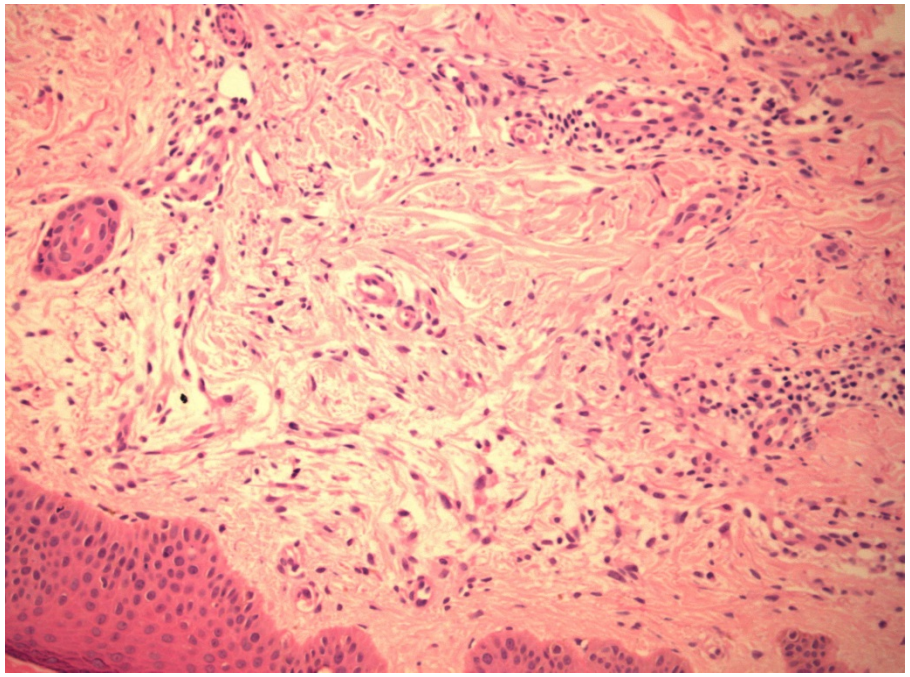
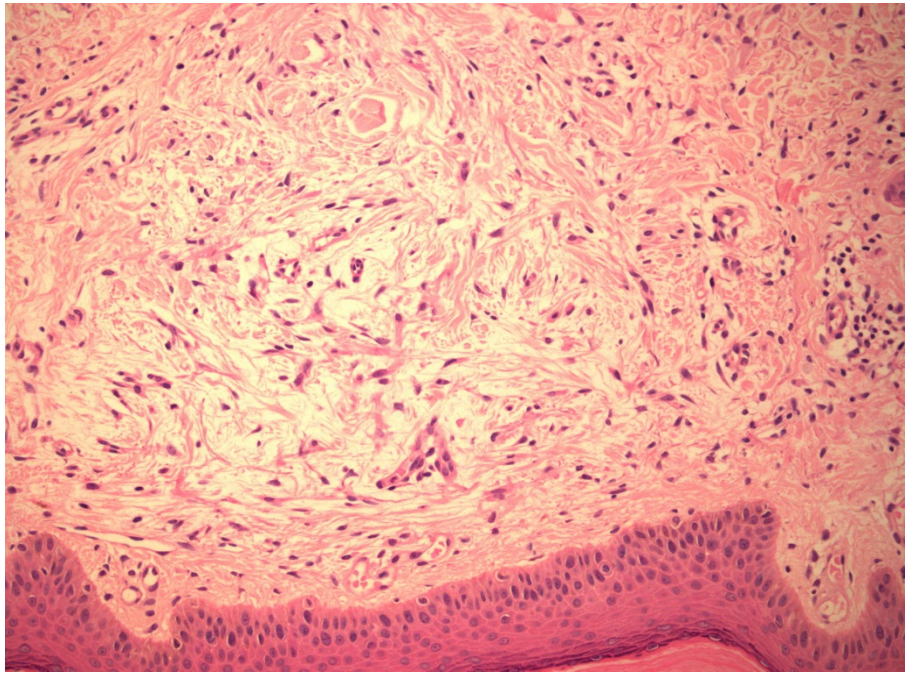
Παρουσίαση Περιστατικού

Παθολογοανατομικό Τμήμα
Χ. Βουρλάκου
Αλέξανδρος Συκαράς





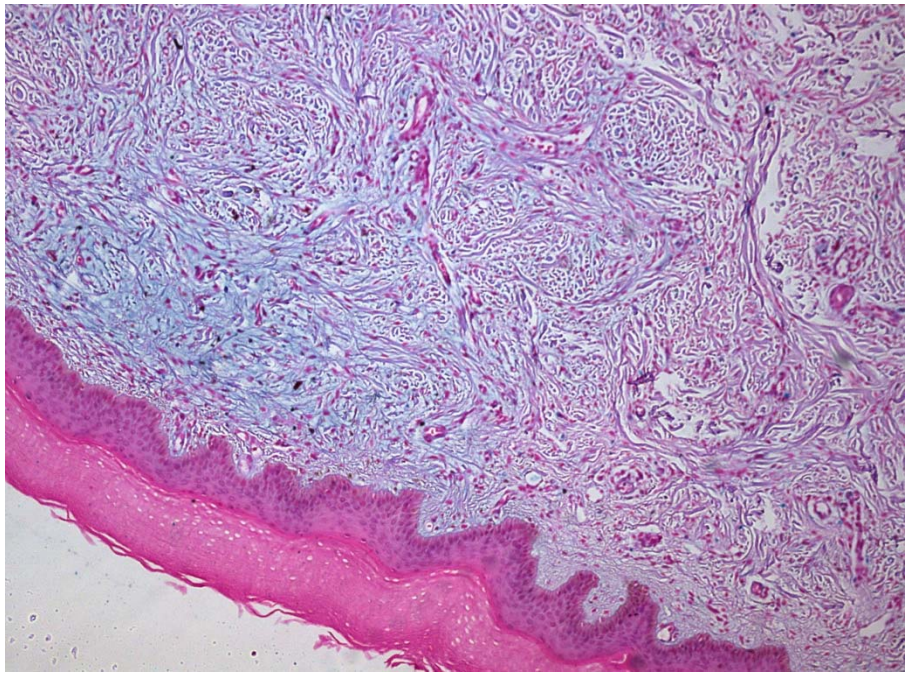
Προέχουσα υπερπλασία των ινοβλαστών του χορίου και αύξηση του κολλαγόνου ιστού (H-E x 200)

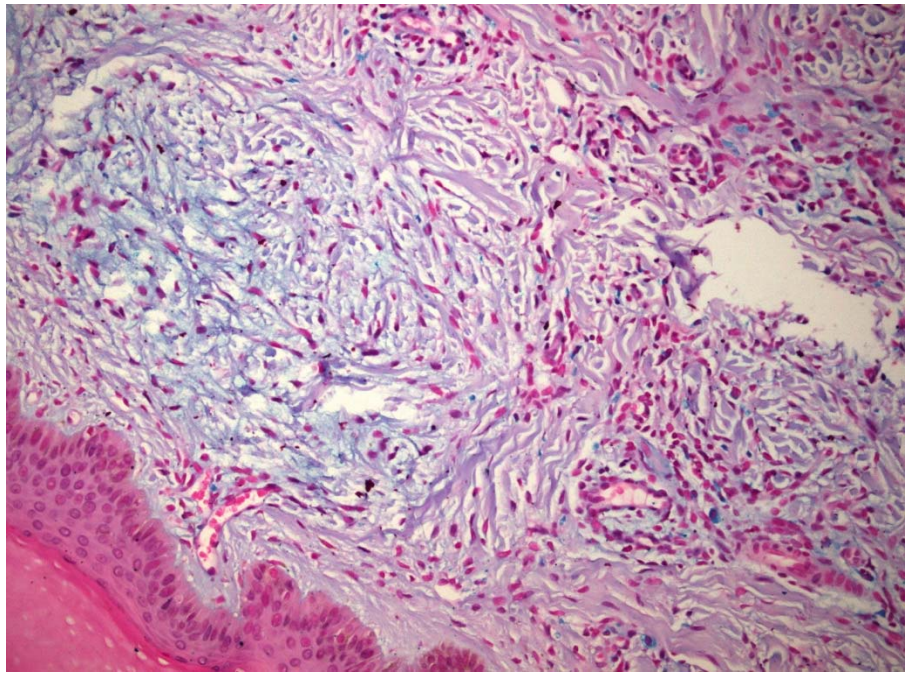
Η επιδερμίδα φαίνεται επίπεδη και τα εξαρτήματα απωθούνται.

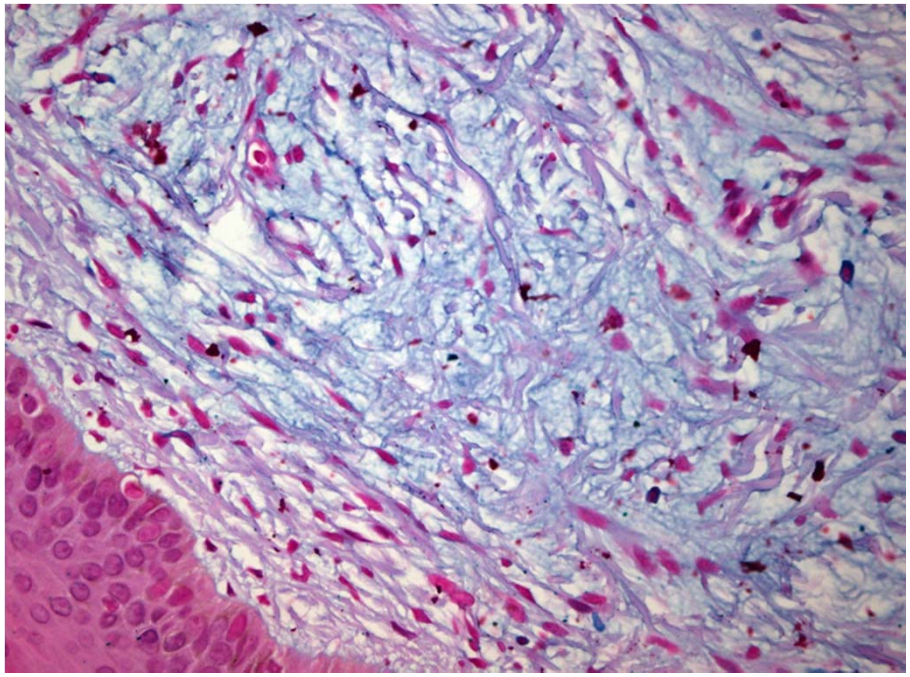
Οι ινοβλάστες διατάσσονται τυχαία ή κατά θέσεις με υποτυπώδες στροβιλοειδές πρότυπο

Εστιακή παρουσία / εναποθέσεις βλέννης

Σπάνια λεμφοκύτταρα και ιστιοκύτταρα.







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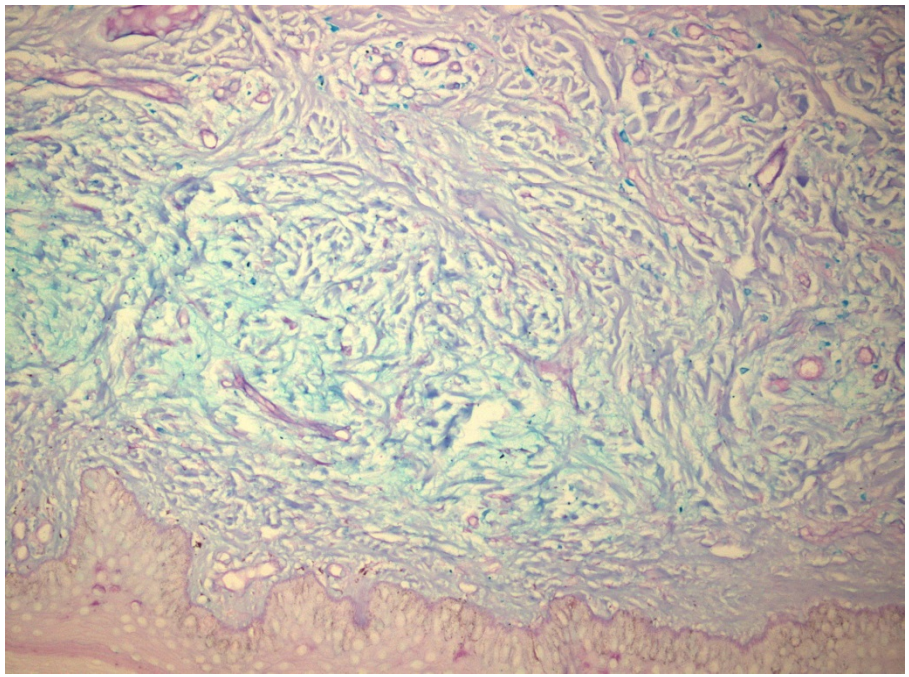
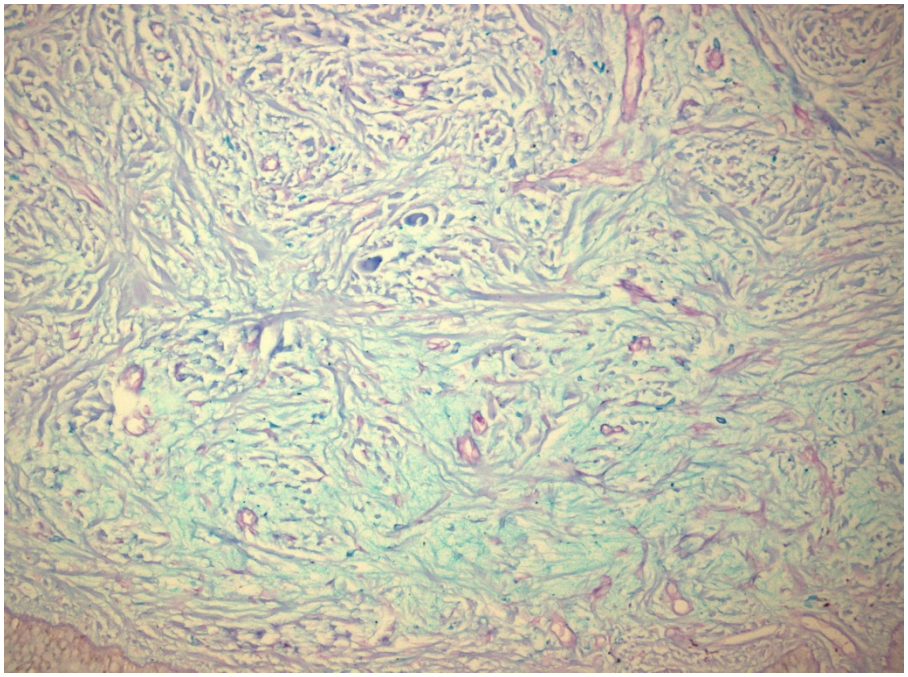
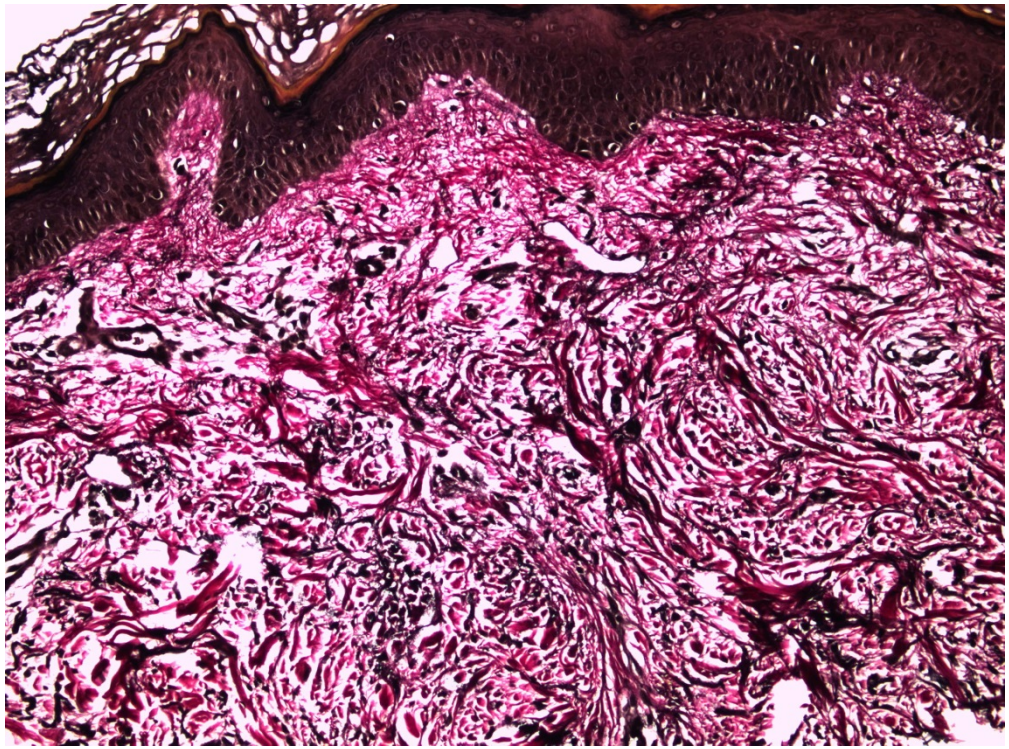




Παρουσία / εναποθέσεις βλέννης οι οποίες είναι ορατές στην ειδική εξέταση PAS/Alcian-blue (x200).



Διάσπαση των ελαστικών ινών του χορίου [χρώση Elastica x 200].

ΔΙΑΓΝΩΣΗ

Τμήμα δέρματος με ευρήματα συμβατά με τα παρατηρούμενα σε βλεννιδώσεις / βλεννινώσεις του δέρματος [cutaneous / dermal mucinoses] με συνολικά μορφολογικά χαρακτηριστικά συμβατά με τα παρατηρούμενα σε σκληρομυξοίδημα [scleromyxedema] επί συμβατής κλινικής εικόνας.

The mucinoses

The mucinoses are a group of conditions in which accumulation of **acid glycosaminoglycans (mucin)**, particularly **hyaluronic acid** and to a lesser extent **chondroitin sulfate and heparin**, occurs either diffusely or focally in the dermis. Mucinosis also may occur as a **secondary phenomenon** in dermatoses such as lupus erythematosus, scleroderma, dermatomyositis, Degos' disease, granuloma annulare, and chronic graft-versus-host disease.

The glycosaminoglycans, which are secreted by **fibroblasts**, are constituents of **normal cell membranes and connective tissue**. This substance is usually secreted in only **small amounts** by fibroblasts. It is not clear **why** mucin production is increased in pathological states. Although the cause is probably **multifactorial,** it has been suggested that **cytokines and/or immunoglobulins** and **unidentified factors** in the serum of affected patients can induce synthesis of glycosaminoglycans.

Cytokines that play an important role in this process include tumor necrosis factor, interleukin-1, and transforming growth factor beta (TGF-β). Actively secreting fibroblasts have a characteristic stellate shape and contain intracytoplasmic secretory vesicles; their presence in sections should therefore prompt a careful search for mucin deposition

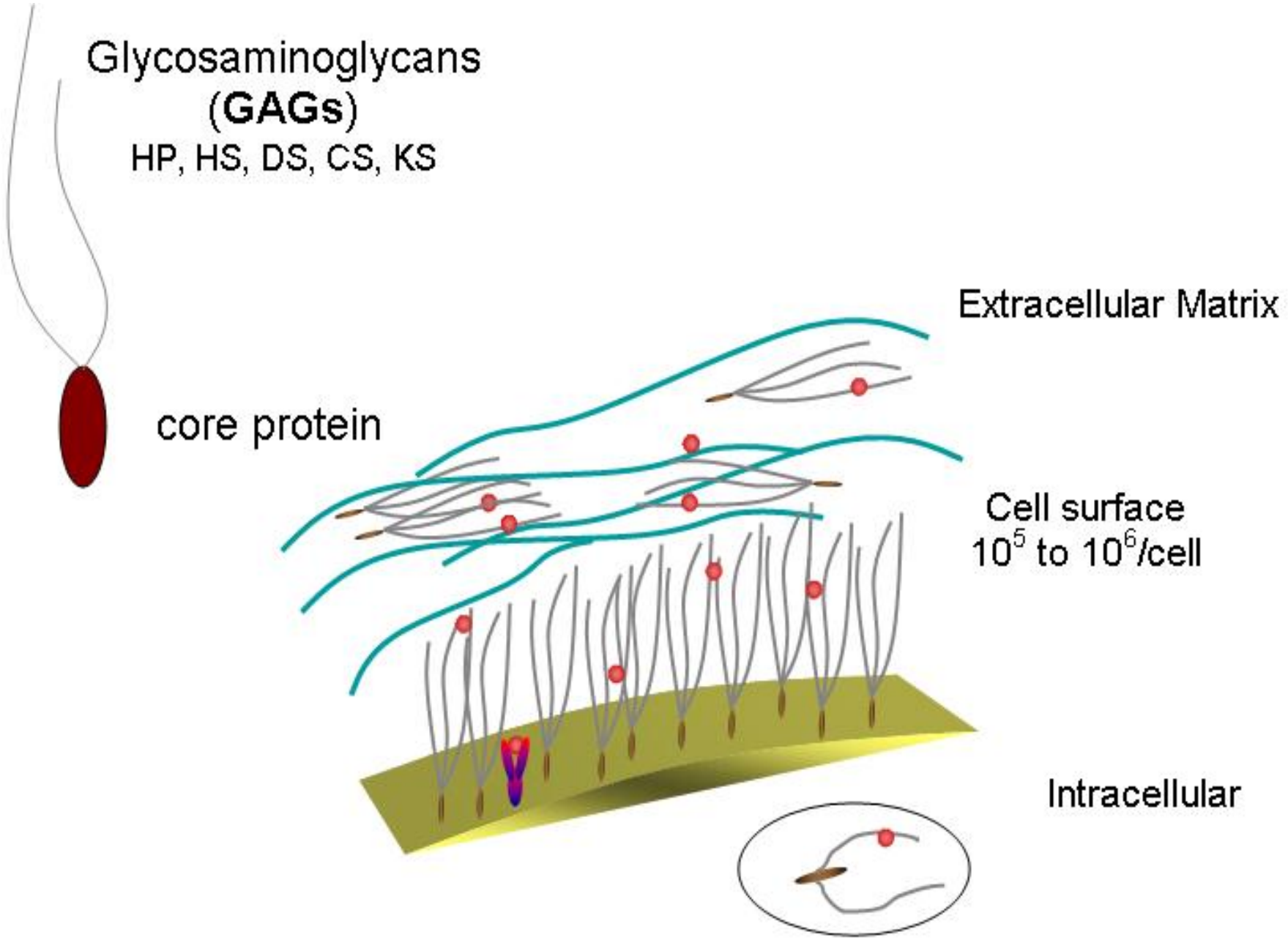
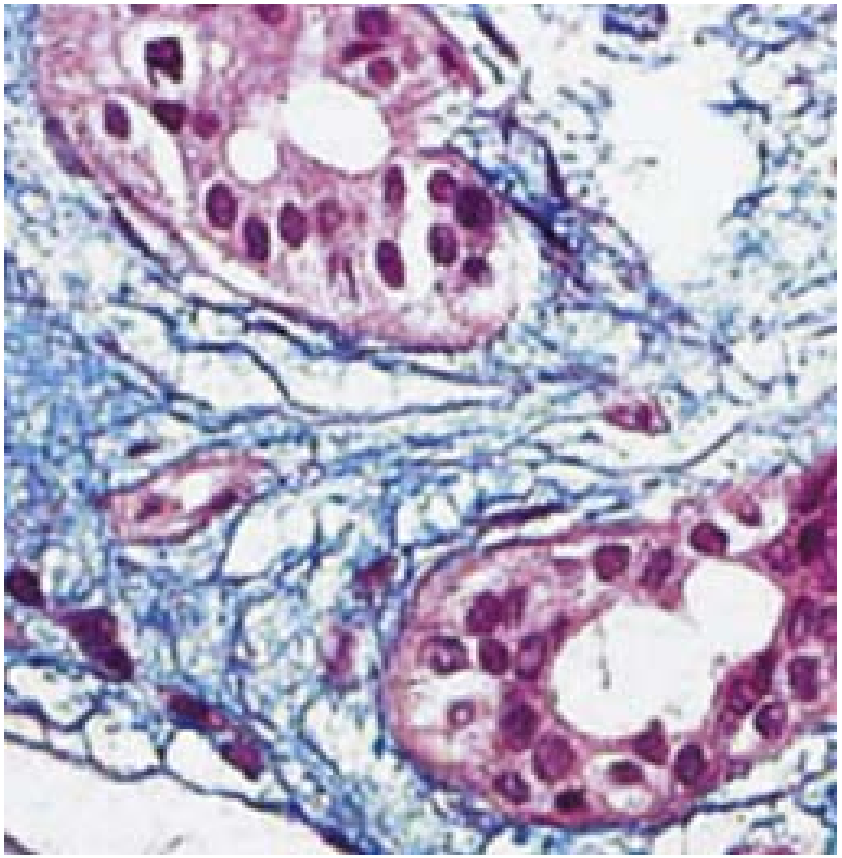

Glycosaminoglycans
(GAGs)
HP, HS, DS, CS, KS
core protein
Extracellular Matrix
Cell surface
10^5 to 10^6/cell
Intracellular

TABLE 13.6 Classification of the dermal mucinoses

Diffuse
lichen myxedematosus – generalized form (scleromyxedema) scleredema reticular erythematous mucinosis generalized myxedema pretibial myxedema
Focal
lichen myxedematosus – discrete papular form acral persistent papular mucinosis papular and nodular mucinosis associated with lupus erythematosus self-healing juvenile cutaneous mucinosis cutaneous mucinosis of infancy cutaneous focal mucinosis myxoid cyst
Follicular
follicular mucinosis

Hyaluronic acid stains with **colloidal iron** (blue–green), **Alcian blue** at pH 2.5 (blue) (but not at pH 0.4), and **mucicarmine** (red) but it is negative for PAS. It also stains metachromatically with **toluidine blue**, **methylene blue**, and **thionine**. Sulfated acid mucins stain with Alcian blue at pH 0.5 and aldehyde-fuschin. Hyaluronic acid absorbs enormous amounts of water, which accounts for the induration and thickening common to this group of conditions.

Routine fixation and processing results in an anhydrous state so that mucin presents as basophilic strands and granules in hematoxylin and eosin stained sections. In normal skin it is found particularly around appendages and the vasculature. In the cutaneous mucinoses the deposits are hyaluronidase sensitive because most of the mucin present is hyaluronic acid. The excessive mucin disrupts the collagen fibers, giving them a frayed appearance. In general, with the exception of **scleromyxedema**, there is considerable histological **overlap** within this group of conditions.
Diagnosis depends considerably upon clinical features and the results of biochemical investigations.



Eccrine sweat gland: this section of normal skin from the sole of the foot shows abundant mucin

STAINING PATTERN

HISTOLOGIC STAIN	NON SULFATED MUCIN	SULFATED MUCIN
COLLOIDAL IRON	+	+
ALCIAN BLUE		
pH 2.5	+	+
PH 0.5	_	+
TOLOUDINE BLUE		
METACHROMACIA		
pH 4	+	+
pH <2	_	+
PERIODIC ACID SCHIFF	_	_
HYALURONIDASE		
SENSITIVITY	+	_

There are five major mucinoses:

generalized myxedema,

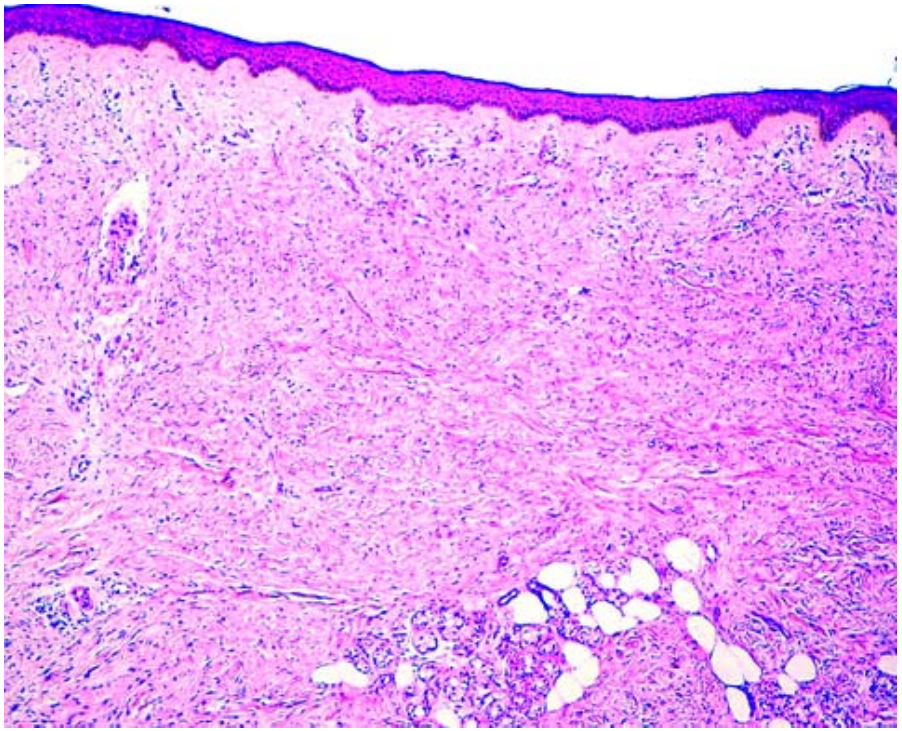
pretibial myxedema,

lichen myxedematosus,

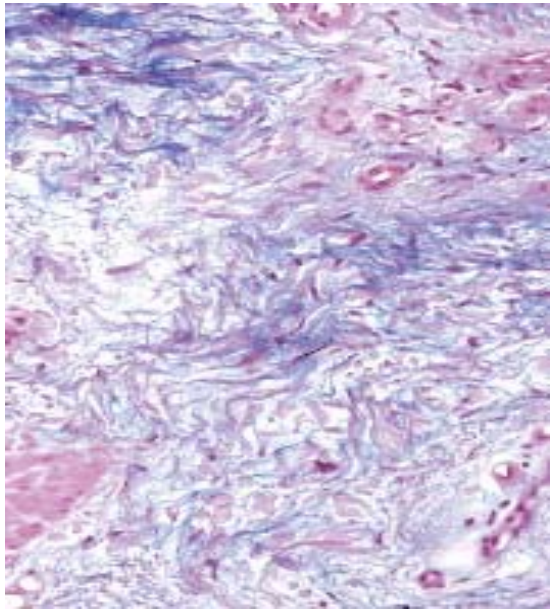
reticular erythematous mucinosis,

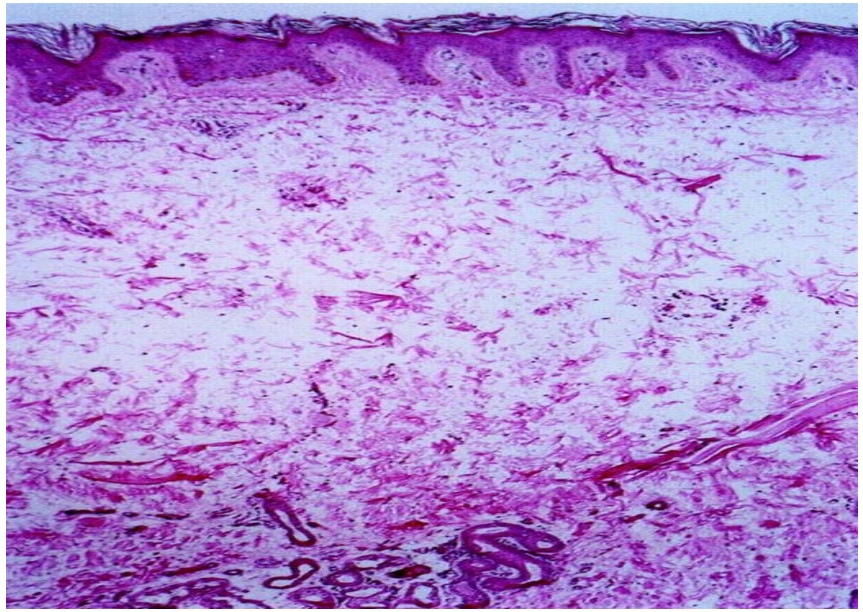
scleredema.

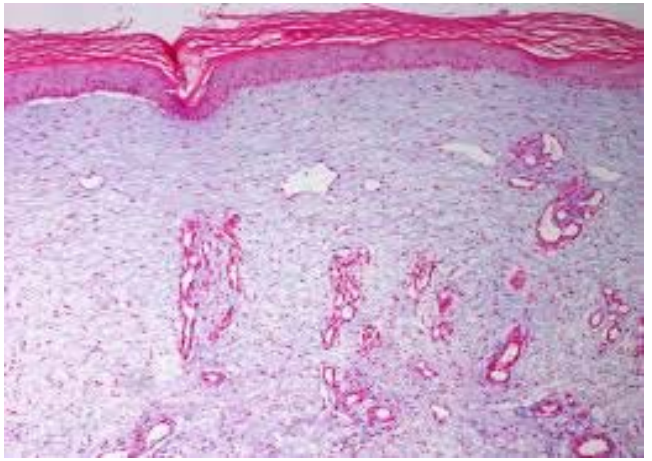
&
Follicular mucinosis



Photomicrograph of skin biopsy specimen from patient with **localized myxedema** showing separation and fraying of connective tissue fibers and edema. The epidermis (at top) is normal.

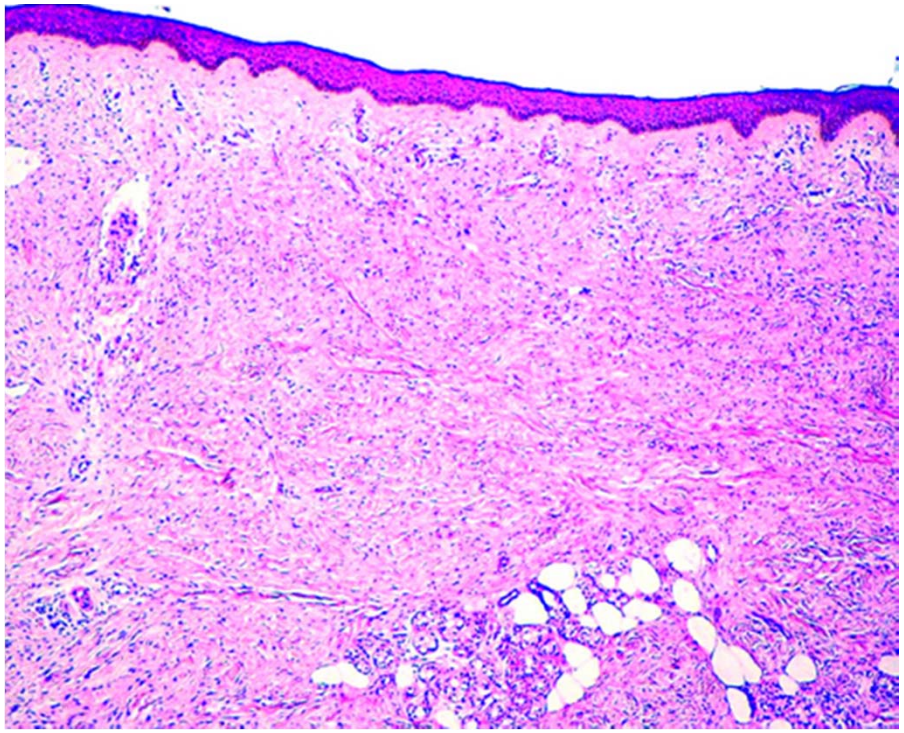






Myxedema

The epidermis may show mild hyperkeratosis with occasional follicular plugging. Most frequently, the dermal changes are subtle and non diagnostic. However, in cases of greater severity, there is slight **swelling** and **separation** of the **collagen bundles** with edema, and special stains show that small quantities of mucin are present within the dermis and occasionally in the subcutaneous fat. **Fibroblastic proliferation is not a feature of generalized myxedema.**



It has been proposed that **autoantibodies** against thyroid-stimulating hormone receptor react with fibroblasts containing these sequences, resulting in production of cytokines and induction of increased glycosaminoglycan secretion.

Lichen myxedematosus/scleromyxedema

Lichen myxedematosus is now divided into **three forms**:

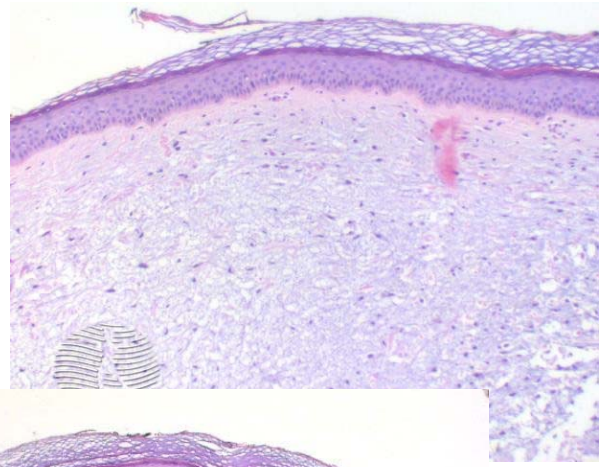
• a **localized** form, which includes several variants: discrete papular lesions occurring at any site, acral persistent papular mucinosis (see below), self-healing papular mucinosis (see below), papular mucinosis of infancy (see below) and nodular mucinosis,

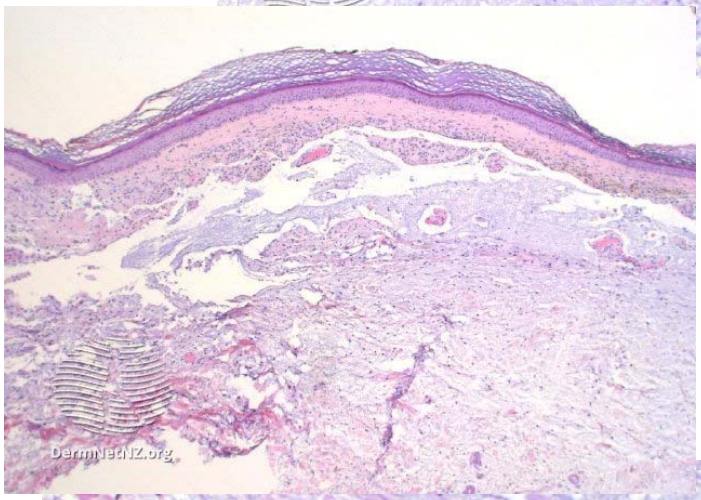
• **a generalized** form (scleromyxedema) characterized by lichenoid papules, indurated and thickened skin and a monoclonal gammopathy; by definition, thyroid function is invariably normal.

• an **atypical or intermediate** form where patients may have generalized lesions without systemic symptoms/gammopathy, localized lesions with systemic symptoms/gammopathy or other manifestations that do not strictly fulfill criteria for either the localized or generalized variants

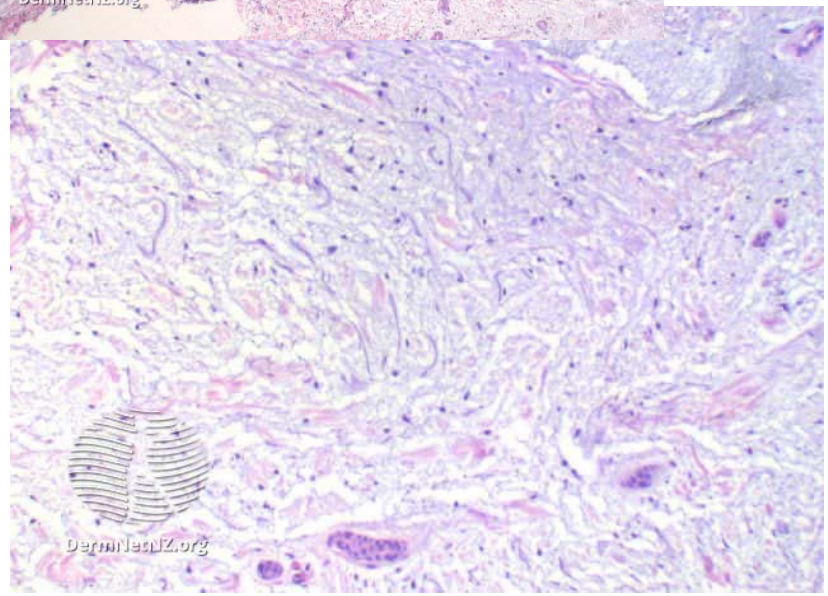
Scleromyxedema is usually (but not invariably) associated with a paraproteinemia; most often this is IgG with lambda light chains. Occasionally it has been of the IgM or IgA class. An occasional association with multiple myeloma has also been noted but occurs in less than 10% of patients.

The epidermis may be normal, acanthotic or atrophic, and sometimes hyperkeratosis with parakeratosis is evident. In early lesions **stellate fibroblasts** are seen between disorganized collagen fibers in the reticular dermis. The papillary dermis is not affected. Increased numbers of mast cells are sometimes present. Focal deposits of mucin are readily identifiable. A slight perivascular chronic inflammatory cell infiltrate is often seen in the superficial dermis.





In the more severe scleromyxedema variant, **fibroblasts are numerous** and there is consequent **fibrosis** and thickening of the dermis. Mucin deposits may be less evident or even absent. **Decreased elastic fibers** have occasionally been reported. A chronic inflammatory cell infiltrate is frequently present surrounding the superficial vasculature.



DIAGNOSTIC CRITERIA OF SCLEROMYXEDEMA VERSUS LOCALIZED VARIANTS OF LICHEN MYXEDEMATOSUS

Scleromyxedema	Localized variants of lichen myxedematosus
Generalized papular eruption and sclerodermoid features	Papular eruption (or nodules and/or plaques due to confluence of papules)
Microscopic triad (mucin deposition, fibroblast proliferation, fibrosis)	Mucin deposition with variable fibroblast proliferation
Monoclonal gammopathy	Absence of monoclonal gammopathy
Absence of thyroid disorder	Absence of thyroid disorder

Ευχαριστώ!

Mucinoses

Definition, Pathogenesis

Mucinosis is a general term for diseases in which acid mucopolysaccharide (mucin) deposits in the skin.
The mucin, produced by fibroblasts, consists of complex of mucopolysaccharides (glycosaminoglycans) and proteins.
The main types of glycosaminoglycan are hyaluronic acid (hyaluronan), dermatan sulfate, chondroitin sulfate and keratan sulfate.
The mucin stains positive with Alcian blue and colloidal iron, and metachromatic with toluidine blue.
Abnormal deposition of mucin among collagen fibers results in swelling and separation of those fibers and the edematous skin.
Mucin deposition is often induced by collagen disease, thyroid dysfunction or tumor; however, the precise mechanism is unknown.
Mucinosis is classified by the location of deposition and clinical features

Classification of major cutaneous mucinoses

Generalized mucinoses

- Scleredema
- Diffuse myxedema
- Pretibial myxedema
- Lichen myxedematosus
- Reticular erythematous mucinoses

Localized mucinoses

- Follicular mucinosis
- Cutaneous focal mucinosis

PRIMARY (DISTINCTIVE) CUTANEOUS MUCINOSES

Degenerative–inflammatory mucinoses

Dermal

Lichen myxedematosus (papular mucinosis)

- Generalized and sclerodermoid (scleromyxedema)
- Localized: discrete type, acral persistent papular mucinosis, self-healing cutaneous mucinosis, cutaneous mucinosis of infancy, nodular type
- Atypical forms

Reticular erythematous mucinosis

Scleredema

Dysthyroidotic mucinoses

- Localized (pretibial) myxedema
- Generalized myxedema

Cutaneous lupus mucinosis

Cutaneous focal mucinosis

Digital mucous cyst

Miscellaneous mucinoses

Follicular

Pinkus' follicular mucinosis

Urticaria-like follicular mucinosis

Hamartomatous–neoplastic mucinoses

Mucinous nevus

(Angio)myxoma

MUCIN

- ACID AMINOGLYCANS SECRETED BY DERMAL FIBROBLASTS
- 2 TYPES → SULFATED

  HEPARANSULFATE,CHONDROITIN SULFATE

  INCREASED IN MPS

  NON-SULFATED (HYALURONIC ACID)

  INCREASED IN MUCINOSES

Classification

- PRIMARY MUCINOSES

DIFFUSE	Generalised myxoedema
	Pretibial myxoedema
	lichen myxoedematoses
	Her.progr. mucinous histiocytosis.
	Reticular erythematous mucinosis
	sclerodema
FOLLICULAR	Follicular mucinoses(alopecia mu.)
	Urticaria like follicular mucinosis

FOCAL NEOPLASTIC HAMARTOMATOUS MUCINOSES

Cutaneous focal mucinosis,Mucinous cyst, Mucinous naevus

SECONDARY

PAPULAR MUCINOSES ASS.WITH LE

COLLAGEN VASCULAR D/S (DM, LE)

M/G ATROPHIC PUSTULOSIS

PAPULAR MUCINOSES ASS. WITH EOSINOPHILIA

- MYALGIA SYNDROME

ASS.WITH MESENCHYMAL & NEURAL TUMOURS

ASS.DISEASES:

Paraprotinemia (scleromyxoedema& scleroedema)

DM (Scleroedema)

Thyroid diseases (pretibial myxoedema,myxoedema)

Connective tissue disorders (LE,Dermatomyositis)

Pretibial myxoedema

Localized edematous thickened Pretibial plaque formation

- ETIOLOGY: unknown
- Increased LATS in patients with Graves ,exophthalmos & Pretibial myxoedema
- Increased production by fibroblasts in the pretibial region.
- HPE similar to Lichen myxoedematosus.

Clinical features

- 3 types
- Sharply circumscribed nodules/ tuberous lesions on the shin &toes
- Diffuse non pitting edematous varient
- Elephenteasic –With both of the above features
- DIFFERENTIAL DIAGNOSIS: Pretibial mucinosis associated with venous stasis.
- TREATMENT :
- Topical glucocorticoids with or with out occlusion
- Intralesional glucocorticoids

GENERALISED MYXEDEMA

- A manifestation of severe hypothyroidism with mucin deposition in the dermis leading to waxy skin.
- PATHOGENESIS : impaired degradation
- It can be associated with : Cretinism , hypothyroidism (Juvenile, adult)
- Pale ,waxy,cool ,skin
- Absence of sweating – acquired ichthyoses /eczema craquelae
- Carotinemia Britle hair &nails
- Diffuse nonscarring alopecia Lateral madarosis
- Purpura over the extrimities Telengiectasia of finger tips
- Delayed wuond healing Xanthomas

- HPE : Mucin deposits –mainly perivascular perifollicular with splaying of collagen bundles
- TREATMENT
- Thyroxine supplementation

Lichen myxoedematosus -Types

Generalised papular &sclerodermoid form(scleromyxoedema

Localised Descrete papular form (any site)

Acral persitent form

Papular mucinosis of infancy

Self healing papular mucinosis juvenile

adult

nodular form

ass.with HIV infection

ass.with HCV infection

ass.with toxic oil syndrome

Atypical (intermediate)

Scleromyxoedema

- Confluent sclerotic papular lesions
- Diffuse thickening of skin underneath the papules (movable over the subcutis)
- Head &neck region,upper trunk,thighs,upper limbs.
- Multiple periorbital myxomas are also seen
- Pseudosclerodactyly
- Dough nut sign
- ALMOST ALWAYS ASS. WITH PARAPROTEINEMIA
- Assosiated with: peripheral neuropathy, arhtropathy, carpel tunnel syndrome
- poor prognosis : Often due to Bronchopneumonia
  Coronary occlusion
  Hematologic abnormalities

Histopathology

- Characterized by triad of :
- Diffuse deposit of mucin in the upper &mid reticular dermis
- Increased deposition of collagen
- A marked proliferation of irregularly arranged fibroblasts
- TREATMENT :
- Melphelan (for ass.paraprotienemia)
- Cyclophosphamide ,methotrexate-of limited value
- Plasmapheresis , extrcorporial photopheresis
- I/V Immunoglobulin
- PUVA /UVA1
- All of limited value.

OTHER LICHEN MYXOEDEMATOSUS

Localised

DESCRETE PAPULAR FORM :2-5 mm papules on symmetric distributionover trunk & limbs. Face spared. System not involved.

ACRAL PERSISTENT :Ivory white nodules on dorsa of hands & forearms .Females are more affected.

PAPULAR MUCINOSIS OF INFANCY: Opalscent papules on upperarm&trunk.Cong.linear varient also there.Neither system involvement nor spontaneous resolution noticed.

Contd……

- SELF HEALING PAPULAR MUCINOSIS :
- Juvenile & Adult types with :
- A/c erruption of multiple papules
- Mucinous subcutaneous nodules in periarticular region
- NODULAR FORM- on limbs &trunk.
- Asssociated with HCV &HIV infection : nosystemic manifesstations recorded.

Histopathology

- Mucinous deposit in the mid &upper layers of dermis
- Dispersed collagen
- Large elongated fibroblasts
- Mucin deposition spares papillary dermis &blood vessels
- TREATMENT :
- " masterly inactivity with watchful expectancy "
- ? topical steroids

Intermediate variant

- Scleromyxoedema with out monoclonal gammopathy
- Localized variety associated with monoclonal gammopathy.
- Mixed form with F/O both scleromyxoedema &localised lichen myxoedematosus
- Poorly specified

COMPARISION BETWEEN SCLEROMYXEDEMA & LOCALISED LICHEN MYXEDEMATOSUS

SCLEROMYXOEDEMA	LOCALISED VARIANTS
• GENERALISED PAPULAR ERRUPTION	• PAPULAR/NODULAR /PLAQUES
• SCLERODERMOID FEATURE	• LOCALISED
• TRIAD OF MUCIN DEPOSITION,FIBROBLEST PROLIFERATION,FIBROSIS	• FIBROBLAST PROLIFERATION-VARIABLE
• MONOCLONAL GAMMOPATHY	• FIBROSIS-ABSENT • NO ASSOCIATION WITH MONOCLONAL GAMMOPATHY
• ABSENCE OF THYROID DISORDER	• ABSENCE OF THYROID DISORDER

SCLEREDEMA ADULTORUM OF BUSHCKE

- SCLEREDEMA DIABETICORUM
- Symmetrical diffuse induration of upper part of body caused by a thickened dermis &deposition of mucin.
- Females are more affected.
- PATHOLOGY :
- Irreversible glycosylation of collagen
- Insulin resistance –excess insulin secretion → mucin
- Microvascular damage –hypoxia
- Streptococcal hypersensitivity
- Injury to lymphatics

CLINICAL FEATURES

- TYPE 1: Affects primarily middle aged women Abrupt onset
- Preceded by constitutional symptoms
- Cervicofacial skin is affected expressionless face
- Different in mouth opening, swallowing ,& protruding tongue
- Resolves in time
- TYPE 2 : Subtle onset similar to type 1.
- persist for years
- Frequently associated with monoclonal gammopathy.

- TYPE3 : IDDM associated
- Subtle onset
- Similar to type 1
- Erythema & induration may also be associated with
- Peau d' orange appearance
- Posterior neck &back are more affected.
- System involvement – serositis, dysarthria ,dysphagia , myalgia may be associated.
- Diseases associated : Hyperparathyroidism, sjogren's syndrome , rheumatoid arthritis ,malignant insulinoma, multiple myeloma , ca gall bladder,HIV infection

- PATHOLOGY : Thickening of reticular dermis with large collagen bundles seperated by mucin
- No increase in collagen bundles
- DIFFERENTIAL DIAGNOSIS :Scleroderma
- TREATMENT :
- Controll of glycemic status –no effect on skin
- PUVA ,DCP,CYCLOSPRINE XIII infusion & electron beam

RETICULAR ERYTHEMATOUS MUCINOSIS

- PLAQUE LIKE ERYTHEMATOUS MUCINOSIS- unknown
- Sun light –Proposed etiology.
- Reticular erythema with a mucinous round cell infiltrate in the dermis
- Trunk is mostly affected site
- HISTOPATHOLOGY :
- 1). Small amount of mucin in the dermis
- 2). Mild –moderate mononuclear infiltrate in the perivascular & periappandageal region.
- Fragmented elastic fibers are also seen.
- Association- hypothyroidism, hyperthyroidism, DLE,TTP,M/G
- Antimalarials – Controll erruption

HEREDITARY PROGRESSIVE MUCINOUS HISTIOCYTOSIS

- Rare
- Autosomal dominant
- Small skin coloured paules or nodules begin to appear in the first decade of life
- No spontaneous resolution

FOLLICULAR MUCINOSIS/ ALOPECIA MUCINOSA OF PINKUS

- Children & adults of 3rd &4th decade are commonly affected.
- Charecterestic lesions are infiltrated scaly plaque with loss of hair, lesion limited to scalp & face with alopecia.
- 3 groups:
- 1). Loccalised lesion that may subside in aperiod of 2 months
- 2). Lesions persist or new lesions appear for many years
- 3). Associated with lymphomas (may show clonal TCR gene re-arrangement)

- HISTOPATHOLOGY
- Oedema of outer root sheath of hair follicle.
- Mucin accumulation in the hair follicles & sebaceous glands.
- Later stages –cystic spaces.
- A/c benign form: skin colored papules / erythematous indurated scaly plaque.
- Prominent follicles.
- C/c : More widespread lesions. Indurated or non-indurated
- Simulates HD
- Nodules or plaques of gelatinous consistency.
- Resolve spontaneously by 2-24 months
- No specific treatment

URTICARIA LIKE FOLLICULAR MUCINOSIS

- Rare
- Primarily middle aged population are affected.
- Pruritic urticarial papules & plaques on an erythematous base – Head & neck
- With resolving lesions - red macular erythema
- Hair bearing areas
- No alopecia
- Waxing &waning nature
- HPE –similar to follicular mucinosis
- Good prognosis
- Moderate response to antimalarial treatment.

PRIMARY HAMARTOMATOUS NEOPLASTIC MUCINOSIS

- MUCINOUS NAEVUS : B/G Hamartoma
- Acquired or congenital
- CLINICAL FEATURES : plaque with unilateral nevoid pattern
- HPE: Mucin deposition in the upper dermis
- Collagen & elastin are absent in the same area .
- Normal or acanthotic epidermis
- ANGIOMYXOMA: Acquired benign neoplasm. Solitary or multiple
- CARNEY COMPLEX : cardiac &cutaneous myxomas ,numerous lentigenes ,multiple naevi, endocrine over activity

- HPE:
- Lobulated lesion with mucinous matrix with in the dermis & subcutis
- Fibroblasts of variable shape , few collagen ,reticulin fibers,&mast cells
- Bizzare multinucleated cells & fibroblasts
- Prominent dilated capillaries (typical)
- EXCISION : Recurrence

CUTANEOUS FOCAL MUCINOSIS

- Adults –mostly
- Asymptomatic nodule or papule <1 cm in diameter
- Site- anywhere including oral cavity
- Association with thyroid disorders . Not with myxoedema
- DD: angiomyxoma
- HPE:
- Mucin –upper &mid dermis
- Spindle shaped or stellate ,vimentin positive fibroblasts
- Reticulin &elastin fibers are absent .
- Blood vessels are normal in number.