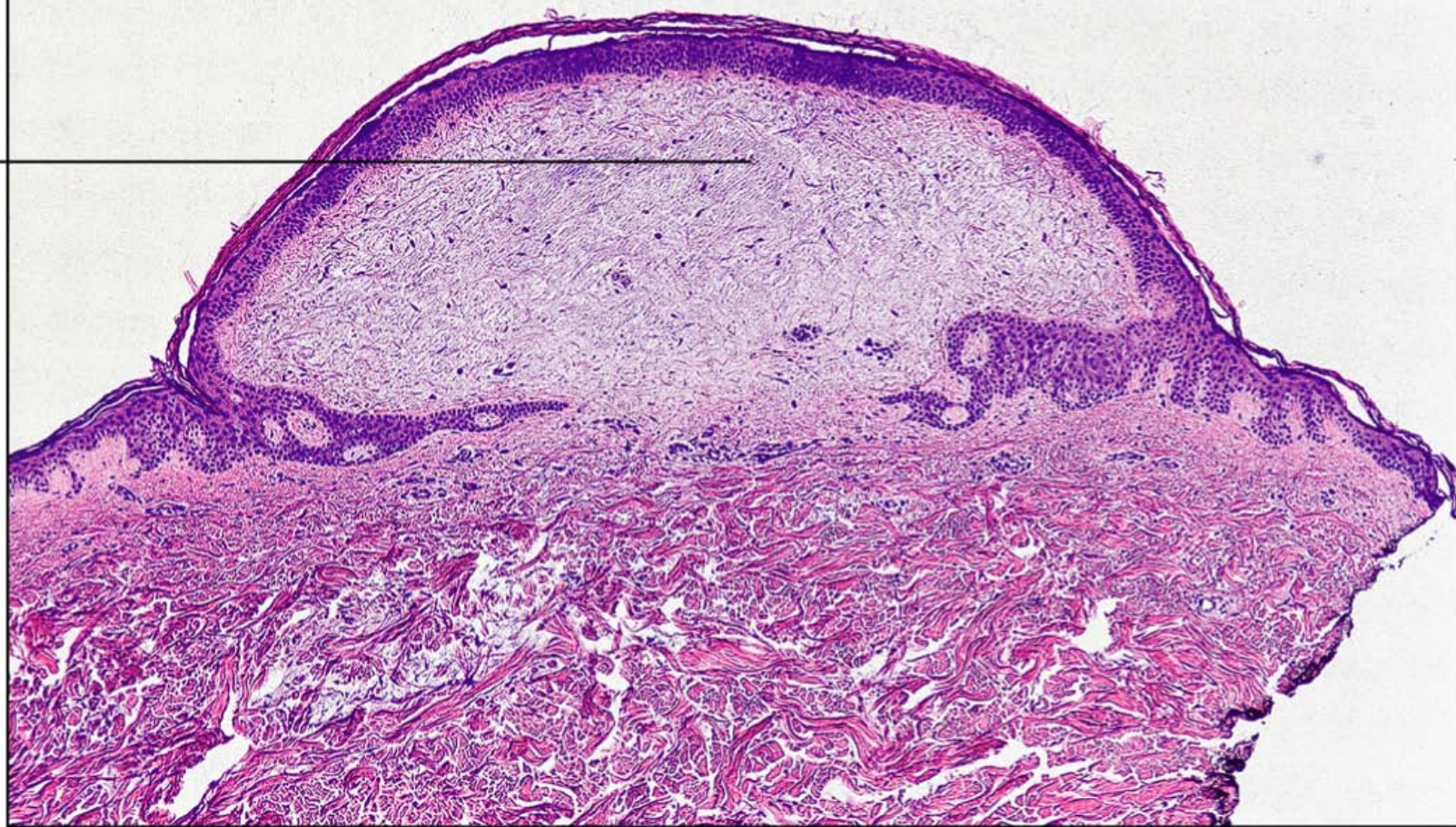
Localized LM – Subtypes - Acral Persistent Papular Mucinosis

- 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

Mucin



© 2005 Elsevier Inc. Rapini, Practical Dermatopathology.

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

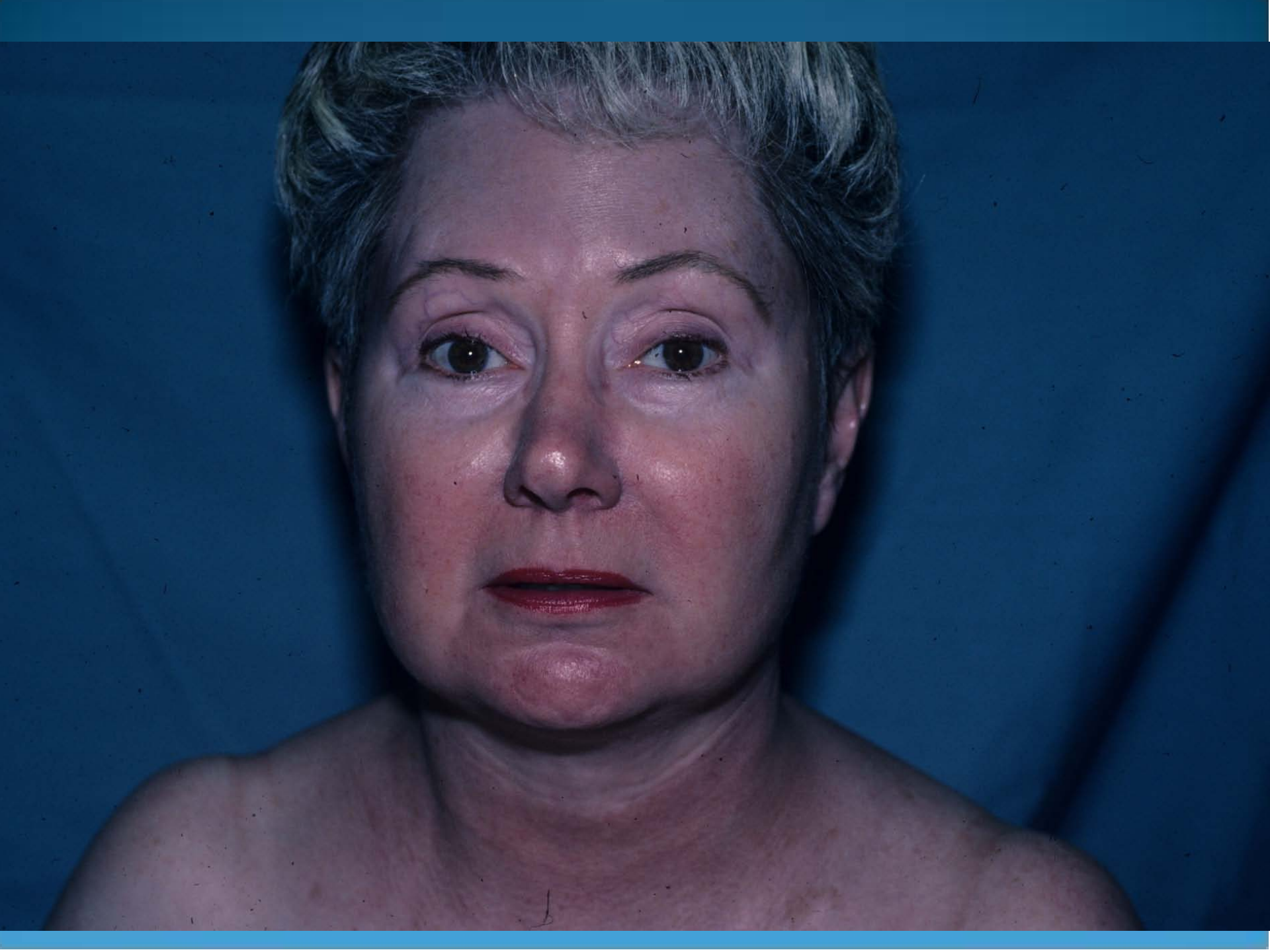


Primary Degenerative-Inflammatory Mucinoses: Scleredema – Pathogenesis

- 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

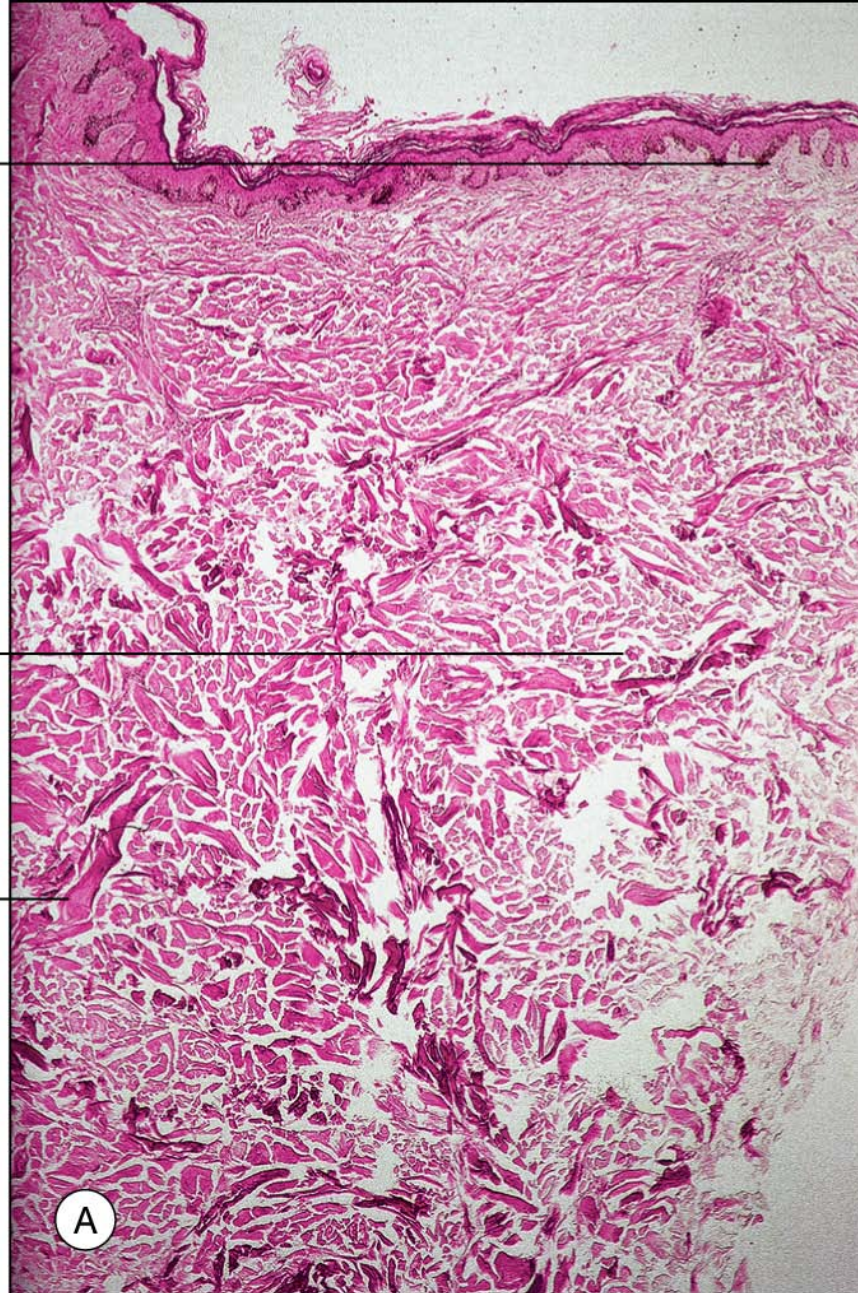
Primary Degenerative-Inflammatory Mucinoses: Scleredema – Histology

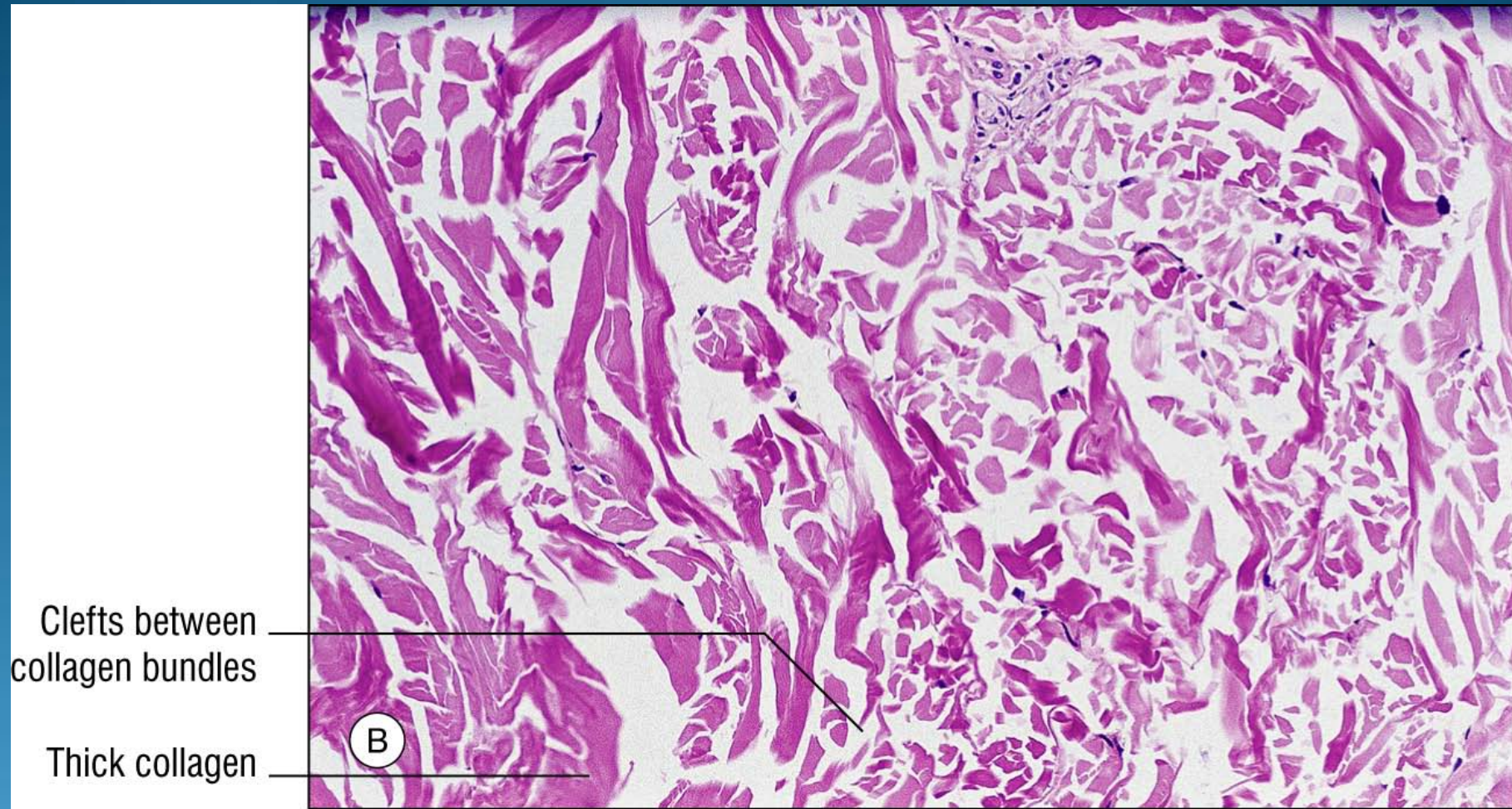
- First notice: sparse perivascular lymphocytic infiltrate
- Marked thickening of reticular dermis, extending below sweat gland coils
- Large collagen bundles separated by clear spaces (mucin) – variable, may need multiple biopsies to diagnose
- Dermis appears “fenestrated”
- No increase in fibroblast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

Pigmented epidermis

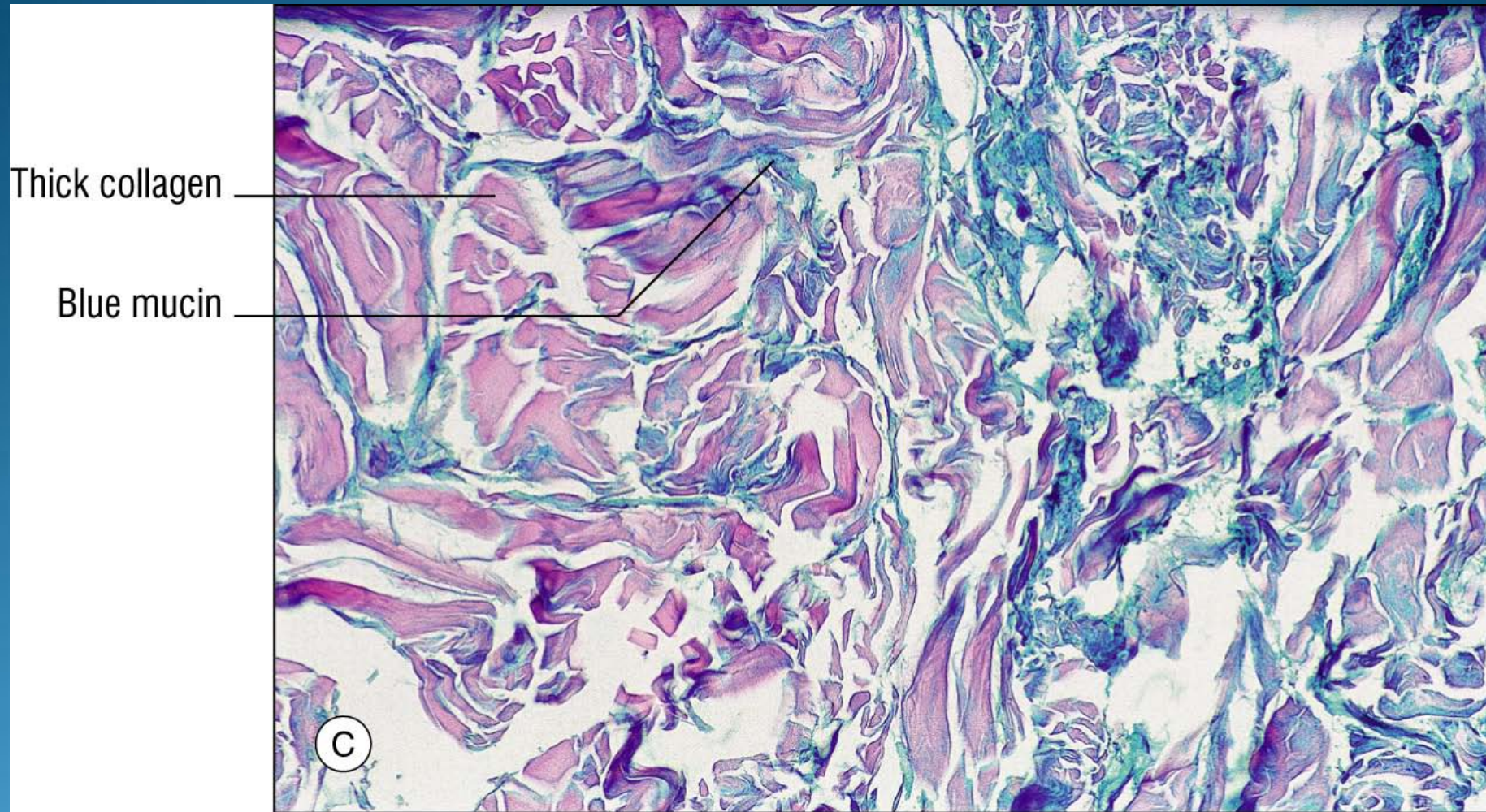
Clefts between
collagen bundle

Thick collagen





© 2005 Elsevier Inc. Rapini, Practical Dermatopathology.



© 2005 Elsevier Inc. Rapini, Practical Dermatopathology.

Primary Degenerative-Inflammatory Mucinoses: Scleredema – Differential Diagnosis

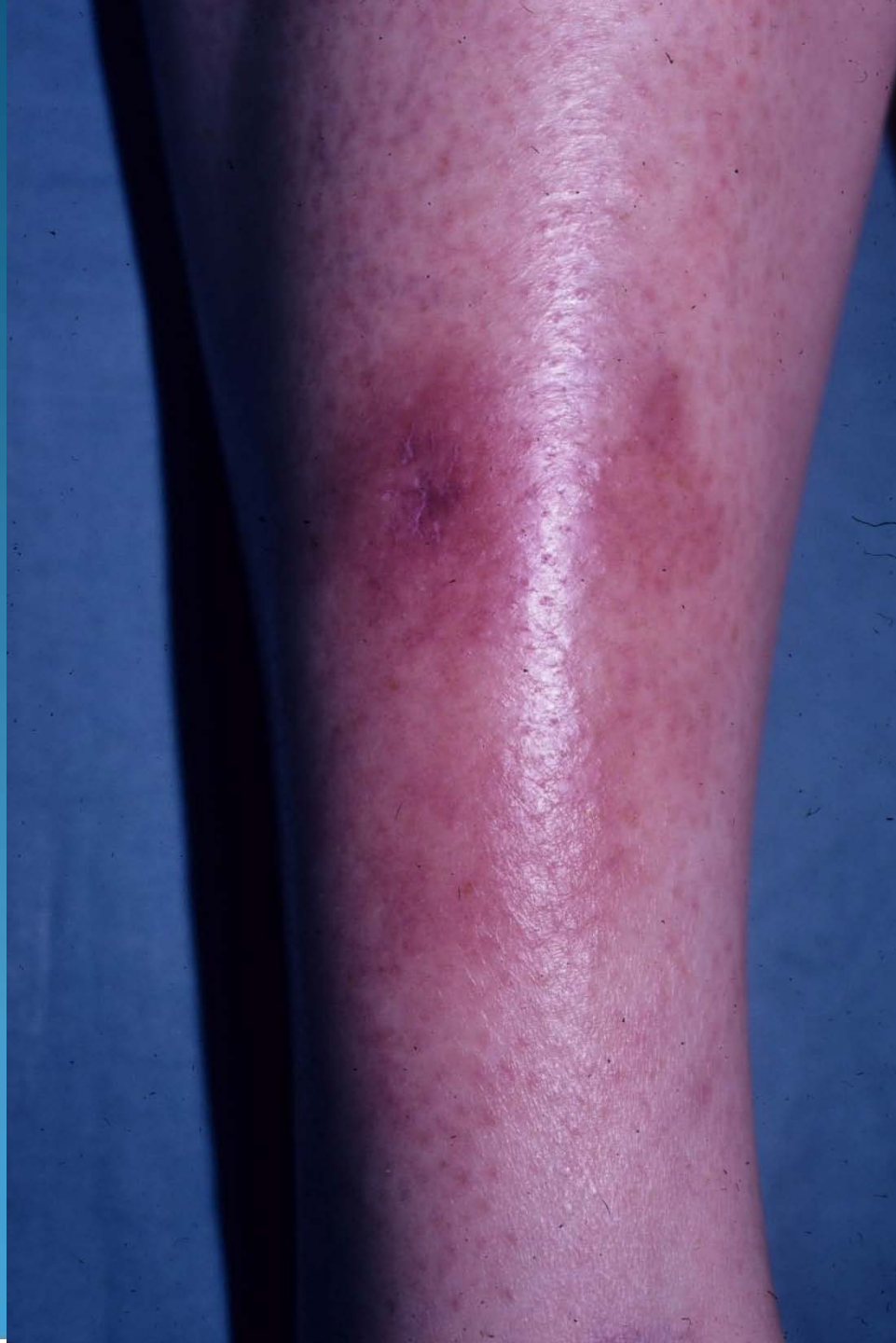
- Scleroderma- scleredema lacks acral involvement, Raynaud's and telangiectasias
- Scleromyxedema – scleredema lacks papules; histologically it lacks fibroblast hyperplasia
- Cellulitis - often misdiagnosed by non-dermatologists due to the erythema

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
 - W:M – 7:1.
 - 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:

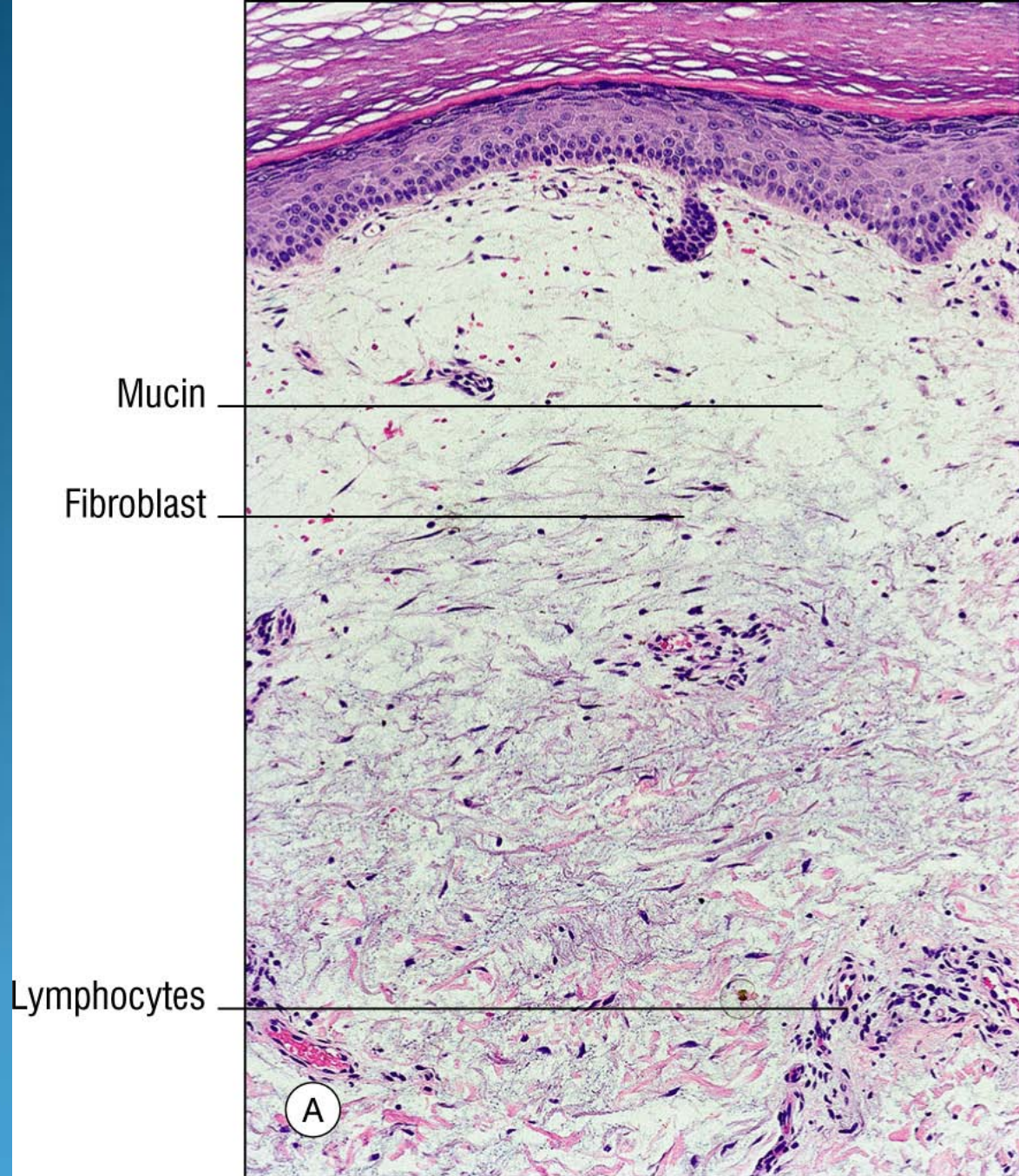
- Cutaneous induration of the shins
- Skin colored, purple-brown, or yellowish
- Waxy indurated nodules or plaques
- Often painful and pruritic
- *Peau d'orange* appearance
- Hypertrichosis and hyperhidrosis confined to pretibial shins
- Can present as a diffuse, nonpitting edema evolving into elephantiasis

- Location:

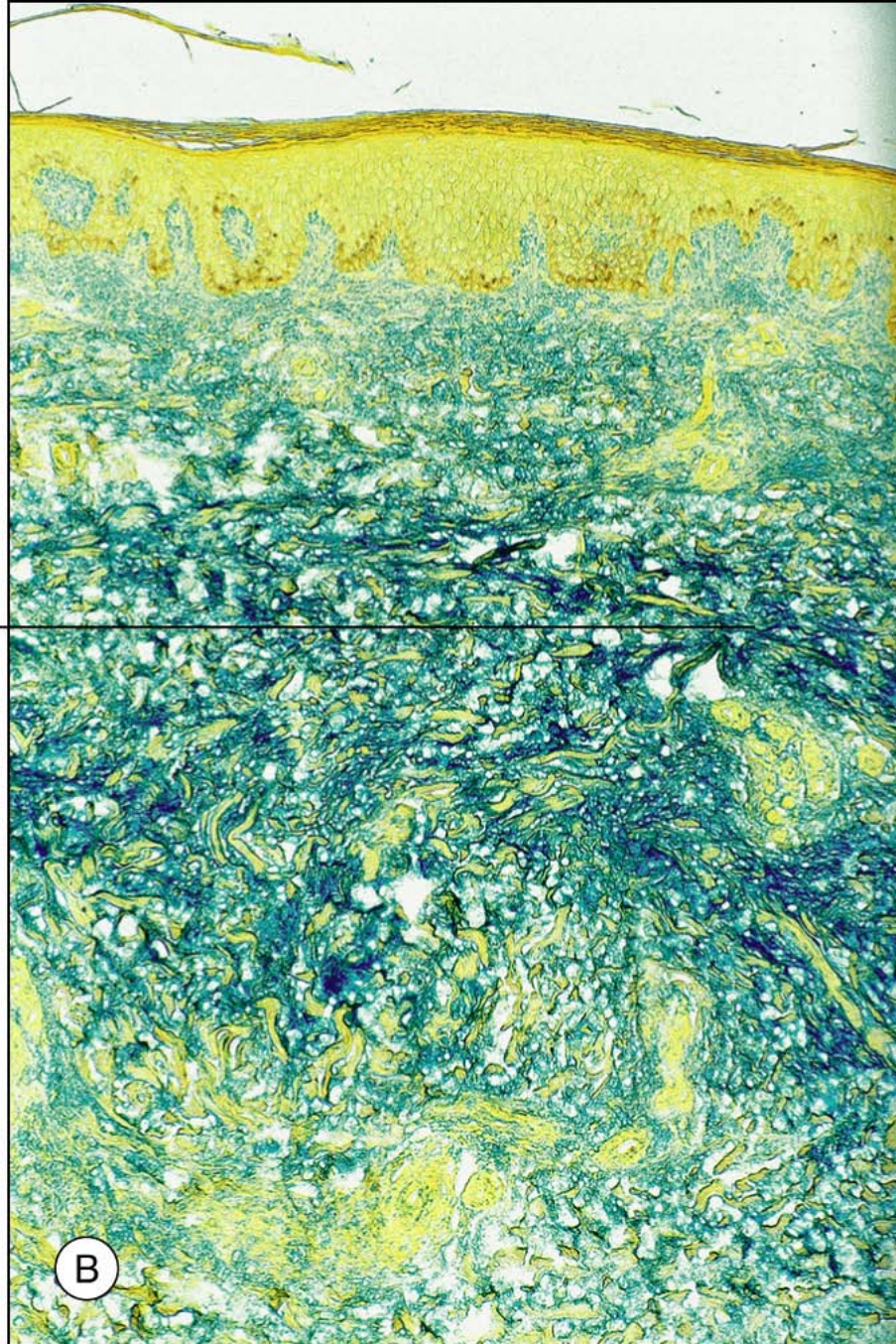
- Anteriolateral aspect of lower legs and feet
- Rarely, but may, affect the face, shoulders, upper extremities, lower abdomen, scars or donor graft sites

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



Blue mucin



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 Mucinosi

- 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 Mucinoses

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



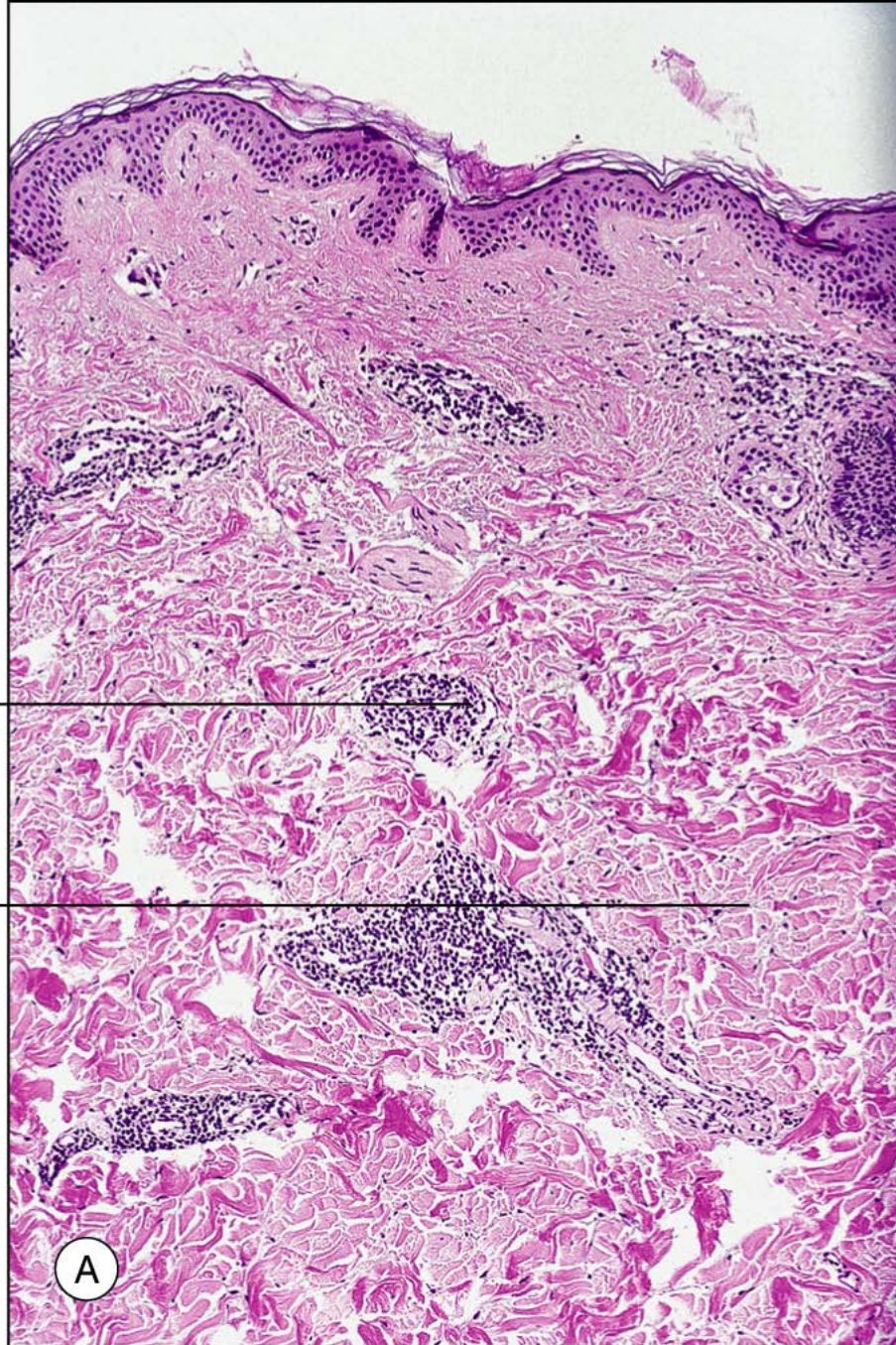


Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosi

- 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)

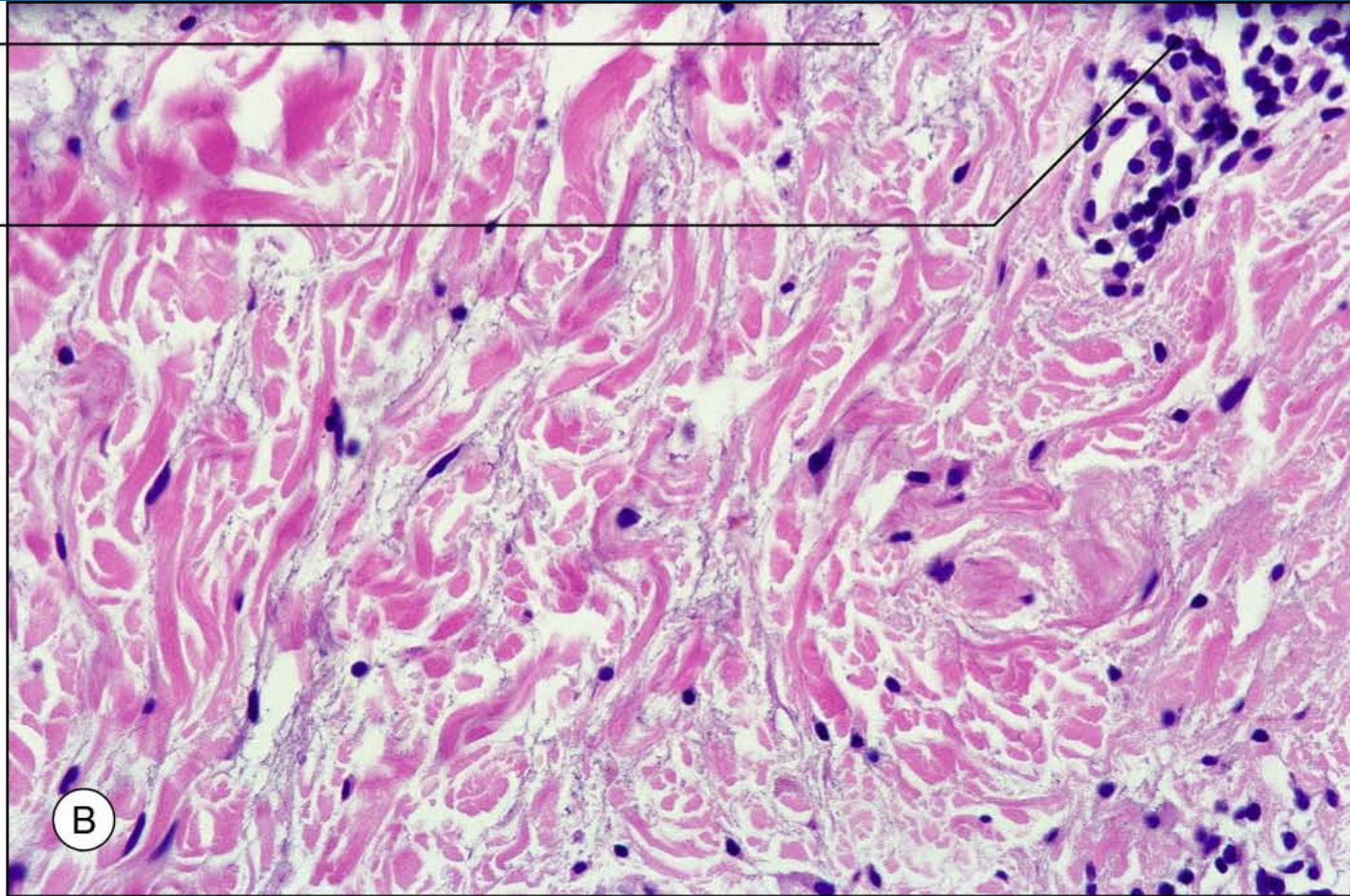
Perivascular lymphocytes

Paleness due to mucin



Wispy blue mucin

Perivascular lymphocytes



© 2005 Elsevier Inc. Rapini, Practical Dermatopathology.

Primary Degenerative-Inflammatory Mucinoses: Reticulated Erythematous Mucinosi - 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

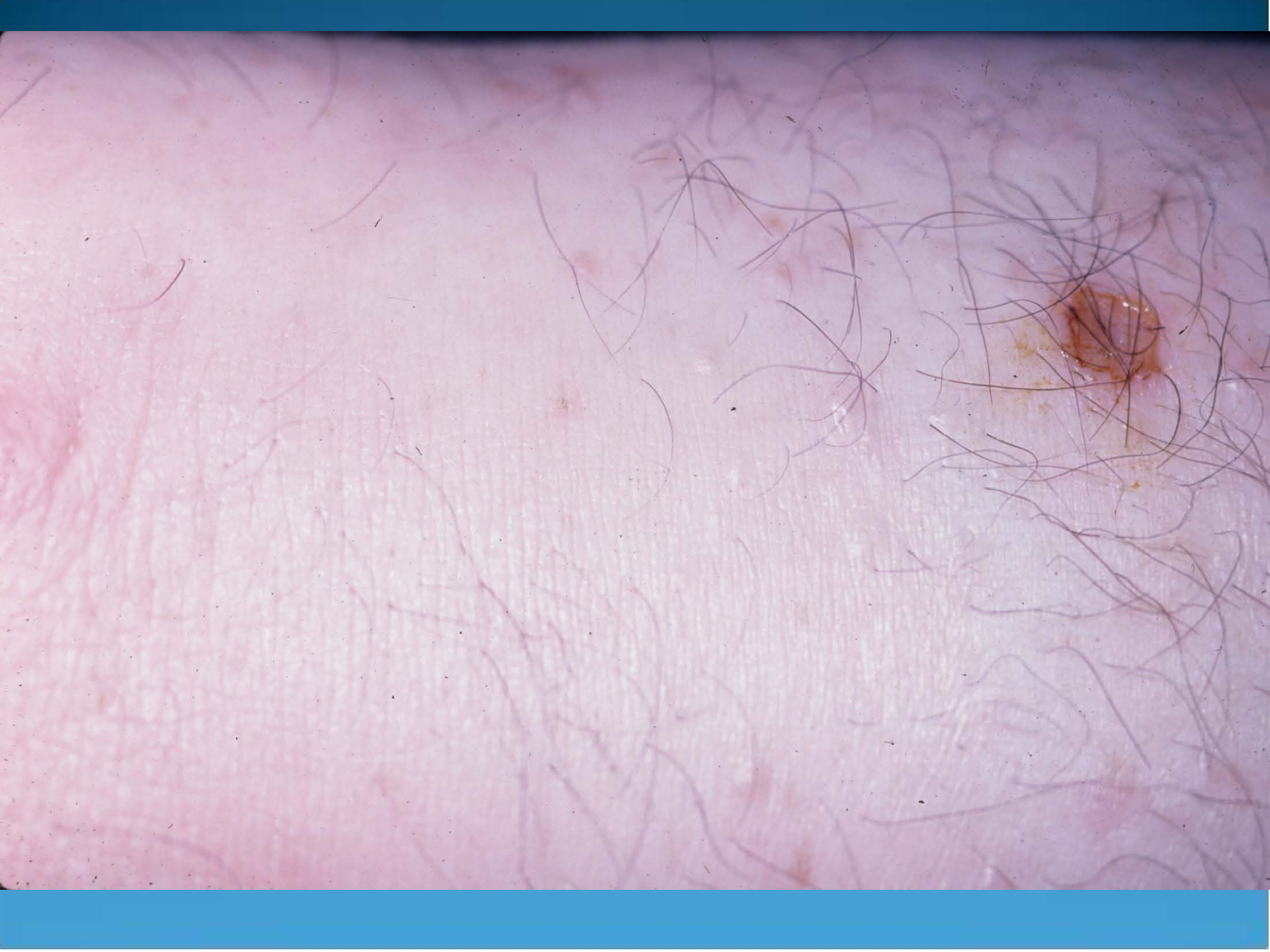
- Histology:
 - Slight to moderately dense perivascular lymphocytic infiltrate
 - Large amounts of mucin in upper and mid dermis, sometimes involving the fat
 - Epidermal changes of LE absent
- Natural History:
 - Clinical course related to underlying disease activity
 - 75% of patients with LE have 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

Follicular plug

Lymphocytes

Mucin

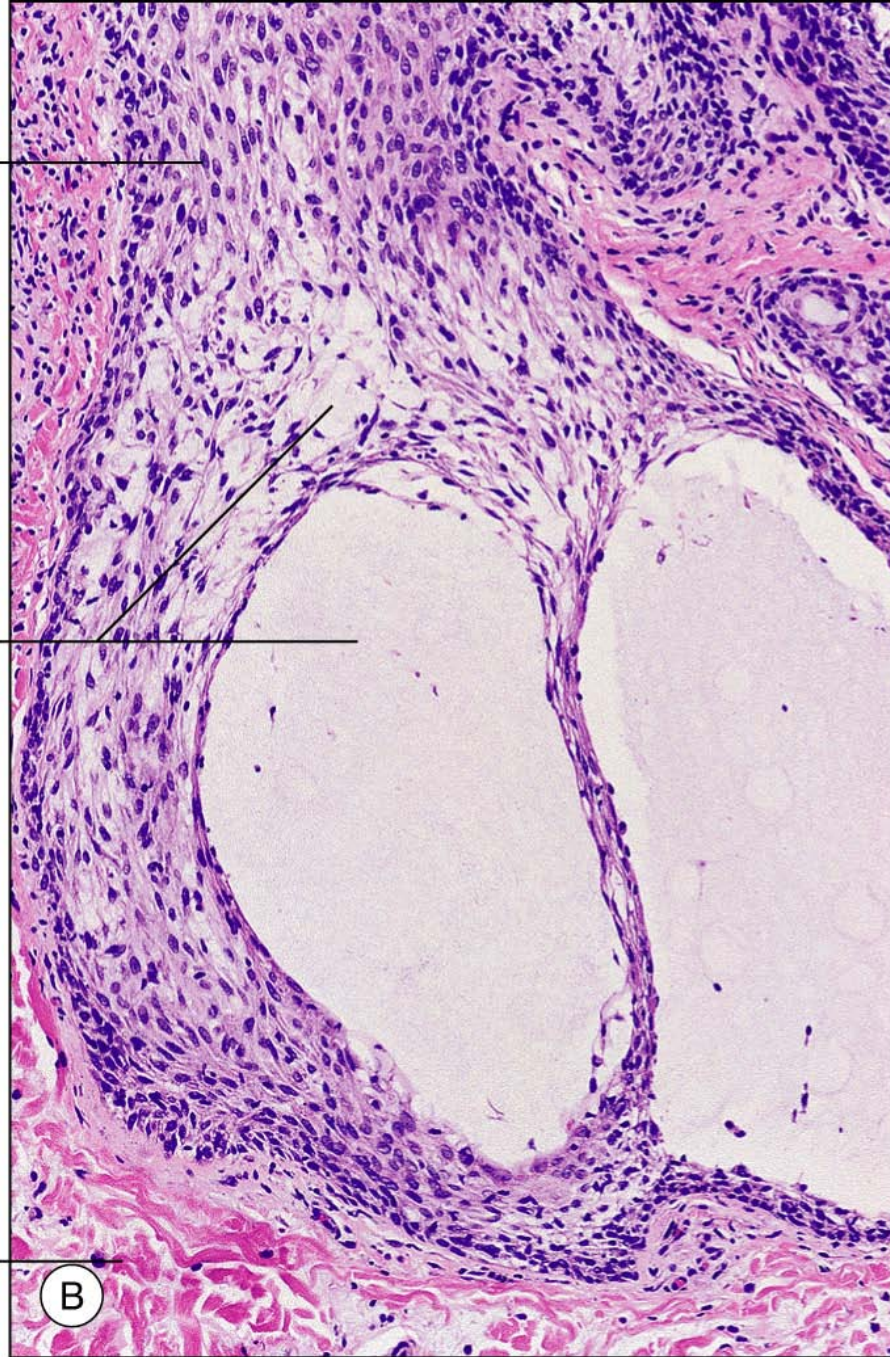
A

Follicular epithelium

Mucin

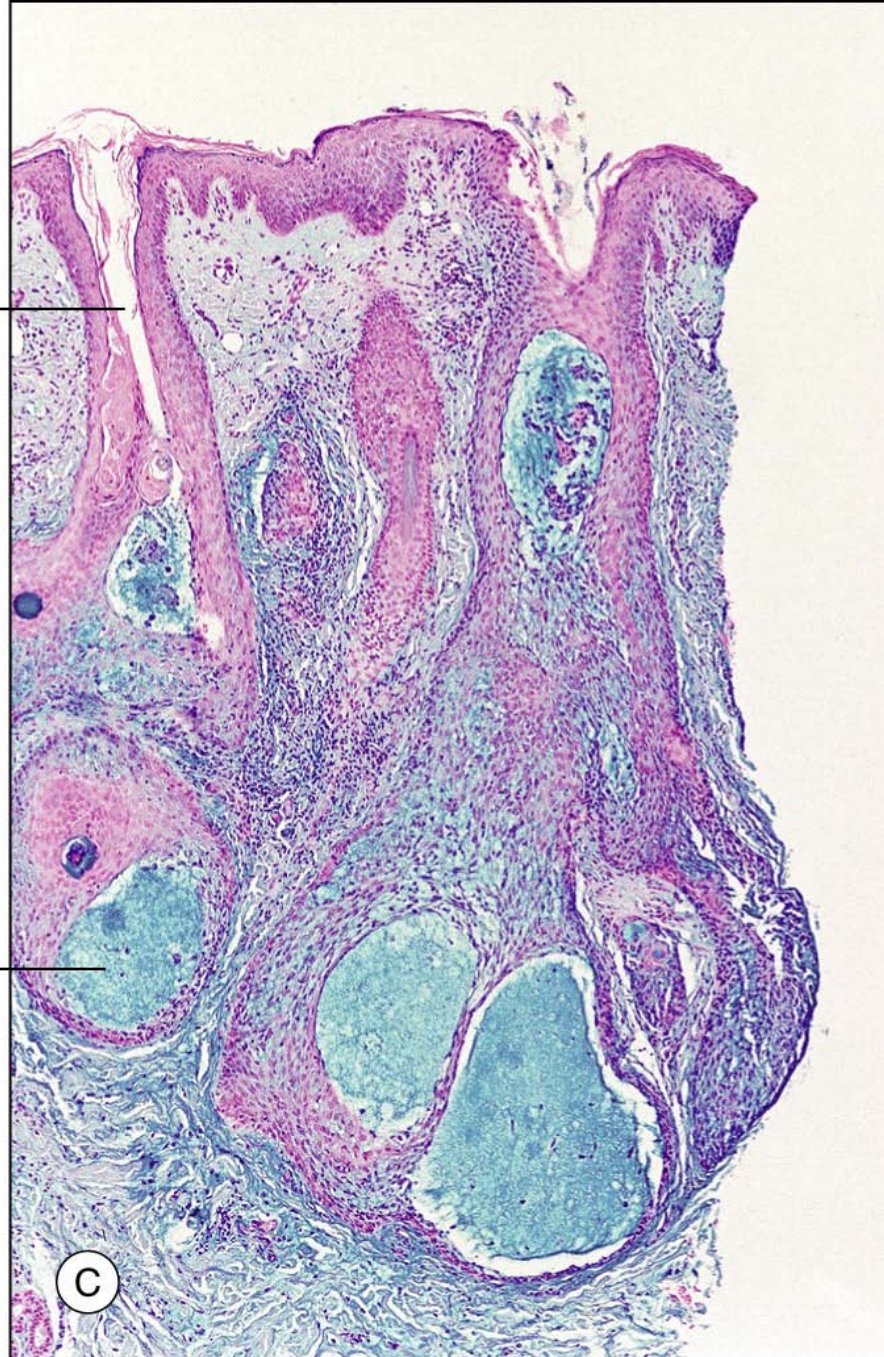
Dermis

(B)



Follicular plug

Blue mucin



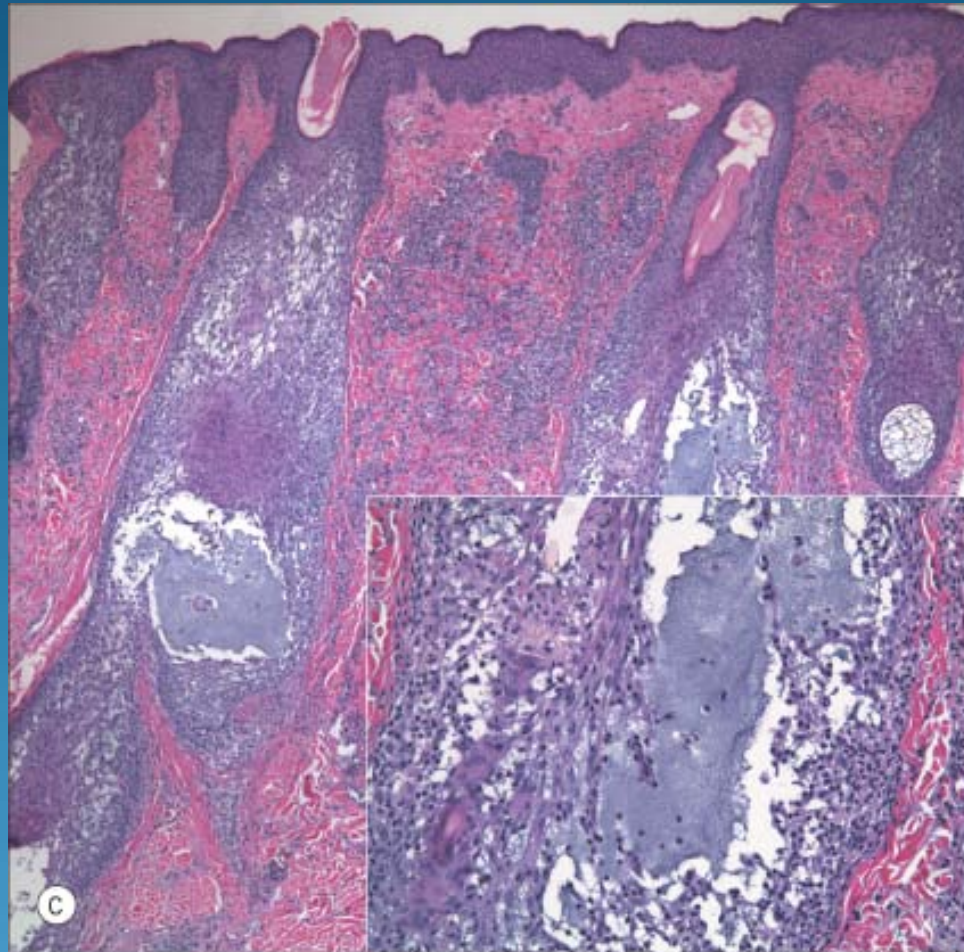


Fig. 46.13C Follicular mucinosis. **A** Several pink plaques on the face of a young girl. **B** Grouped follicular papules on the leg of an older adult in association with erythematous plaques. Note the associated alopecia. The hemorrhagic crust is the site of a previous biopsy. **C** Histology of follicular 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 dapsons reported as effective

Primary Hamartomatous-Neoplastic Mucinosi

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

Primary Hamartomatous-Neoplastic Mucinosi- 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 Mucinosi - (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 Mucinosi s - (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 mucinosi s – myxomas are true benign neoplasms and can recur after excision