

# Spectrum of cutaneous mucinoses

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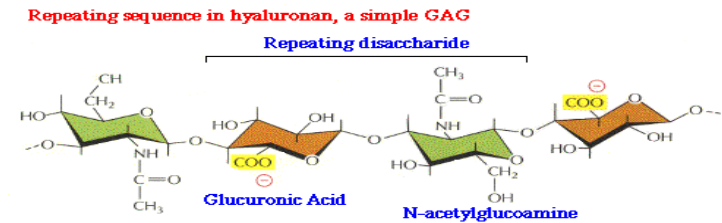


**No conflict of interest  
for this presentation**

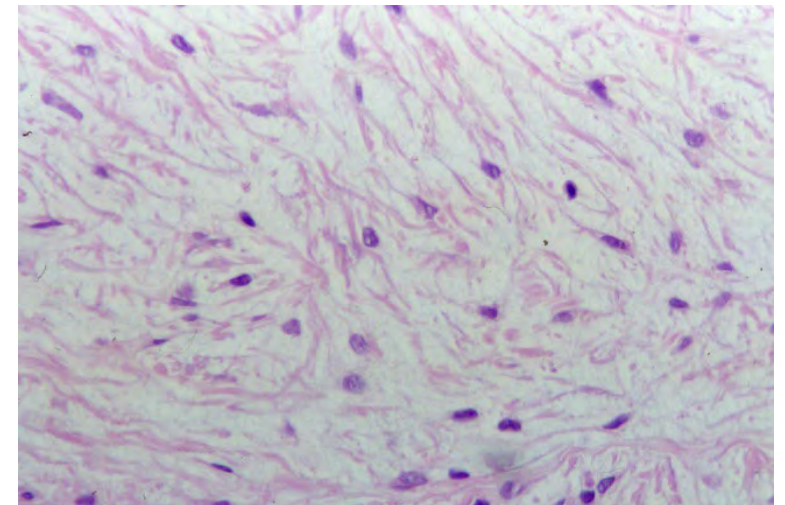
# Dermal Mucin

Acid glycosaminoglycans (GAGS)  
(formerly mucopolysaccharides)

- **Jelly-like complex carbohydrate (made by hyaluronic acid)**



- **Normal component of skin connective tissue in the dermis produced in small amount by fibroblasts**



In disease conditions, mucin is increased



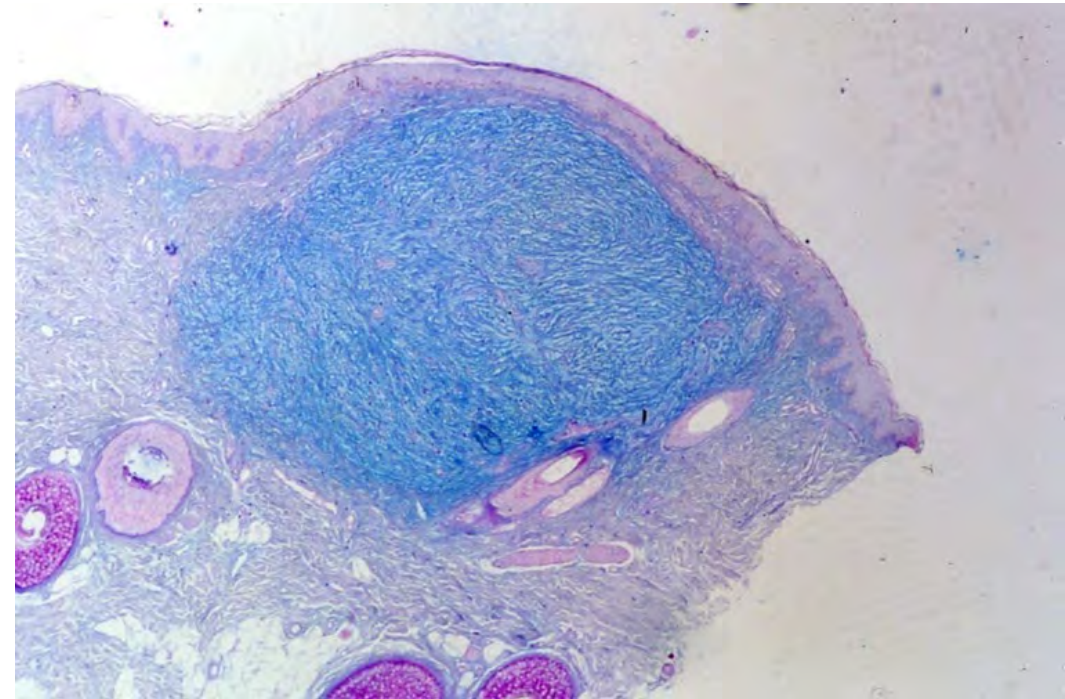
and since it holds water (hygroscopic)



the dermal connective tissue is swollen

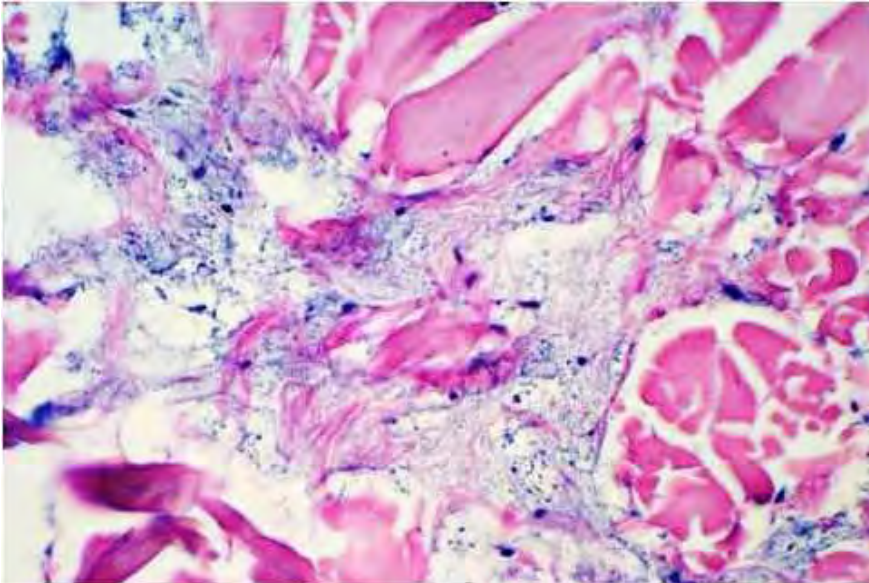
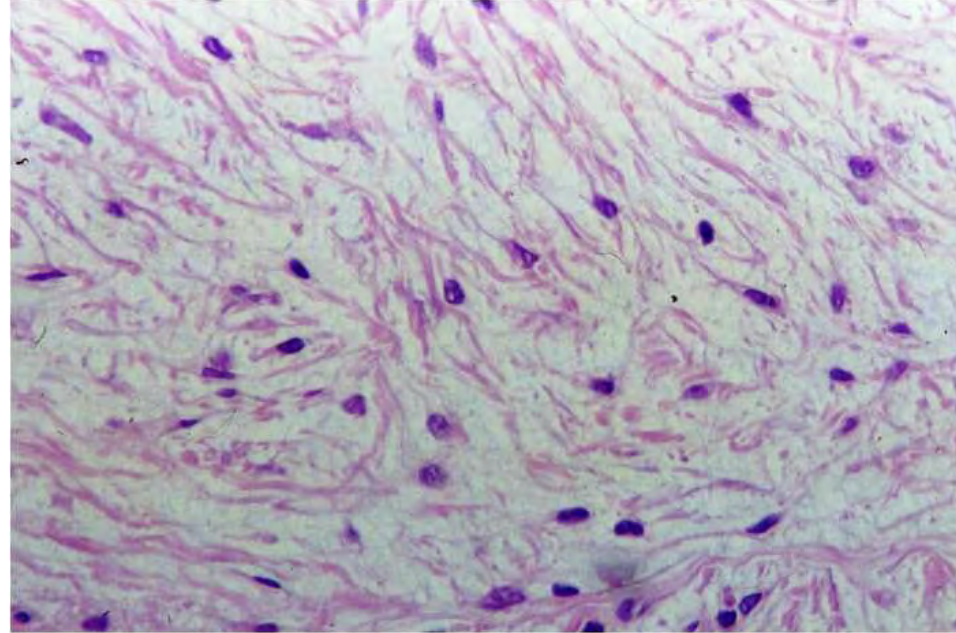
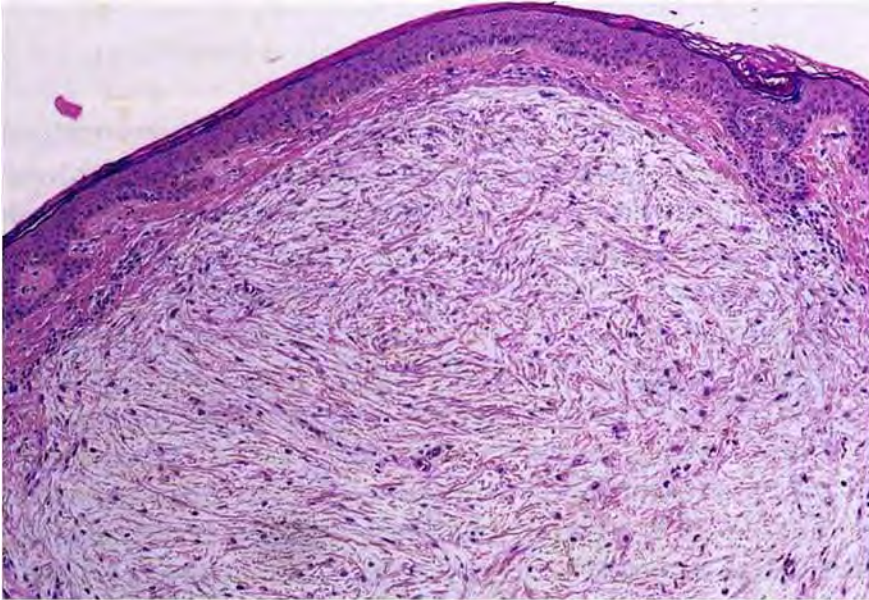


**Cutaneous mucinosis in Shar-pei**



**Alcian blue**

# Mucin



**Collagen bundles widely spaced  
with basophilic finely granular material  
and fibroblasts(H-E stain)**

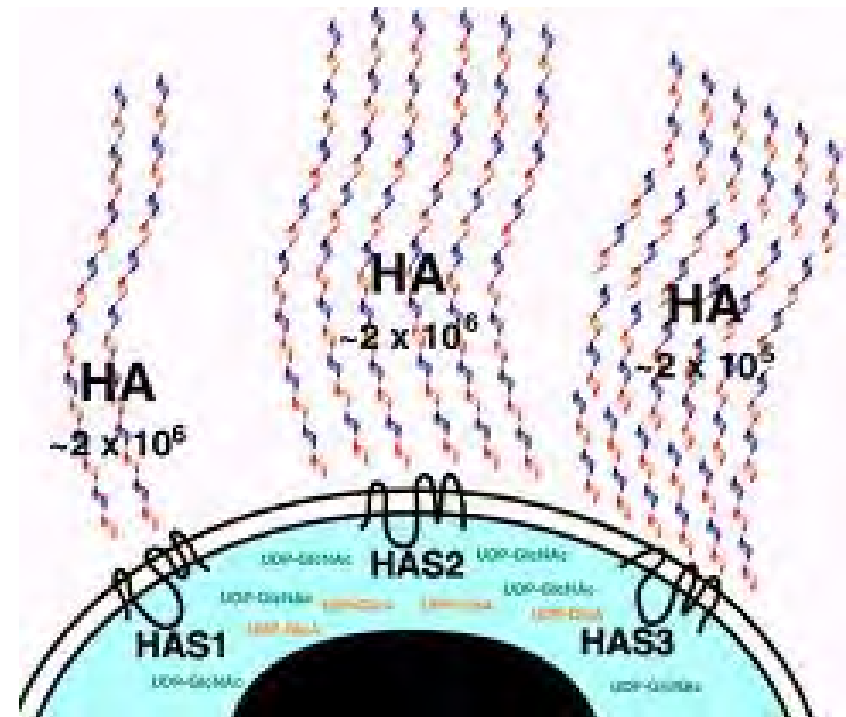
**Table 47.1 Staining characteristics of acid glycosaminoglycans (mucopolysaccharides)**

STAINING CHARACTERISTICS OF ACID GLYCOSAMINOGLYCANS (MUCOPOLYSACCHARIDES)		
Histologic stain	Acid glycosaminoglycan (mucopolysaccharides)	
	Non-sulfated (hyaluronic acid*)	Sulfated (chondroitin sulfate dermatan sulfate**)
Colloidal iron	⊕	⊕
Alcian blue		
pH 2.5	⊕	⊕
pH 0.5	⊖	⊕
Metachromasia with toluidine blue		
pH 4.0	⊕	⊕
pH <2.0	⊖	⊕
PAS***	⊖	⊖
Hyaluronidase-sensitive	⊕	⊖

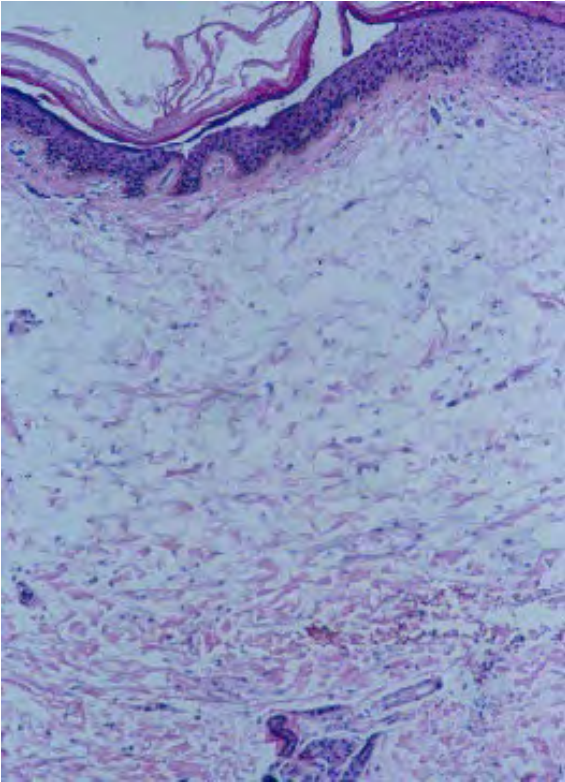
\*Major GAG in the disorders discussed in this chapter; not bound to protein core  
 \*\*Major GAG in the mucopolysaccharidoses, e.g., Hunter's syndrome, Hurler's syndrome; bound to protein core (proteoglycan), such as collagen, elastin, MPS  
 \*\*\*Stains neutral mucopolysaccharides

# New techniques to detect glycosaminoglycans

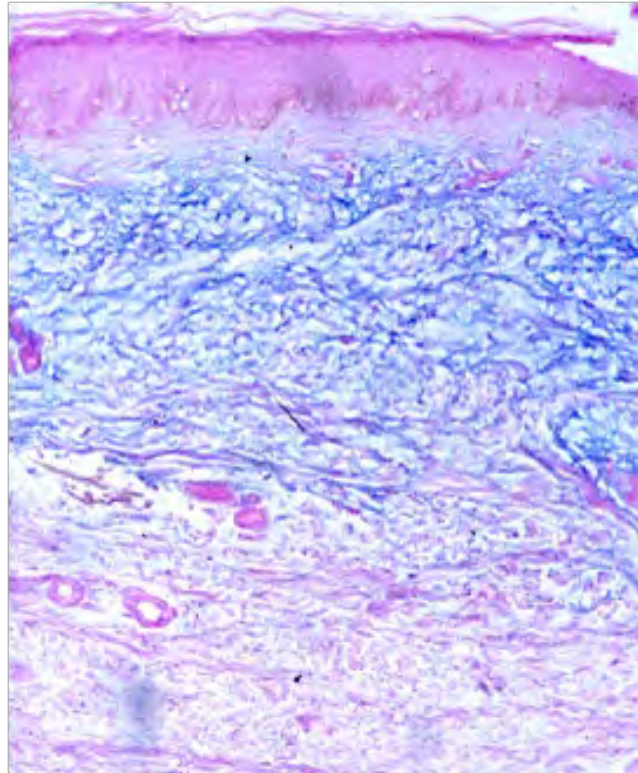
- MUC1 staining
- Antibodies to family of hyaluronan synthases (HS1,HS2,HS3), hyaluronidases (HYAL1,HYAL2)
- CD44 receptor for [hyaluronic acid](#)



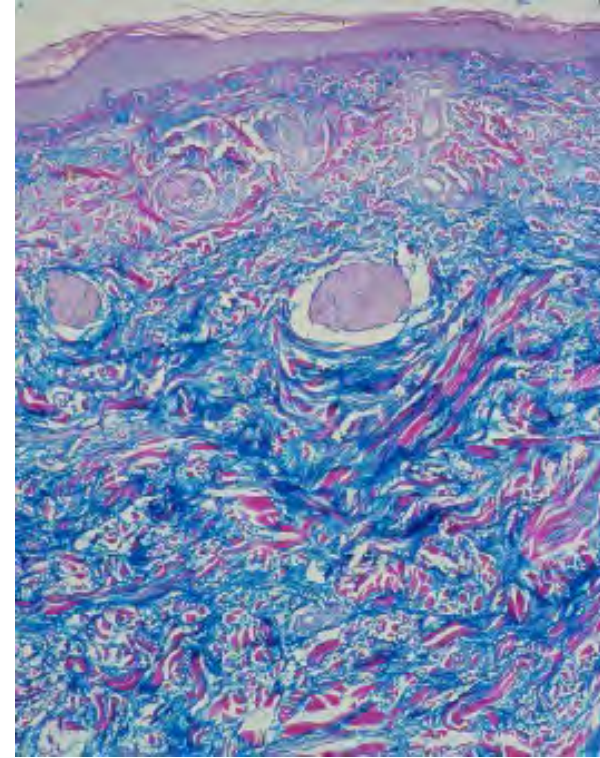
# Cutaneous mucinosis



**Hematoxylin-eosin**



**Alcian blue pH 2.5**



**Colloidal iron**

# The cutaneous mucinoses

Heterogeneous group of disorders

- **Primary Mucinoses**

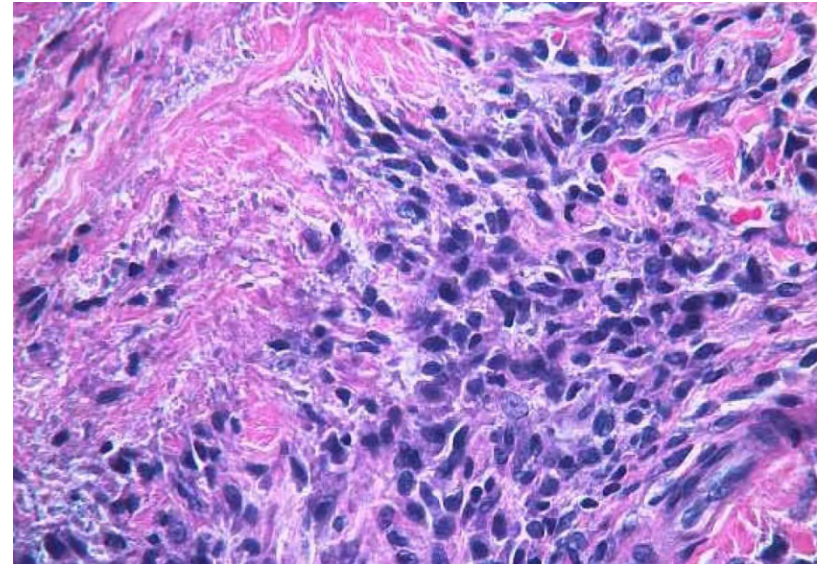
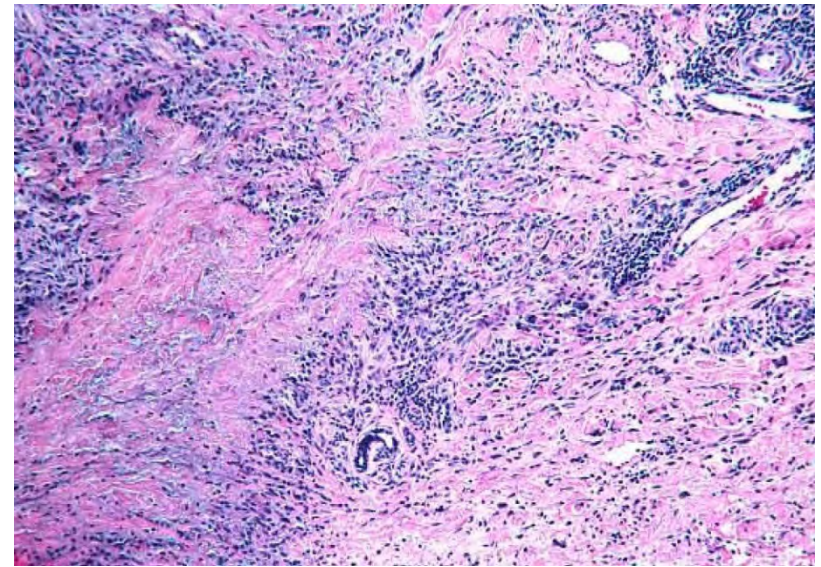
**Mucin deposit is the main histologic finding resulting in clinically distinctive lesions**

- **Secondary Mucinoses**

**Mucin deposit is only an additional histologic finding that is secondary or reactive to another condition**

# Secondary mucinoses

- Granuloma annulare
- Dermatomyositis
- Scleroderma
- Lupus erythematosus
- Degos' diseases
- .....



Granuloma annulare

## Classification of the primary cutaneous mucinoses.

### CLASSIFICATION OF THE PRIMARY CUTANEOUS MUCINOSES

#### Degenerative–inflammatory mucinoses

##### Dermal

Scleromyxedema or papular mucinosis\*

Lichen myxedematosus (localized variants)

- Discrete papular form<sup>†</sup>
- Acral persistent papular mucinosis
- Cutaneous mucinosis of infancy
- Nodular form

Self-healing cutaneous mucinosis

- Juvenile type
- Adult type

Scleredema

- Non-diabetic type (types I and II)
- Diabetic type (type III)

Mucinoses associated with altered thyroid function

- Localized (pretibial) myxedema
- Generalized myxedema

Reticular erythematous mucinosis

Papulonodular mucinosis associated with autoimmune connective tissue diseases (most commonly LE)

Cutaneous focal mucinosis

Digital mucous cyst (myxoid cyst)

Miscellaneous mucinoses

##### Follicular

Follicular mucinosis (Pinkus)

Urticaria-like follicular mucinosis

# DERMAL



From Rongioletti F. Mucinoses in Bologna J et al  
Dermatology, Elsevier 54th Ed. 2024

# FOLLICULAR

# Classical Dermal Mucinoses

From Rongioletti F. Mucinoses in Bologna J et al Dermatology, Elsevier 4th Ed. 2024

## Lichen Myxedematosus

- Diffuse and sclerodermoid (Scleromyxedema)
- Localized (acral persistent papular mucinosis, discrete lichen myxedematosus, nodular lichen myxedematosus)

## Scleredema

Localized (pretibial) myxedema  
(Thyroid dermopathy)

## Reticular erythematous mucinosis (REM)

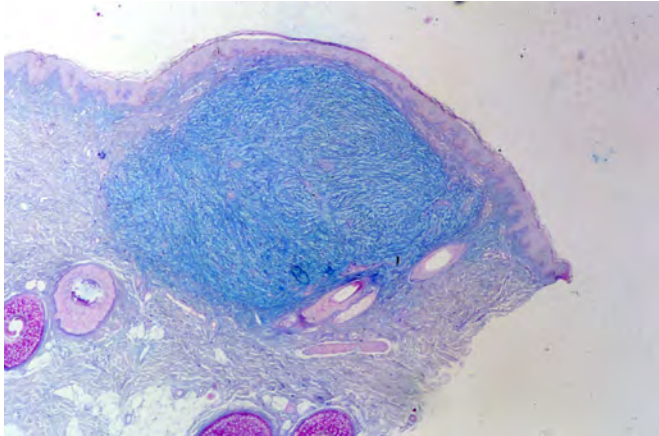


# Histopathology-based classification of dermal cutaneous mucinoses

- **Distribution of mucin (focal vs diffuse)**
- **Level of deposition (superficial, mid to deep dermal)**
- **Fibroblast proliferation**
- **Additional findings**

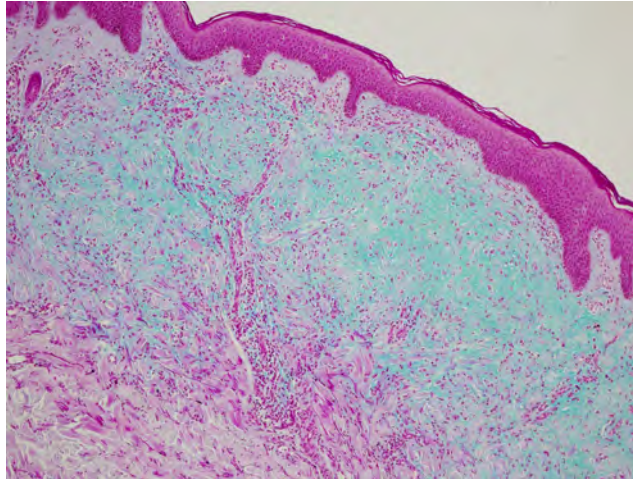
# 1. Pattern of mucin distribution

**Focal**



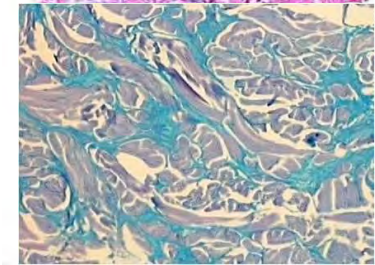
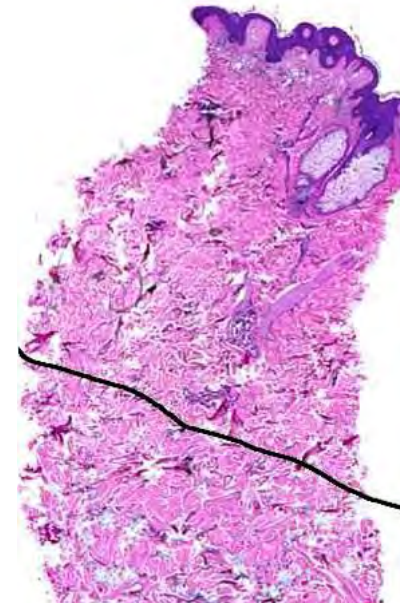
**Acral persistent  
papular mucinosis**

**Diffuse**



**Scleromyxedema**

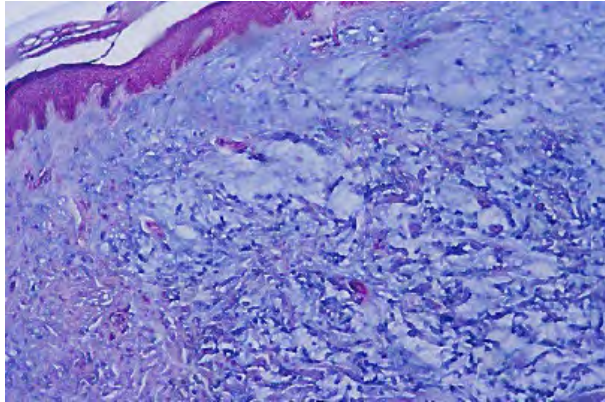
**Interstitial**



**Scleredema**

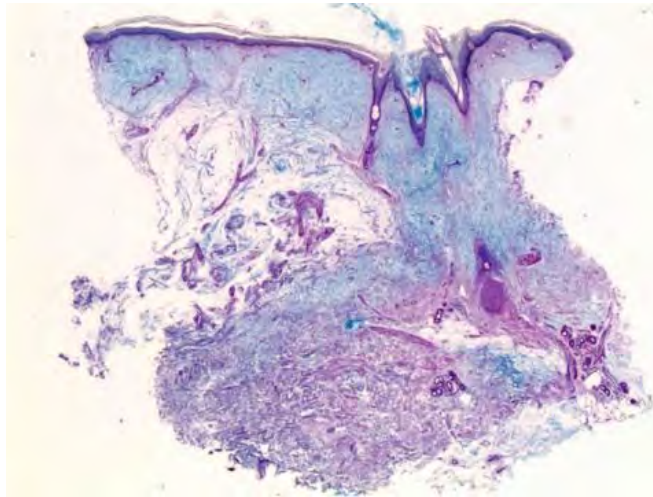
## 2. Level of mucin deposit

Superficial/upper dermis



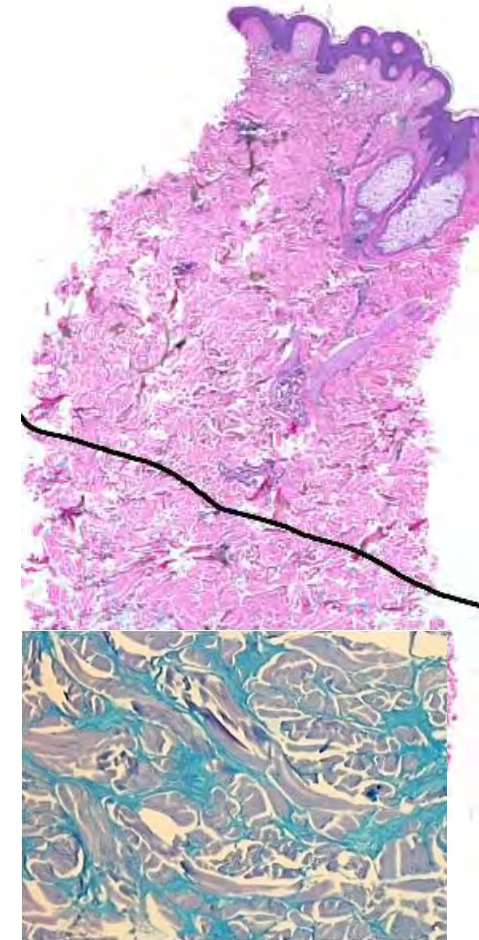
Localized  
lichen  
myxedematosus

Reticular dermis



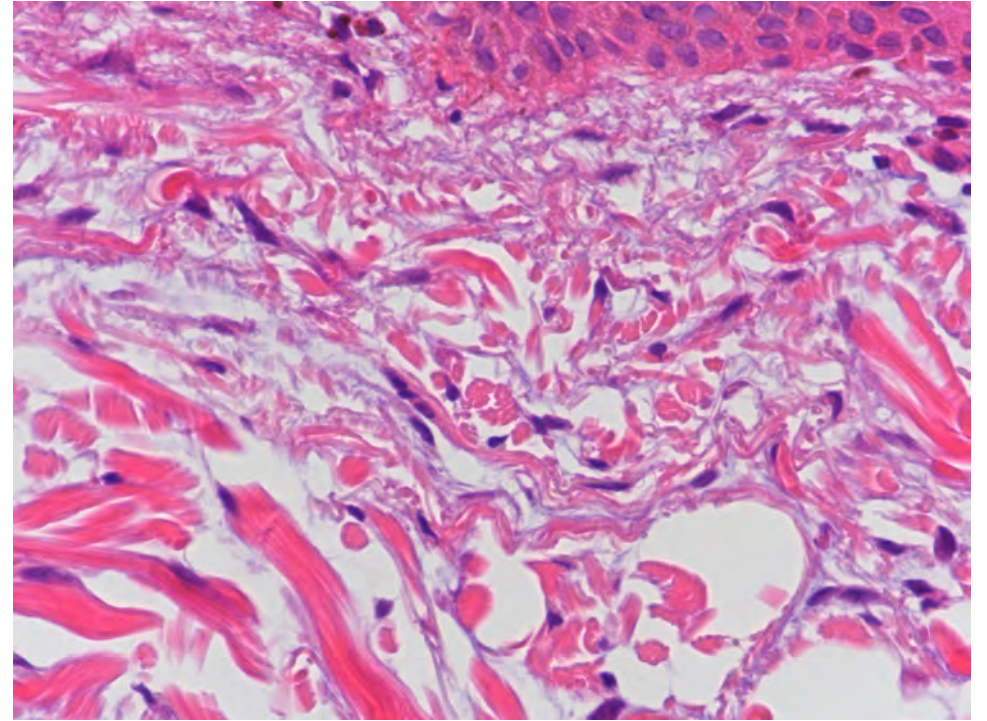
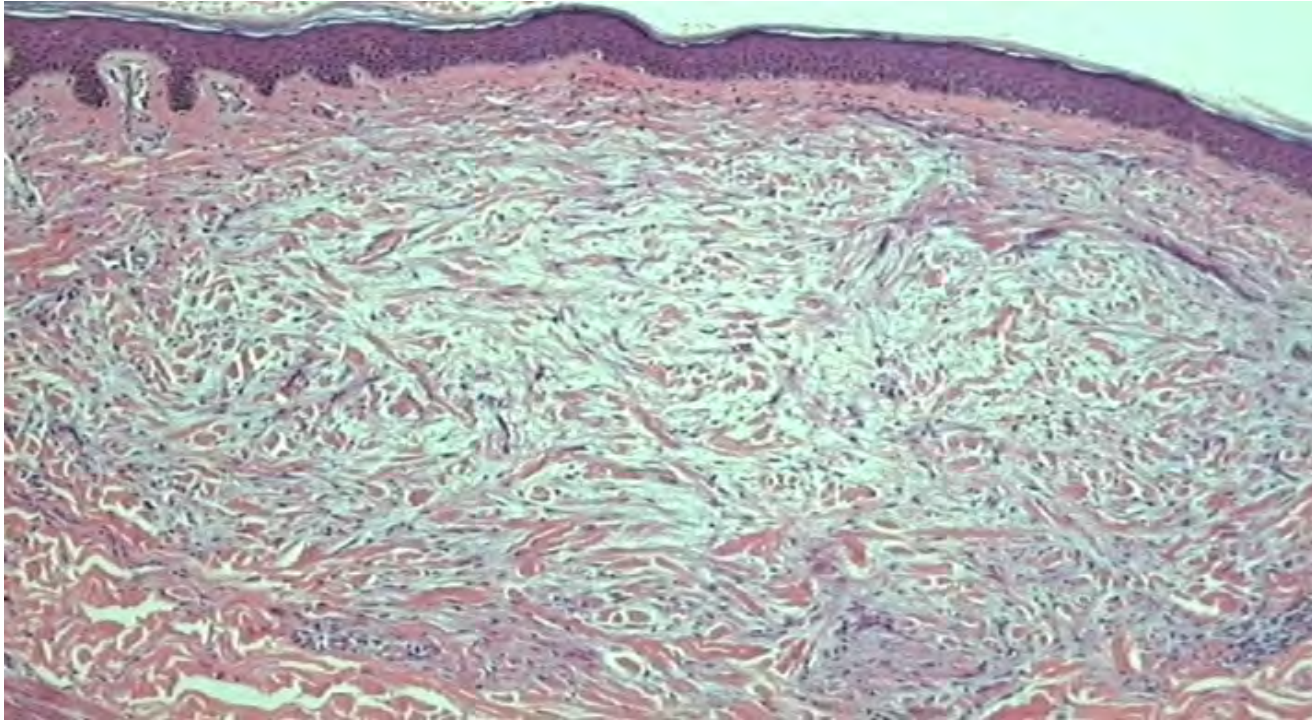
Pretibial myxedema

Deep reticular dermis



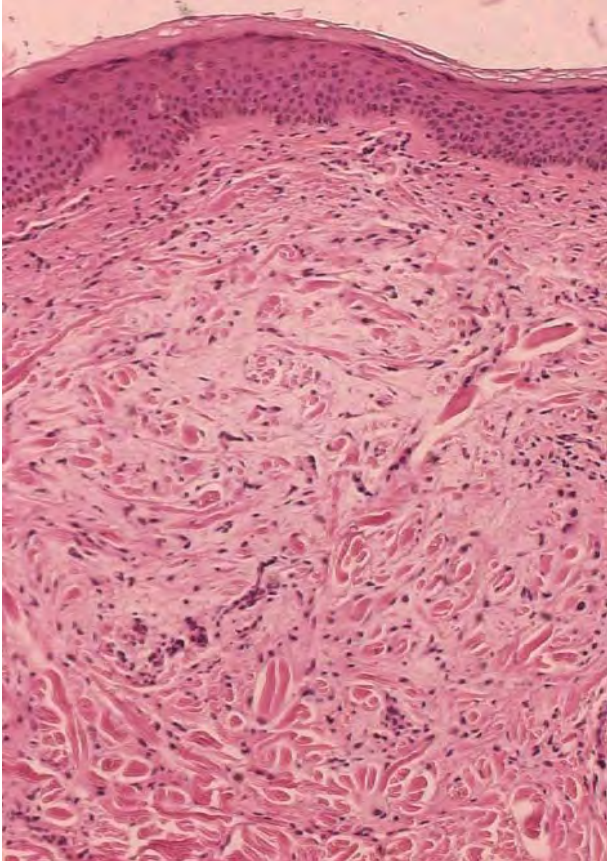
Scleredema

### 3. Fibroblast proliferation



## 4. Additional findings

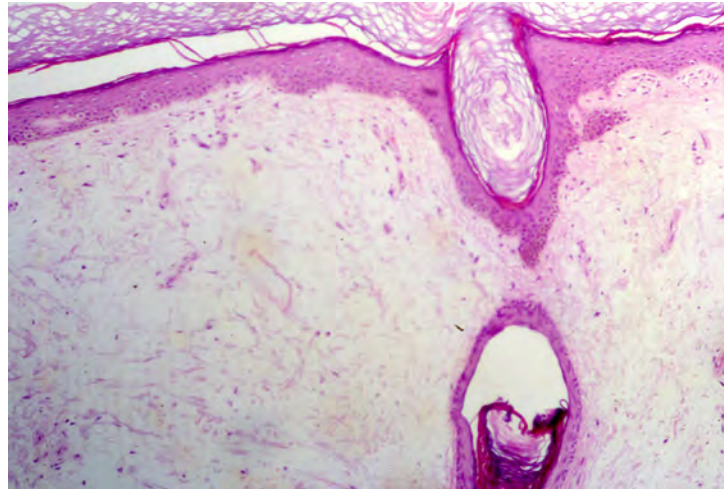
### Scleromyxedema



#### Triad:

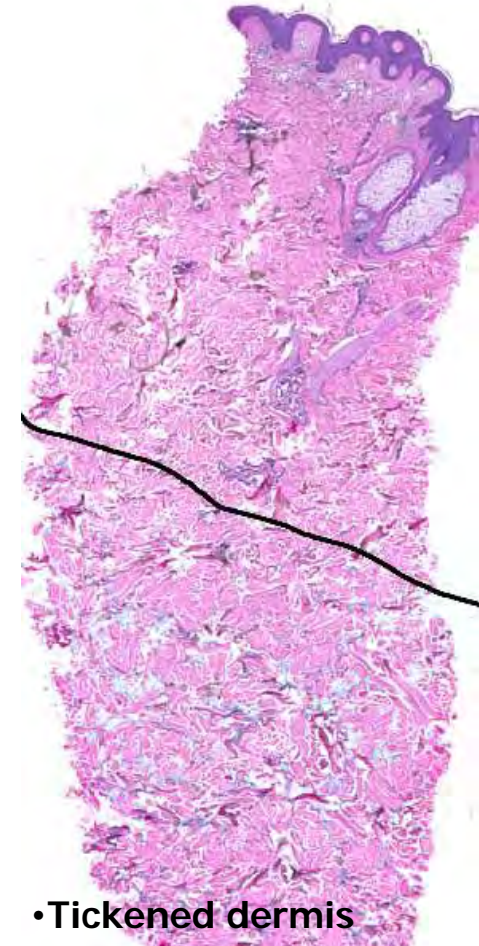
- mucin,
- fibroblast proliferation
- fibrosis

### Pretibial myxedema



- Hyperkeratosis
- Follicular plugging
- Mast-cells

### Scleredema



- Thickened dermis
- Fenestration of collagen
- No fibroblast proliferation

# Scleromyxedema

Rongioletti et al. J Am Acad Dermatol 2013



Shar-pei sign



- Described by Gottron in 1954
- No gender predominance
- Adults in their fifties or sixties

# Scleromyxedema



**Closely spaced papules  
on sclerodermoid skin**

**Papules in a  
linear fashion**



# Scleromyxedema

Rongioletti et al. J Am Acad Dermatol 2013



**Shar-pei sign**



**Generalized sclerodermod eruption with stiff infiltration and redundant folds**

# Scleromyxedema



# Scleromyxedema



**Doughnut sign**



# Scleromyxedema



**Stiffness of the facial skin and muscles with difficulty in opening the mouth**

# Scleromyxedema

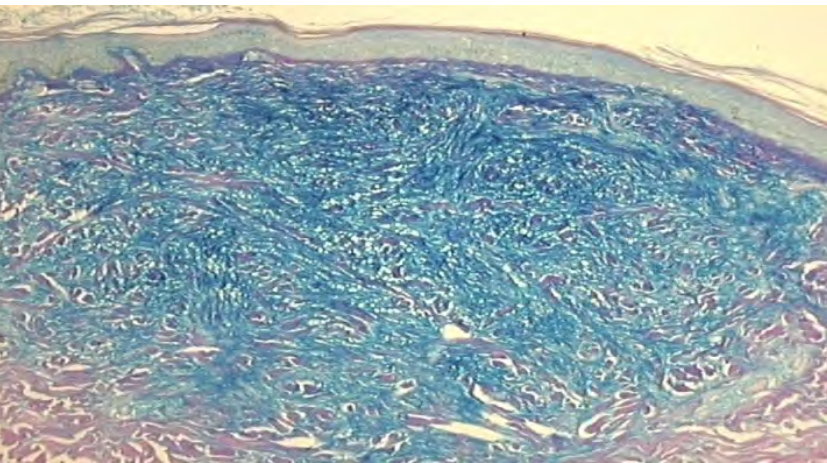


**Inability to fully flex the fingers**

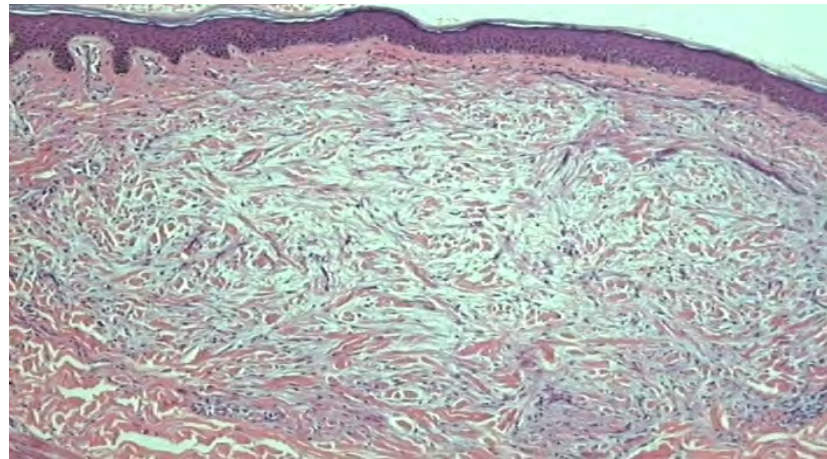


# Histopathology: microscopic triad of scleromyxedema

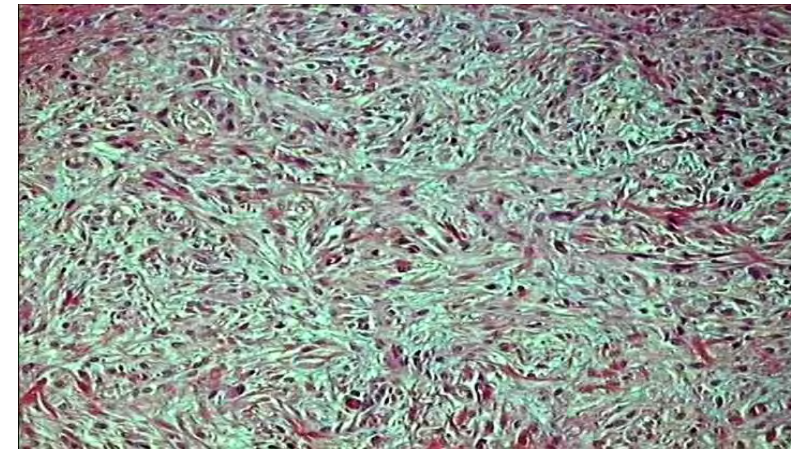
Rongioletti F (2021). Scleromyxedema. In UpToDate. Retrieved from <http://www.uptodate.com/home/index.html>



**1. Mucin**

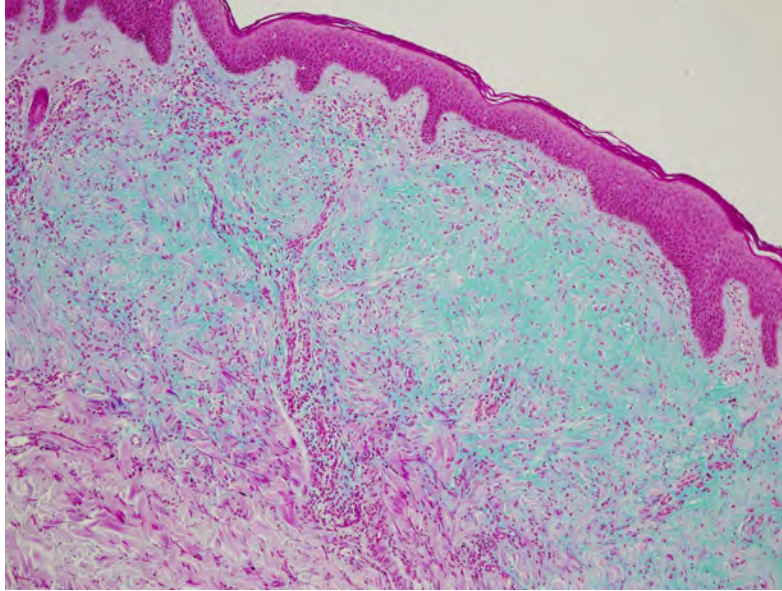


**2. Fibroblast proliferation**

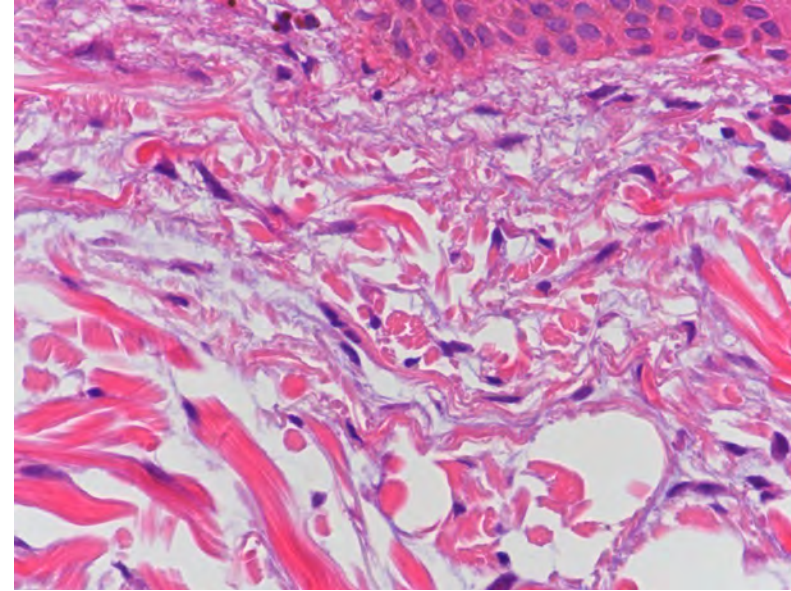


**3. Fibrosis**

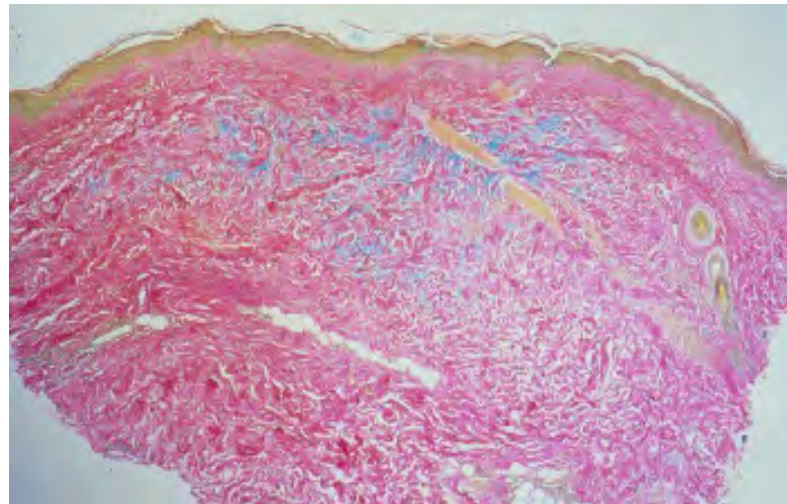
# Histopathology: microscopic triad of scleromyxedema



**1.Mucin**

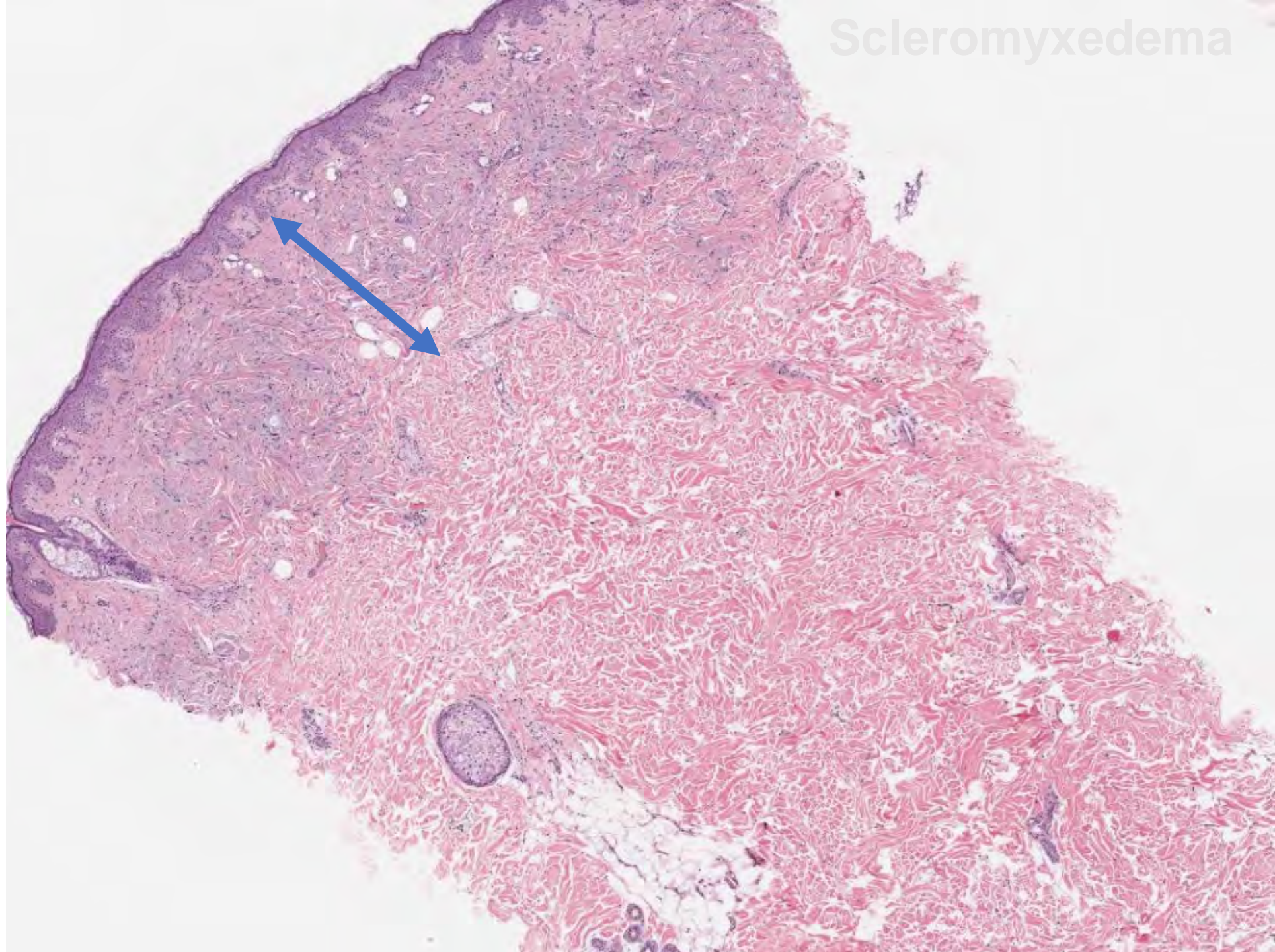


**2.Fibroblast  
proliferation**



**3.Fibrosis**

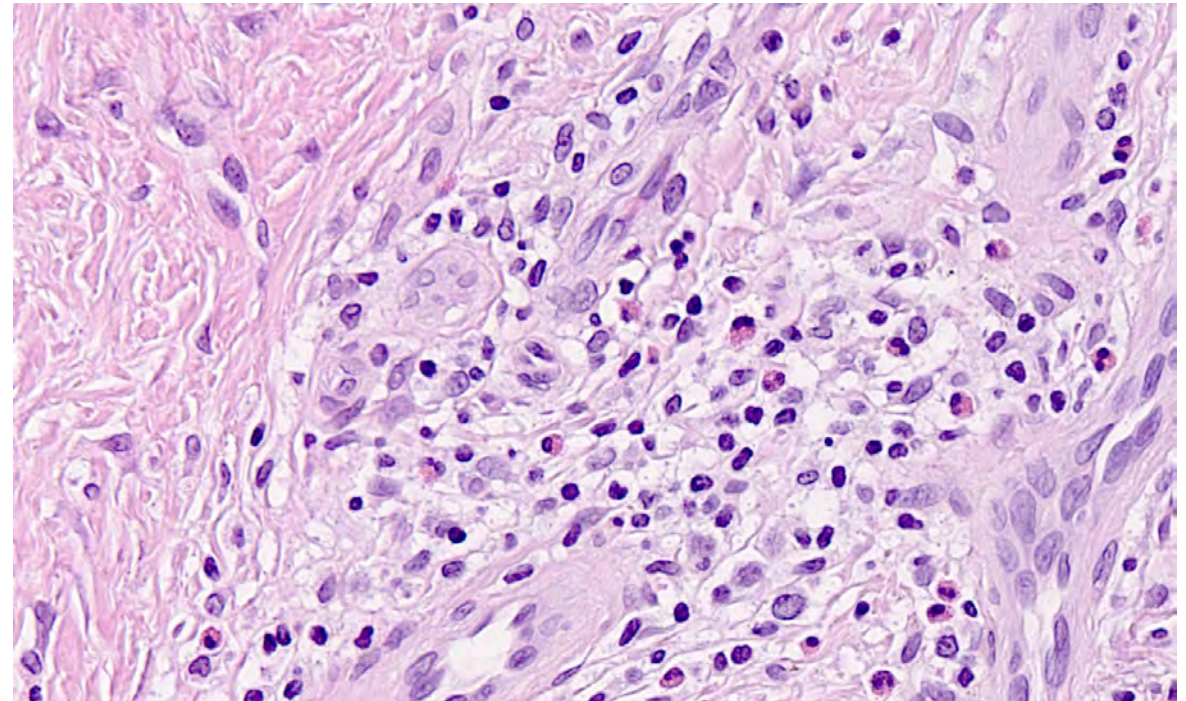
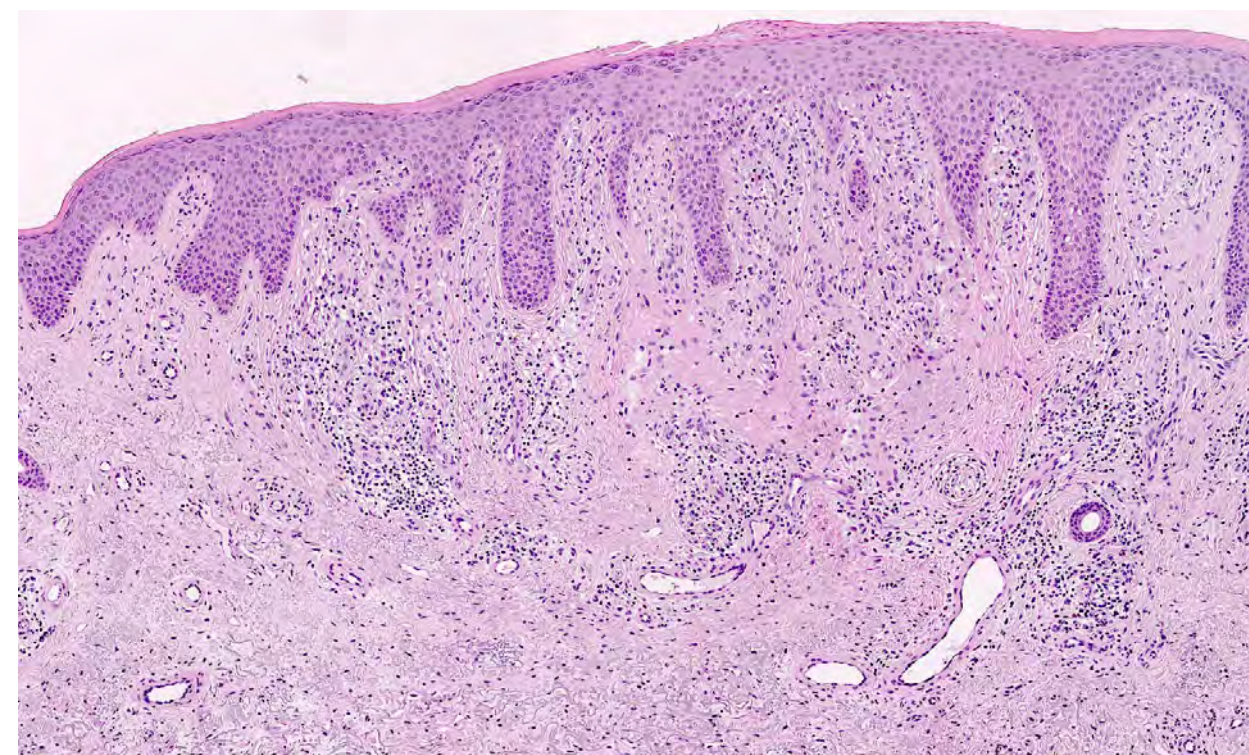
# Scleromyxedema



# Scleromyxedema

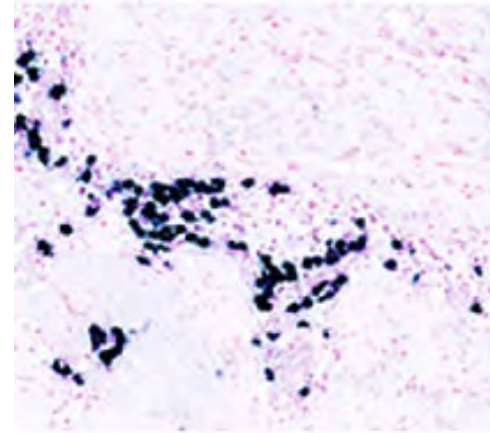
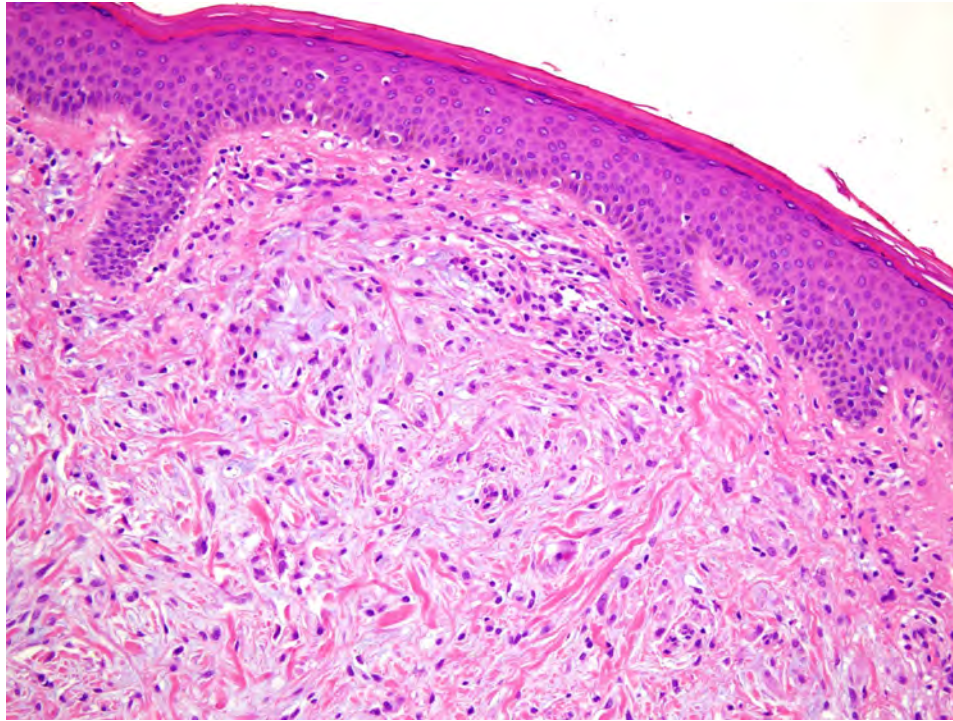
**Slight to moderate perivascular  
lymphoplasmacytic infiltrate**

**Lymphocytes, plasma cells and  
sometimes eosinophils**

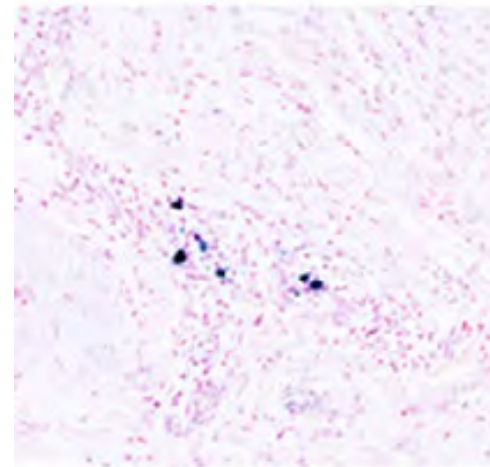


# Plasma cells sometimes monoclonally restricted

Mitteldorf C, Rongioletti F, Kempf W, Tronnier M. J Eur Acad Dermatol Venereol 2017

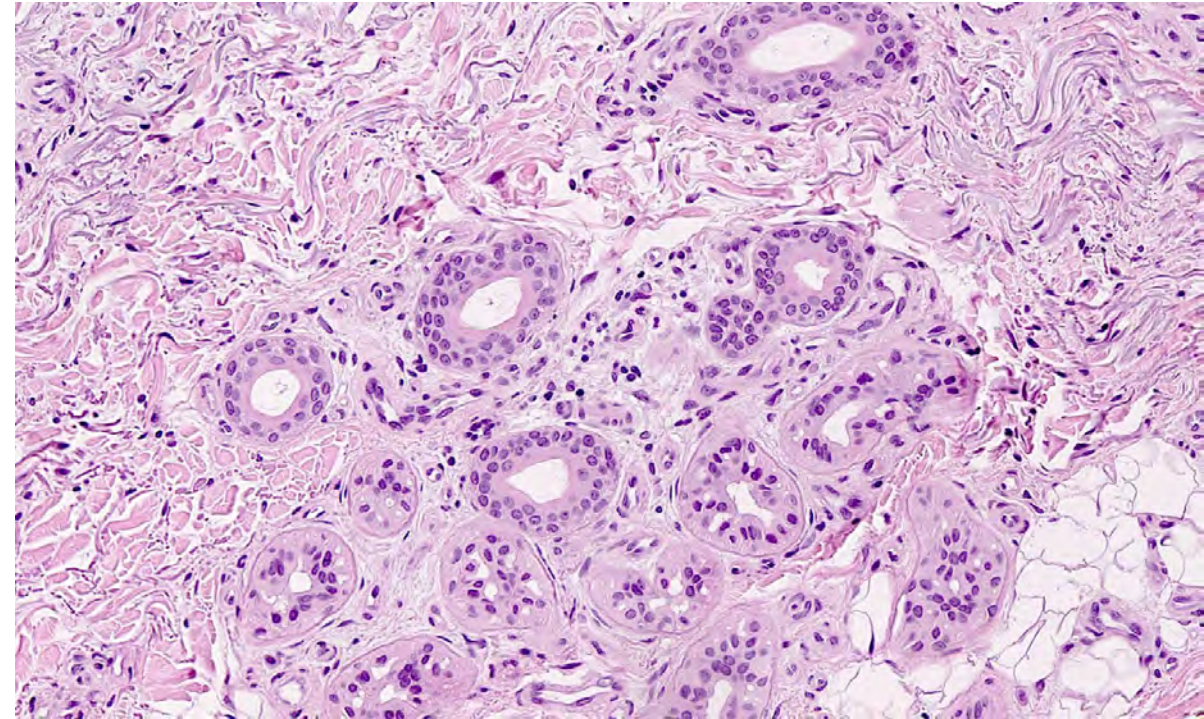
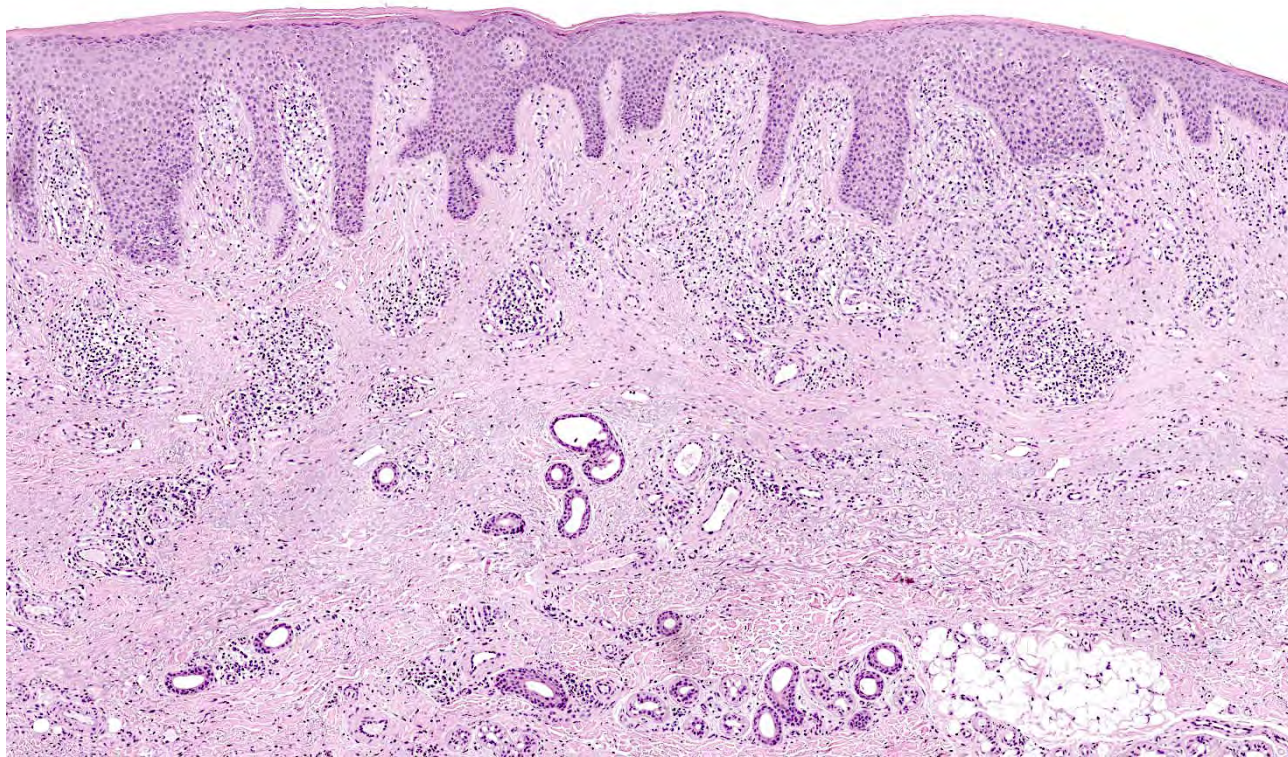


*In situ* hybridisation  
for Ig light chain  
lambda



*In situ* hybridisation  
for Ig light chain  
kappa

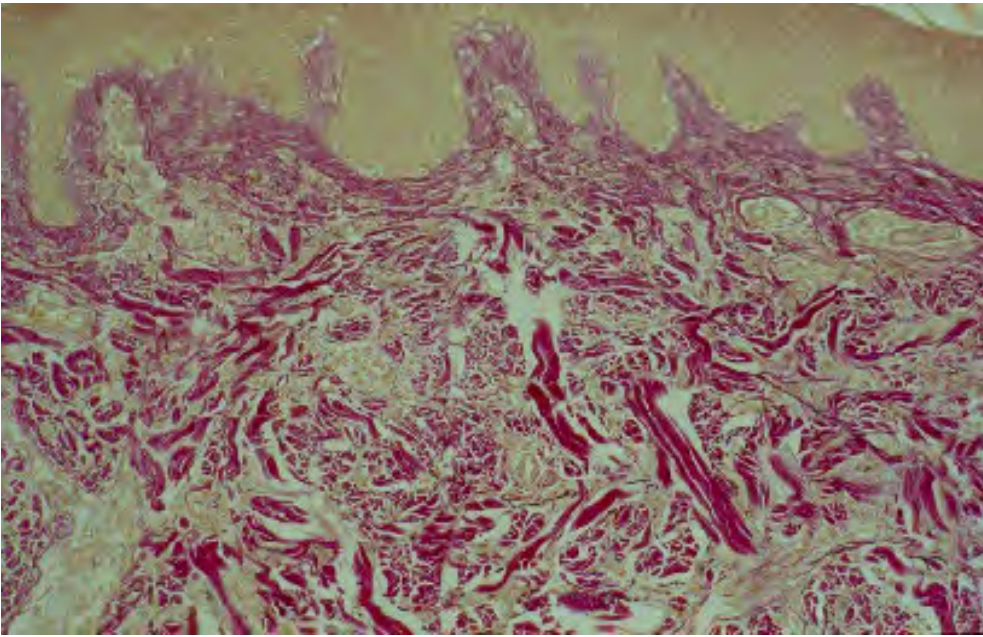
# Scleromyxedema



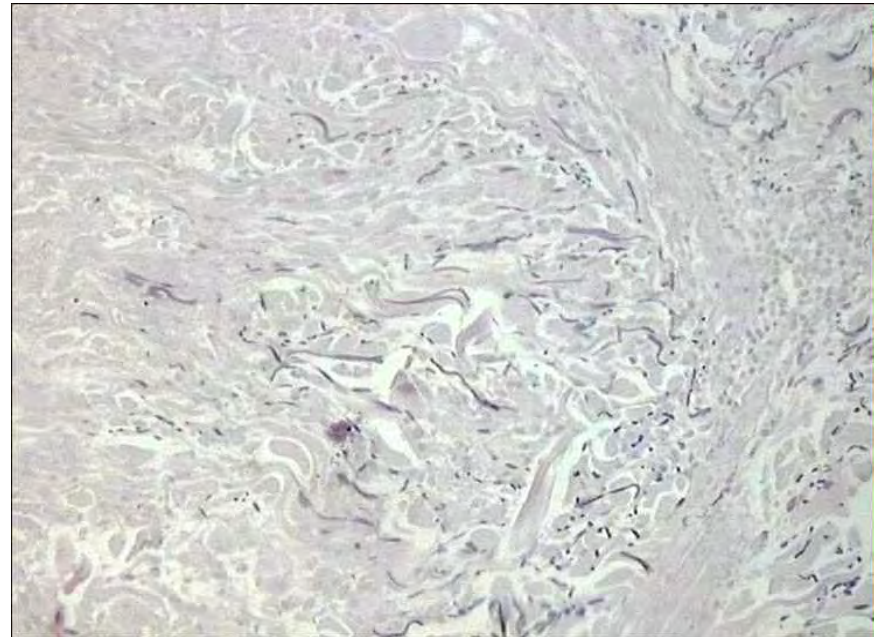
**Eccrine sweat gland proliferation as unusual clue**

# Scleromyxedema

loss or decrease of the elastic tissue



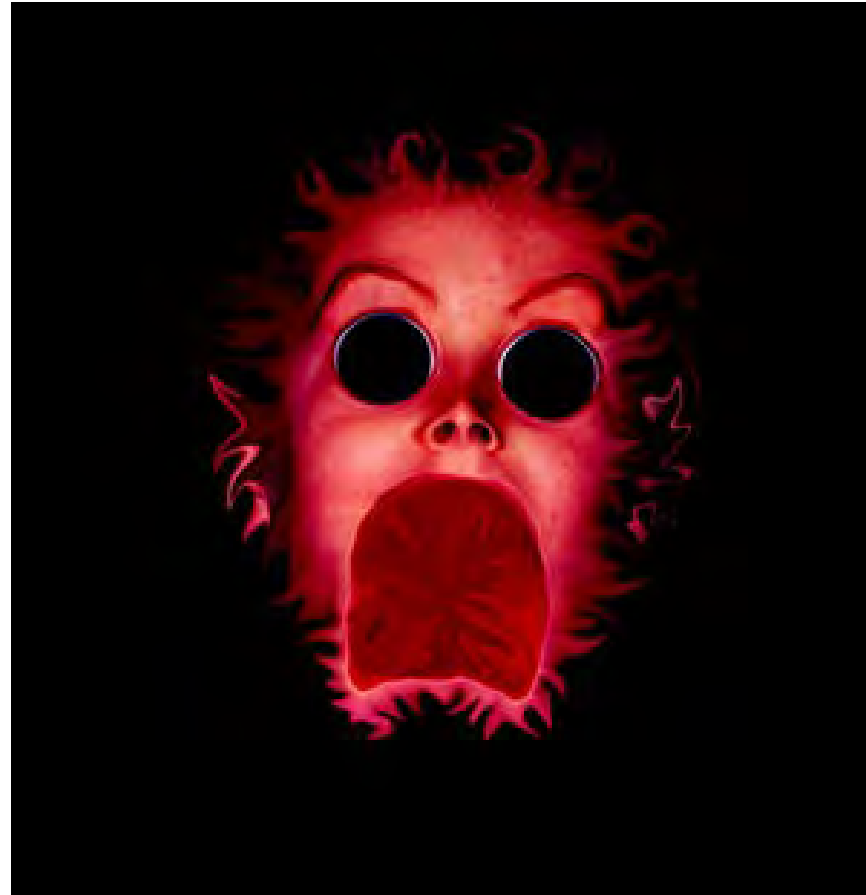
**Weigert  
stain**



**Orcein  
stain**

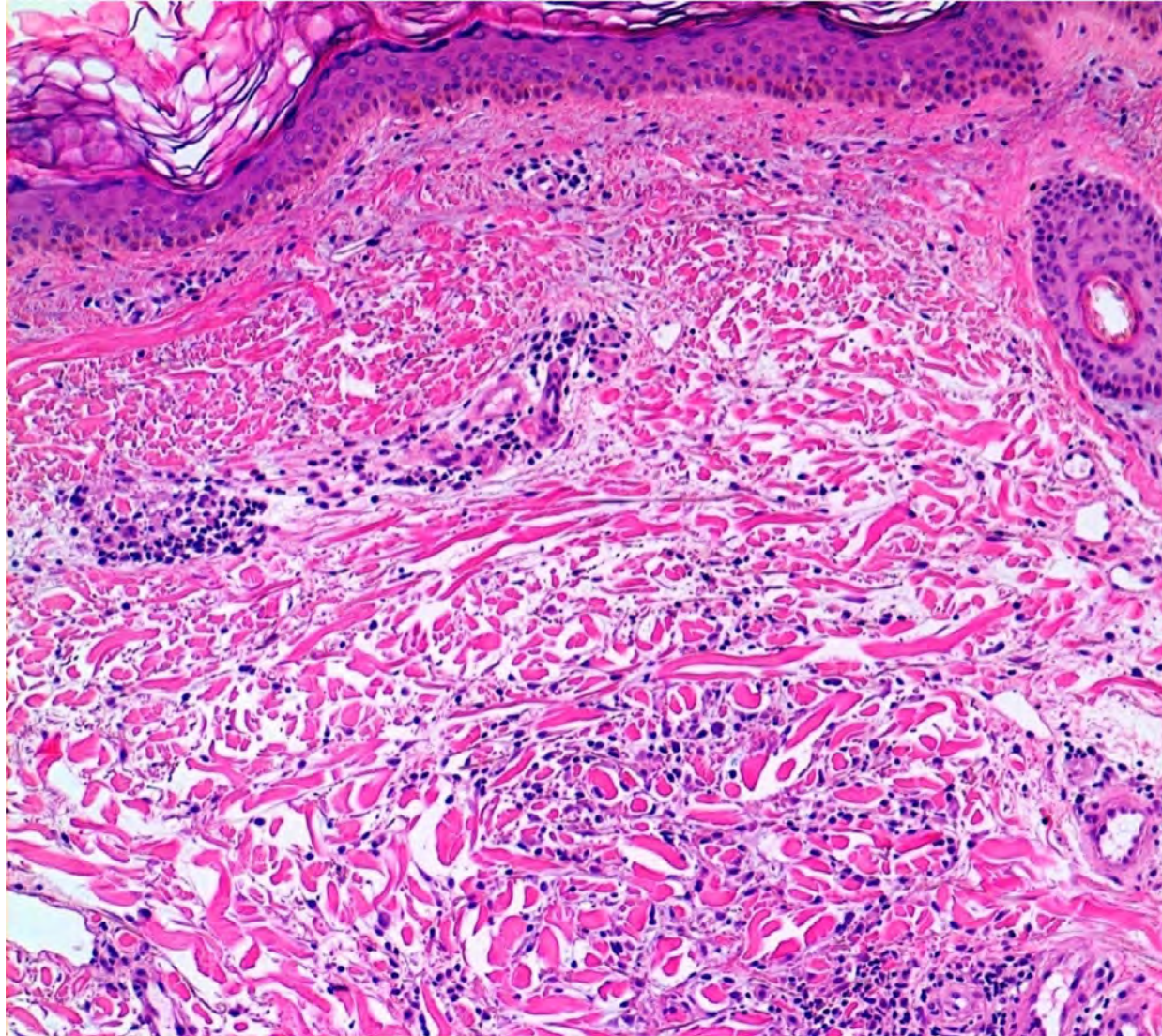


# Pitfalls



# Scleromyxedema with an interstitial granulomatous-like pattern

Rongioletti F. J Cutan Pathol 2010

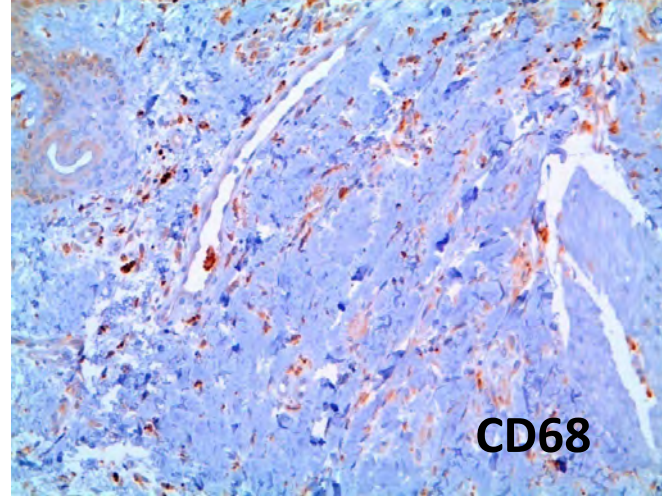
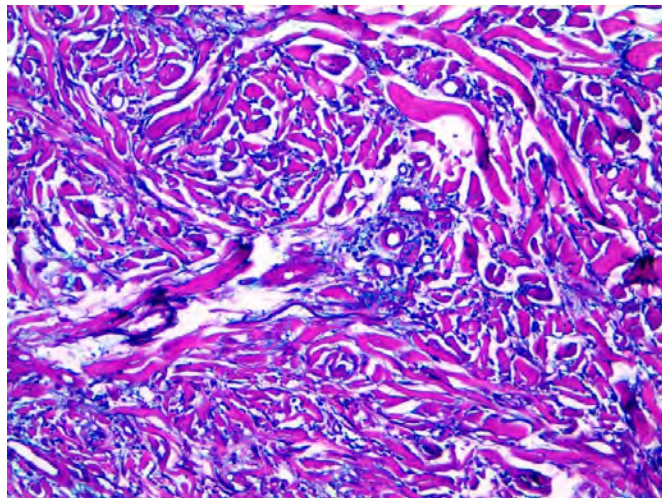
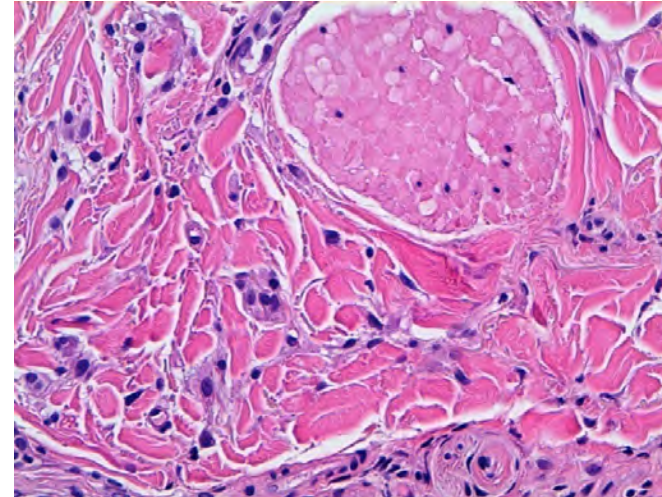
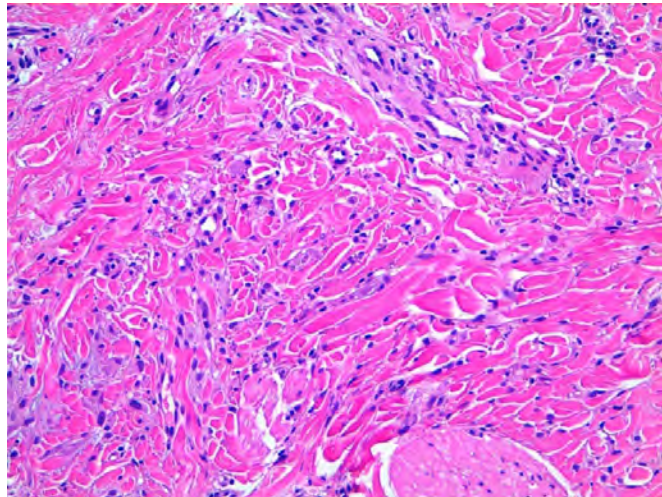


- About 20% of the cases



# Scleromyxedema with an interstitial granulomatous-like pattern

Rongioletti F. J Cutan Pathol 2010



*J Cutan Pathol* 2010; 37: 1084-1087  
doi: 10.1111/j.1509-0502.2009.01586.x  
John Wiley & Sons, Periodicals Department

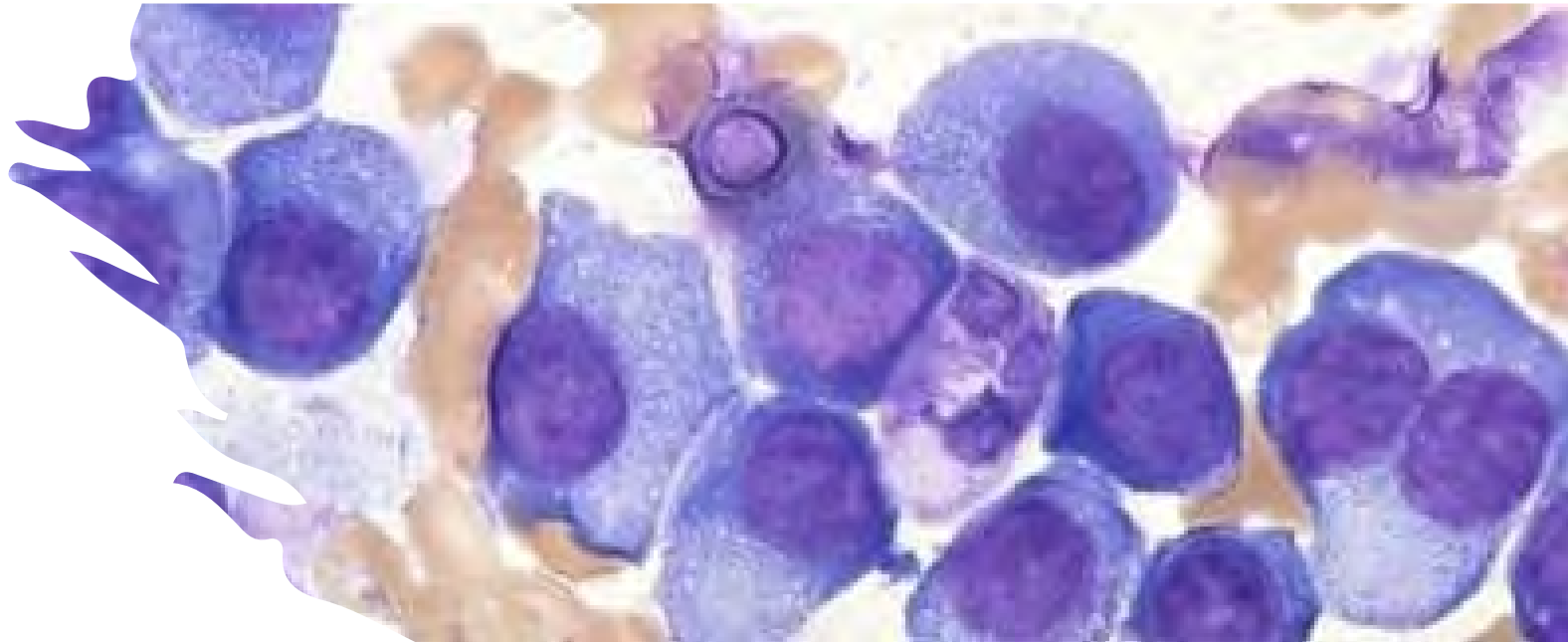
Copyright © 2009 John Wiley & Sons, A/S  
Journal of  
Cutaneous Pathology

Scleromyxedema with an interstitial  
granulomatous-like pattern: a rare  
histologic variant mimicking  
granuloma annulare

Scleromyxedema is the generalized and sclerodermoid form of lichen  
myxedematous. Its typical histological features include a diffuse  
deposition of mucin in the papillary and mid reticular dermis, an  
increased of collagen deposition, and a proliferation of irregularly

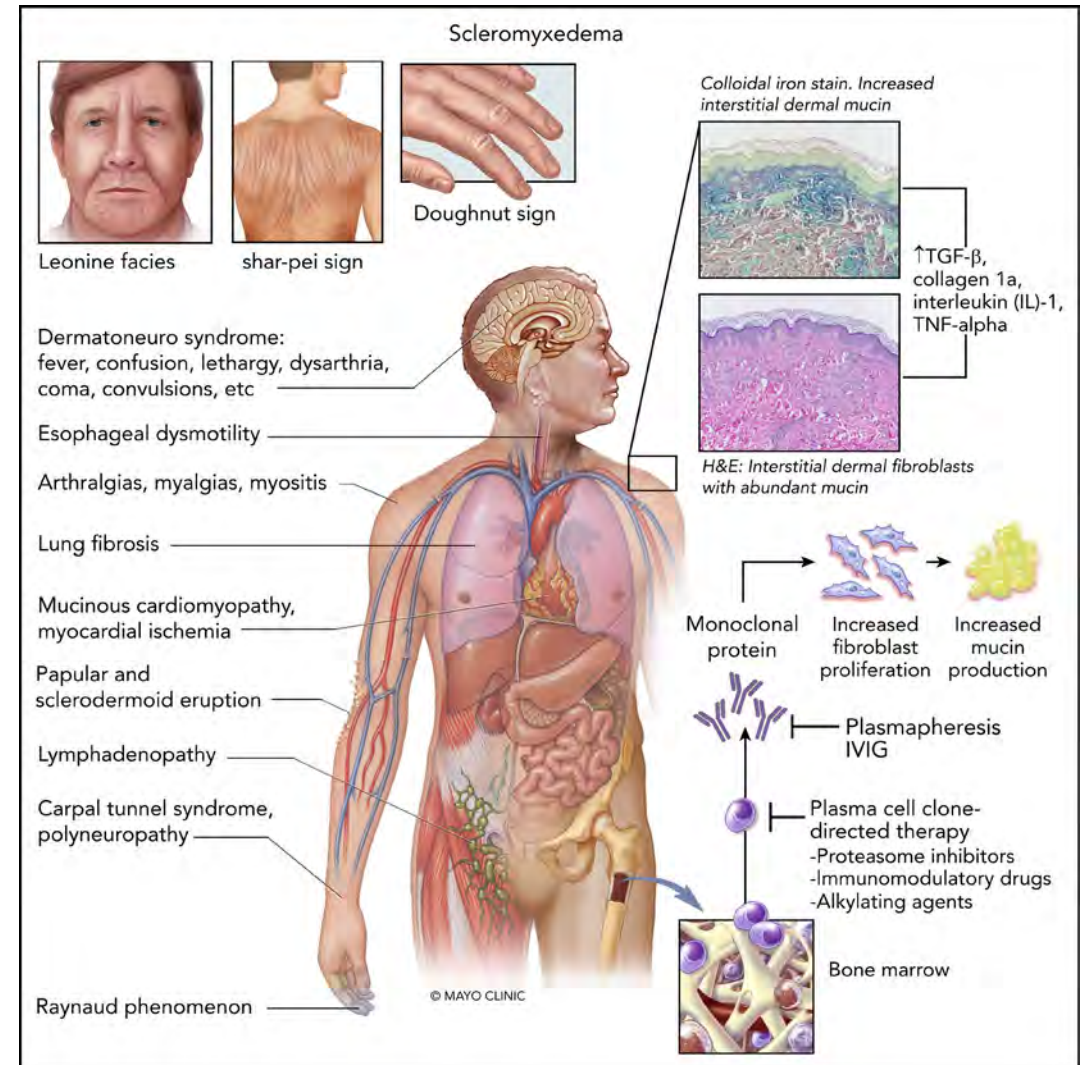
Franco Rongioletti, Emanuele  
Cozzani and Aurora Parodi  
Section of Dermatology, DISEM, University of  
Genoa, Italy

Scleromyxedema is associated with a monoclonal gammopathy, usually IgG lambda (rarely progressing to myeloma)



# Scleromyxedema is associated with systemic manifestations

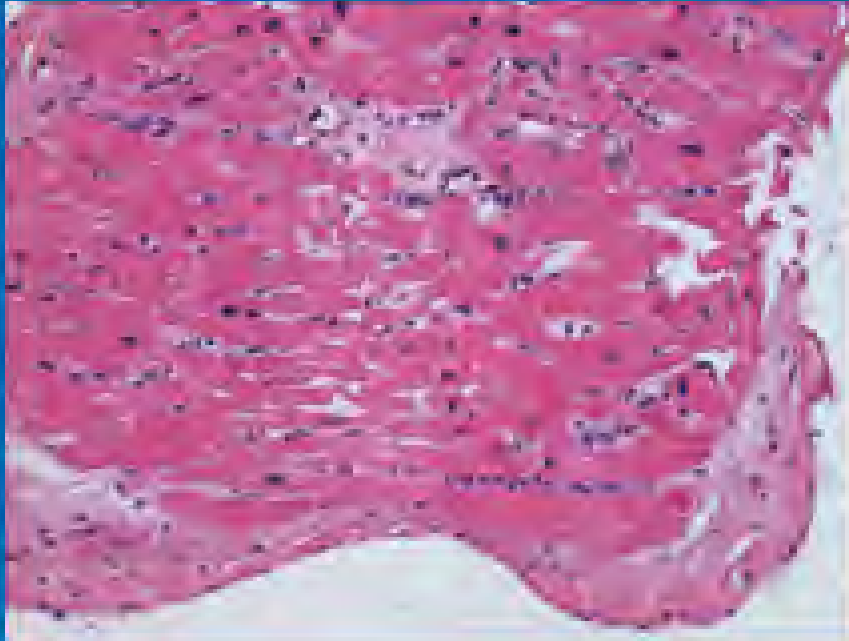
- **Neurologic 30%**
  - Peripheral and central nervous system, Dermato-neural syndrome
- **Rheumatologic 25%**
  - Arthralgias/arthritis, carpal tunnel
- **Cardiovascular 22%**
  - Heart failure
- **Gastrointestinal manifestations (20%)**
  - Dysphagia due to esophageal dysmotility
- **Pulmonary involvement (17%)**
  - Obstructive or restrictive lung disease



Prashant Kapoor, et al Of lions, shar-pei, and doughnuts: a tale retold, Blood, 2020,

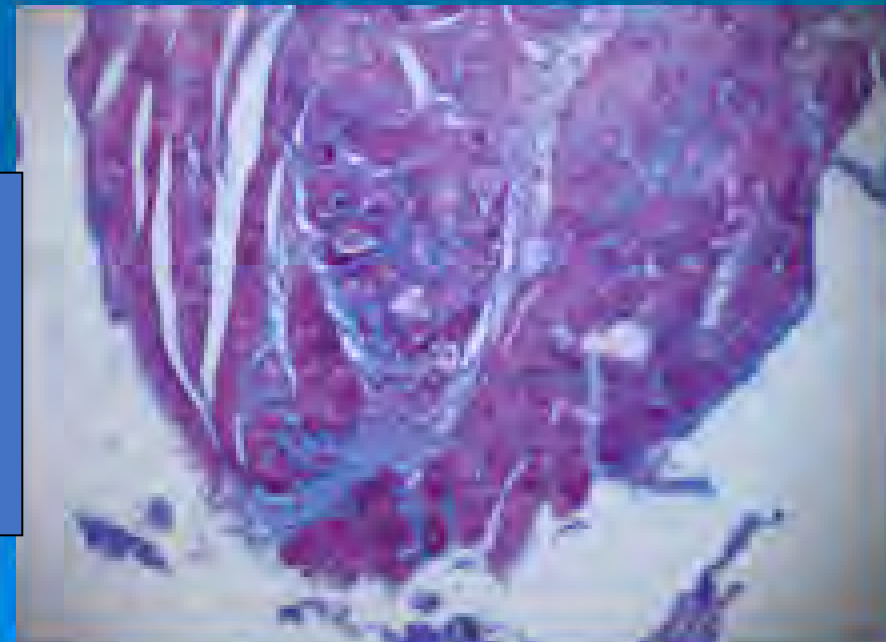
# Scleromyxedema

Eur J Dermatol 2010;20



- **Congestive heart failure**
  - **Myocardial ischemia**
    - **Heart block**
  - **Pericardial effusion**

- **Mucin deposition in cardiac muscle**



# Scleromyxedema and coma (Dermato-neural syndrome)

Rongioletti et al, Br J Dermatol, 2001

- Worsening skin lesions with flu-like prodromes, fever, dysarthria, seizures, and **coma**
- Recovery over 1 month with supportive therapy or **death**
- Encephalopathy of obscure pathogenesis
- Brain autopsy non-contributory
  - gliosis, no mucin



Rongioletti F, personal collection

# Scleromyxedema and coma (Dermato-neural syndrome)

## Viral infections can act as a trigger?

Case Reports > [Eur J Neurol](#). 2021 Aug;28(8):e65-e66. doi: 10.1111/ene.14886.

Epub 2021 May 20.

### Two patients with dermatoneuro syndrome after influenza A infection

[Galia Valentinova Anguelova](#)<sup>1</sup>, [Korné Jellema](#)<sup>1</sup>, [Sander Wagemakers](#)<sup>2</sup>, [Ron Peters](#)<sup>3</sup>

Case Reports > [JAAD Case Rep](#). 2021 Dec;18:99-102. doi: 10.1016/j.jdcr.2021.10.027.

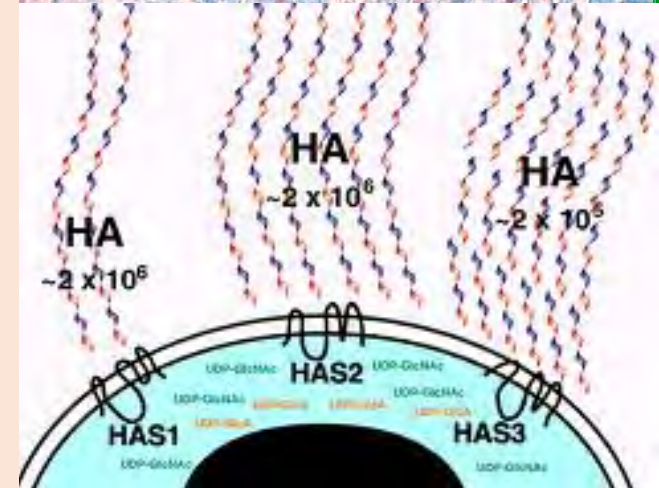
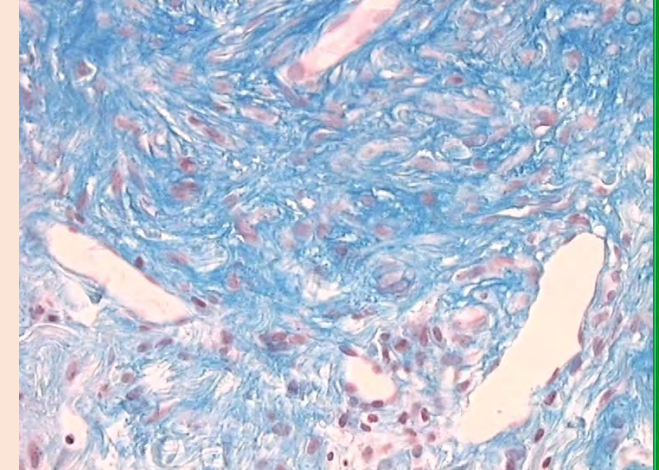
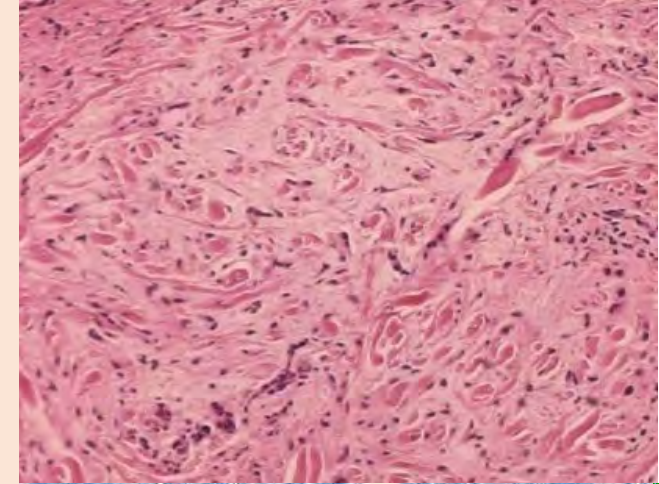
Epub 2021 Nov 6.

### SARS-CoV-2: A potential trigger of dermatoneuro syndrome in a patient with scleromyxedema

[Mike Fritz](#)<sup>1</sup>, [Daniel Tinker](#)<sup>2</sup>, [Alex W Wessel](#)<sup>3</sup>, [Gabriela M Morris](#)<sup>2</sup>, [Linda Goldenberg](#)<sup>4</sup>, [Mark Fesler](#)<sup>4</sup>, [Lokesh Rukmangadachar](#)<sup>5</sup>, [M Yadira Hurley](#)<sup>2</sup>

# Pathogenesis of scleromyxedema

- Increased serum Ig (mono or polyclonal) or cytokines (IL-1, TNF, TGF $\beta$ ) stimulate mucin synthesis and fibroblast proliferation



## ORIGINAL ARTICLE

## Increased frequency of interleukin-4 and reduced frequency of interferon- $\gamma$ and IL-17-producing CD4<sup>+</sup> and CD8<sup>+</sup> cells in scleromyxedema

F. Kalli,<sup>1</sup> M. Cioni,<sup>2,3</sup> A. Parodi,<sup>1</sup> T. Altosole,<sup>1</sup> F. Ferrera,<sup>1</sup> G. Barra,<sup>4</sup> R. De Palma,<sup>5,6</sup> D. Fenoglio,<sup>1,6</sup> G. Filaci,<sup>7,8,†</sup> F. Rongioletti<sup>3,9,\*,†</sup>

<sup>1</sup>Centre of Excellence for Biomedical Research, University of Genoa, Genoa, Italy

<sup>2</sup>Section of Dermatology, DISSAL, University of Genoa, Genoa, Italy

<sup>3</sup>Section of Pathology, Department of Surgical and Morphological Sciences, University of Genoa, Genoa, Italy

<sup>4</sup>Department of Precision Medicine, Università della Campania "L. Vanvitelli", Napoli, Italy

<sup>5</sup>Institute of Protein Biochemistry, CNR, Napoli, Italy

<sup>6</sup>Department of Internal Medicine, University of Genoa- IRCCS Ospedale Policlinico San Martino, Genoa, Italy

<sup>7</sup>Department of Internal Medicine and Centre of Excellence for Biomedical Research, University of Genoa, Genoa, Italy

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\*Correspondence: F. Rongioletti. E-mail: franco.rongioletti@unige.it

Table 1 Clinical data of scleromyxedema patients enrolled in the study

Patients #	Sex/Age	Systemic implications	Disease duration (months)	Activity level of disease (mRSSS/PGA)	Current therapy/ duration	Type of monoclonal gammopathy
1	M/71	Dysphagia	12	37/2	IVIg/7 months	MGUS IgG kappa
2	M/53	Carpal tunnel syndrome, arthralgias	12	55/3	IVIg + Systemic steroids/40 months	MGUS IgG lambda
3	F/70	Dermatoneuro syndrome	48	25/2	IVIg/6 months	MGUS IgG lambda
4	F/35	Arthralgias, peripheral neuropathy	22	105/4	IVIg, systemic steroids/4 months	MGUS IgG lambda
5	M/61	None	8	130/4	None	MGUS IgG lambda
6	F/52	Arthralgias, Dysphagia	19	28/2	IVIg/17 months	MGUS IgG lambda
7	M/54	Peripheral neuropathy	14	10/1	IVIg/32 months	MGUS IgG lambda
8	M/50	Dyspnoea	26	30/2	IVIg/23 months	MGUS IgG lambda
9	F/68	Dyspnoea	10	45/3	IVIg + Systemic steroids/10 months/13 months	MGUS IgG lambda
10	M/65	Dermatoneuro syndrome	20	8/1	IVIg/28 months	MGUS IgG lambda

mRSSS, modified Rodnan Score System for Scleromyxedema; PGA, Physician Global Assessment.

JEADV 2020, 34, 1082–1097

© 2019 European Academy of Dermatology and Venereology

# Conclusions: Abnormally high secretion of IL-4 a profibrotic cytokine

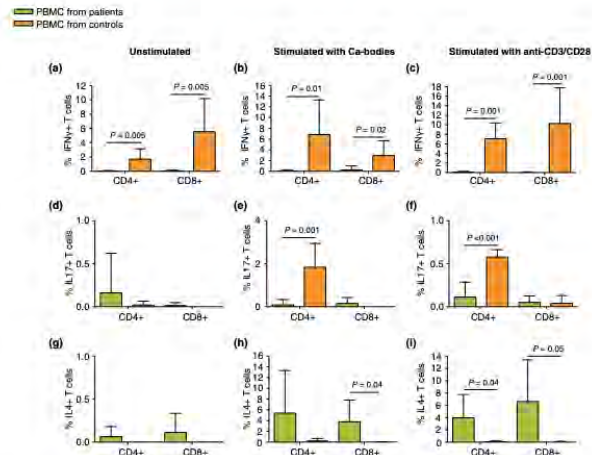


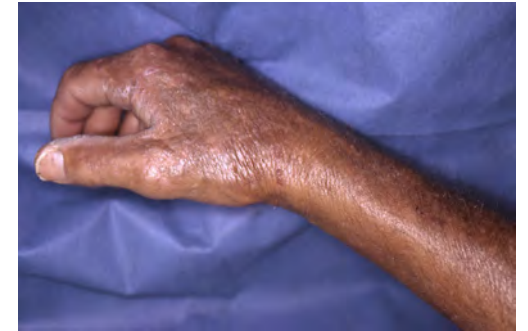
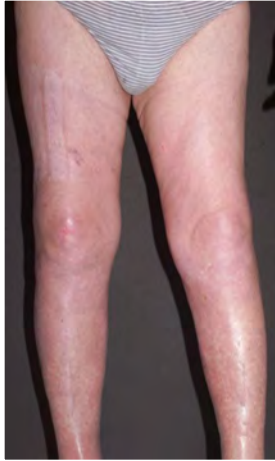
Figure 3 Scleromyxedema patients show a Th2 profile. PBMC obtained from peripheral blood of patients (green bars) and controls (orange bars) were analysed *ex vivo* in unstimulated conditions (a, d, g) and after stimulation with either Ca-bodies (b, e, h) or anti-CD3 and anti-CD28 mAbs (c, f, i).

# Pitfalls



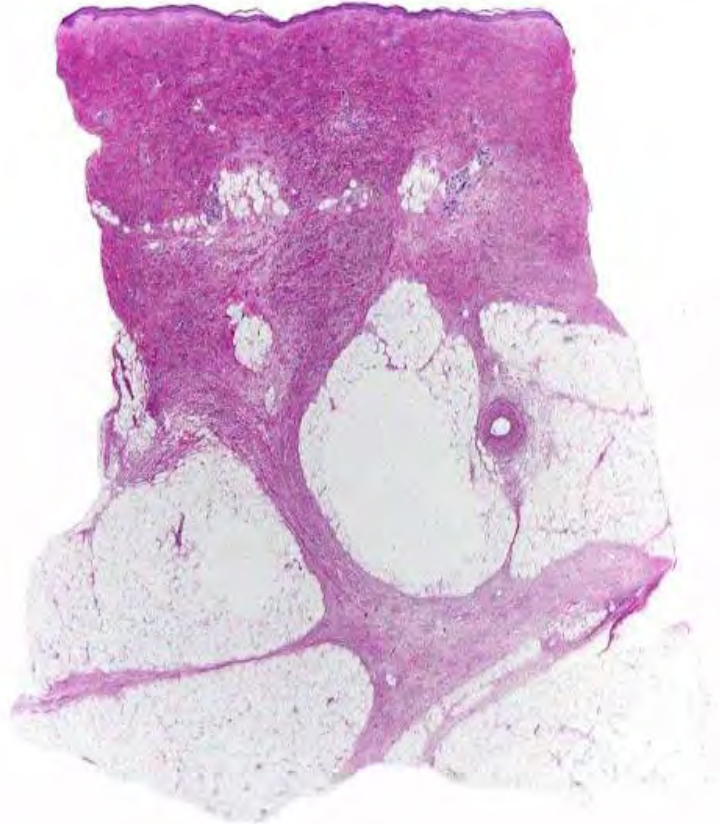
# Nephrogenic systemic fibrosis

(Scleromyxoedema-like disease in renal-dialysis)

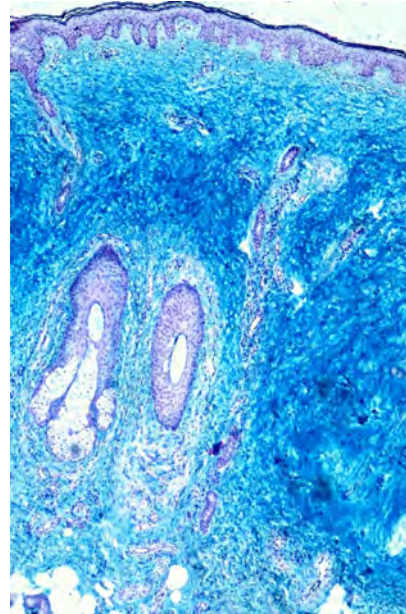


- Sclerodermoid mucinosis
- Skin infiltration, sclerosis and hyperpigmentation on extremities sparing the face
- Firm nodules and confluent plaques without papules more similar to **eosinophilic fasciitis**
- **Severe renal failure**
- Exposure to **gadolinium-based contrast** agents which stimulate monocytes to secrete pro-fibrotic cytokines (TGF- $\beta$ , VEGF, PDGF)

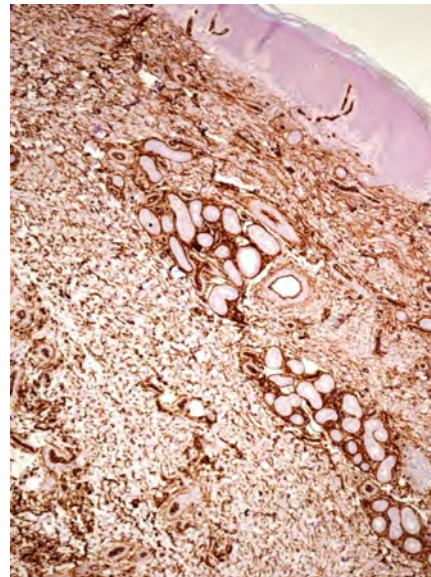
# Nephrogenic systemic fibrosis



**Dermal and septal fibrosis with thickened collagen bundles extending into subcutis**

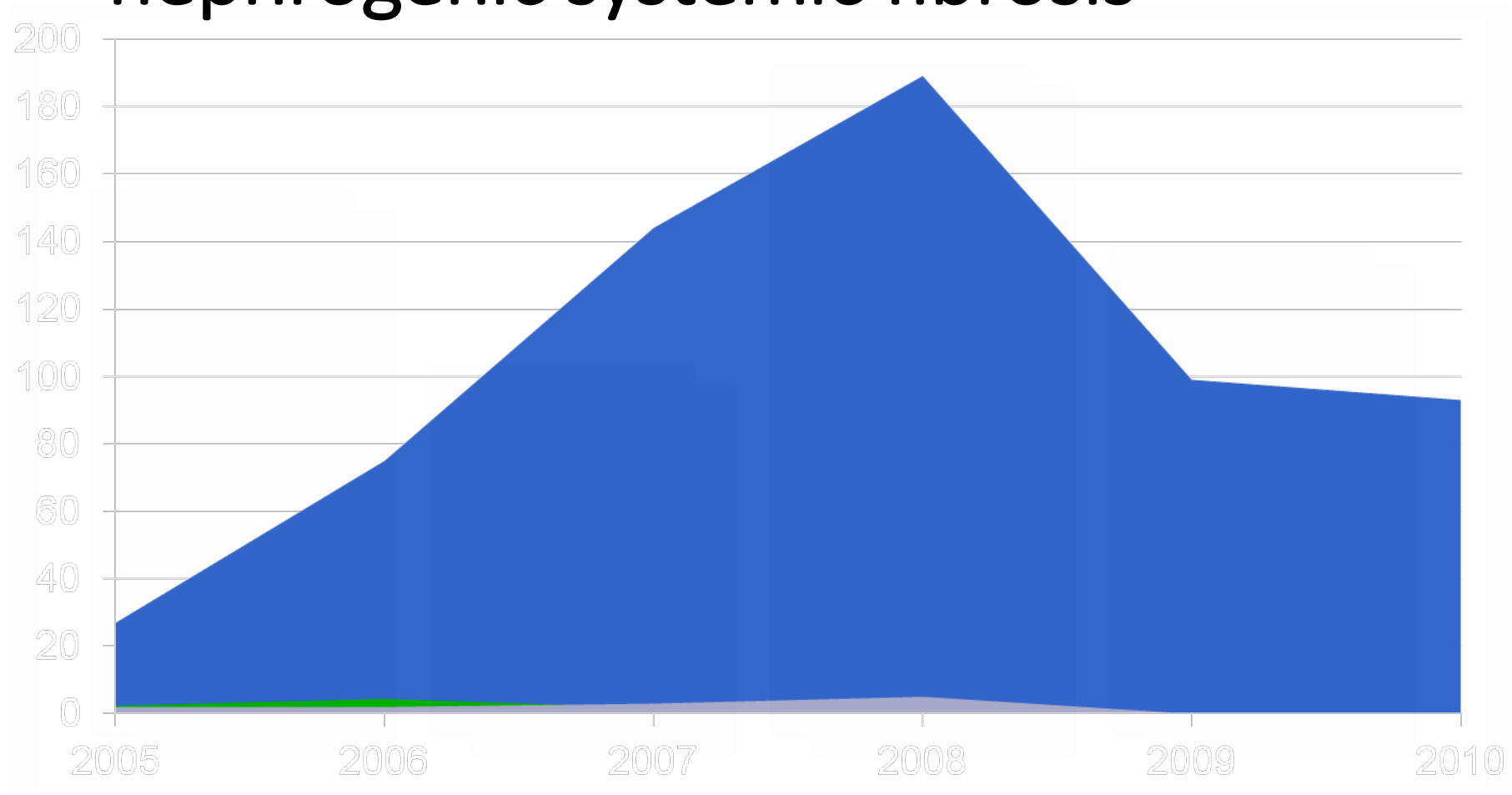


**Diffuse, deep deposition of mucin throughout reticular dermis**



**Proliferation of dermal fibroblasts and dendritic cells (CD34+) (tram-tracking)**

# Decreased incidence of nephrogenic systemic fibrosis



**Due to restricted use of high risk gadolinium  
and application of macrocyclic chelates**

# Lichen Myxedematosus (Papular mucinosis)

Rongioletti & Rebra, JAAD,2001

- SCLEROMYXEDEMA

- LOCALIZED LICHEN MYXEDEMATOSUS



Variations on a same background...

# Lichen Myxedematosus (Papular mucinosis)

Rongioletti & Rebra, JAAD,2001



- SCLEROMYXEDEMA

Generalized papular and sclerodermoid

Mucin with fibrosis

Monoclonal gammopathy  
(systemic involvement)

Chronic disabling course  
Unpredictable prognosis

- LOCALIZED LICHEN MYXEDEMATOSUS

Papular eruption  
(nodules, plaques)

Mucin without fibrosis

No monoclonal gammopathy or  
systemic involvement

Good prognosis



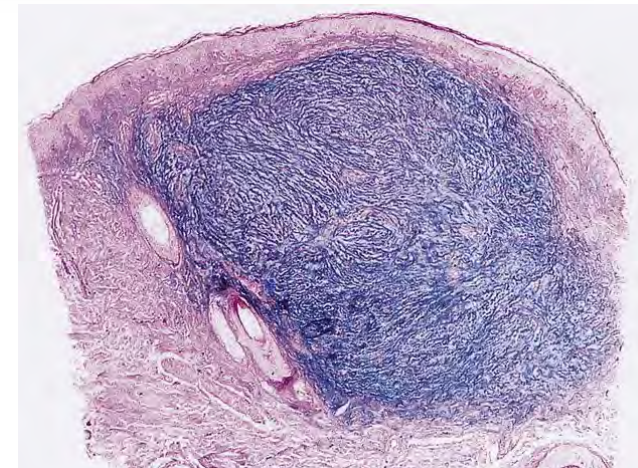
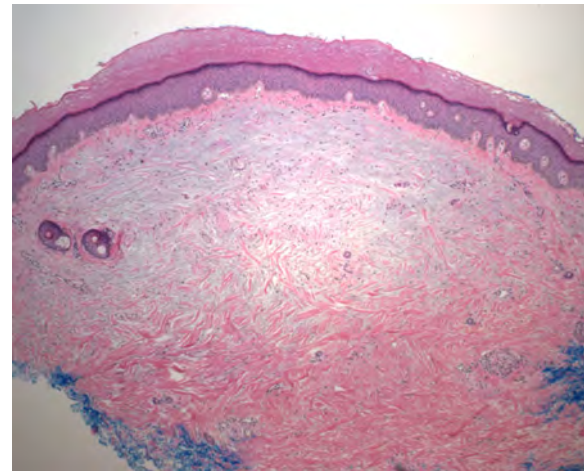
# Different subtypes of localized lichen myxedematosus

- **Acral persistent papular mucinosis**
- **Discrete type**
- **Nodular lichen myxedematosus**

# Acral persistent papular mucinosis

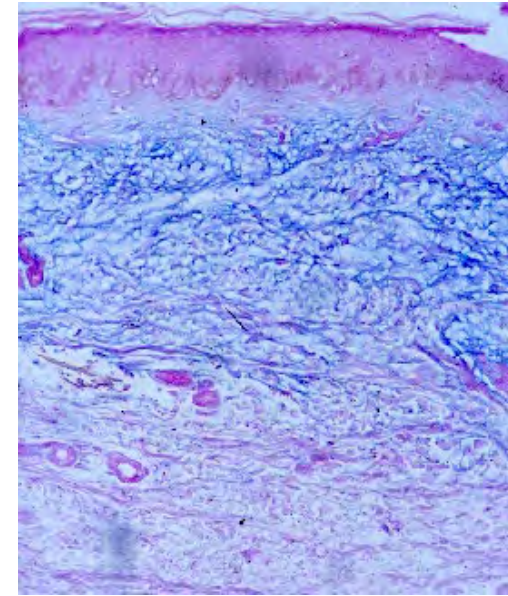
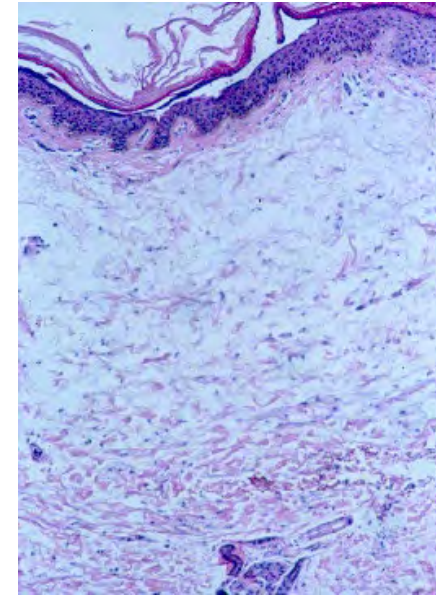
Rongioletti et al, Arch Dermatol 1986

- Small papules localized exclusively on the back of the hands, wrists and extensor aspects of distal forearms
- Focal superficial deposition of mucin in upper dermis with grenz zone
- Neither fibroblast proliferation nor fibrosis



# Acral persistent papular mucinosis

Rongioletti et al, Arch Dermatol 1986





# Localized diffuse lichen myxedematosus (discrete-type)

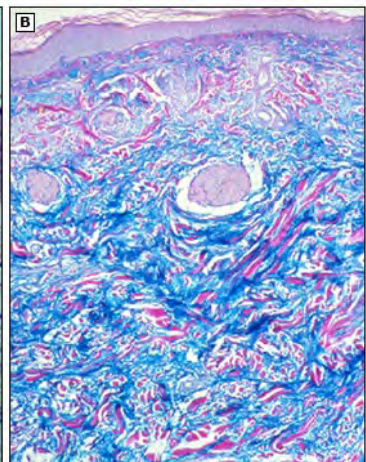
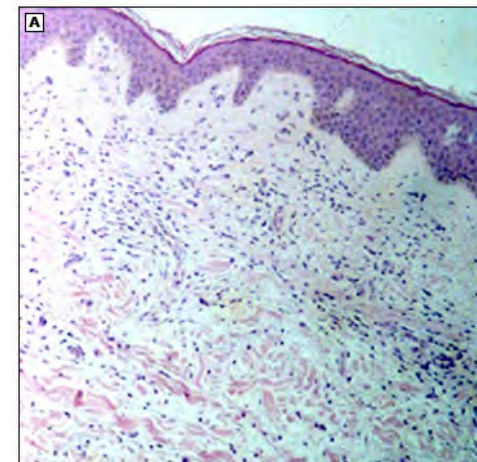
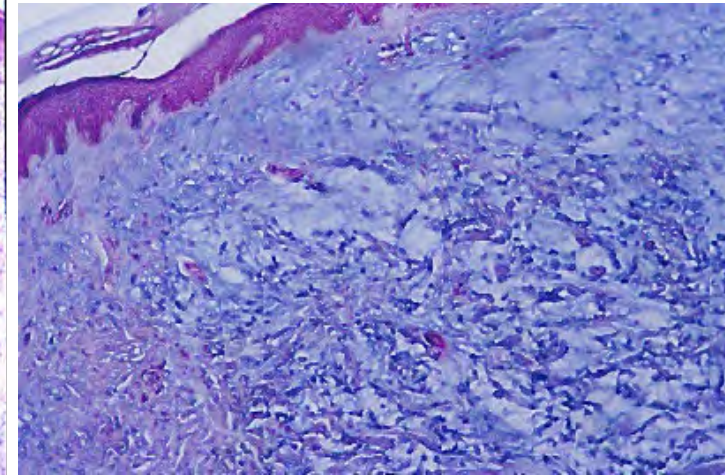
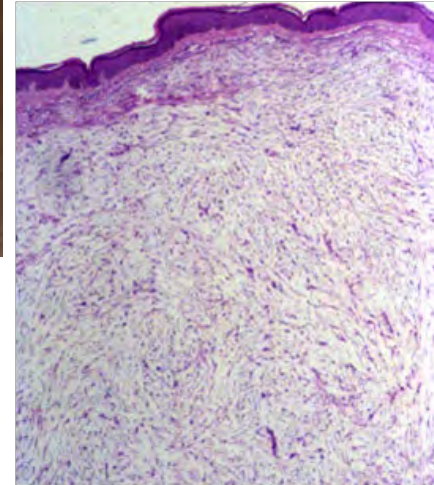


Chronic eruption  
of papules  
from just a few  
to hundreds on  
trunk and limbs  
in the absence of sclerosis and  
systemic involvement

# Localized lichen myxedematosus (discrete type)



**Diffuse deposition of mucin in the upper/mid dermis with variable fibroblast proliferation and without fibrosis**



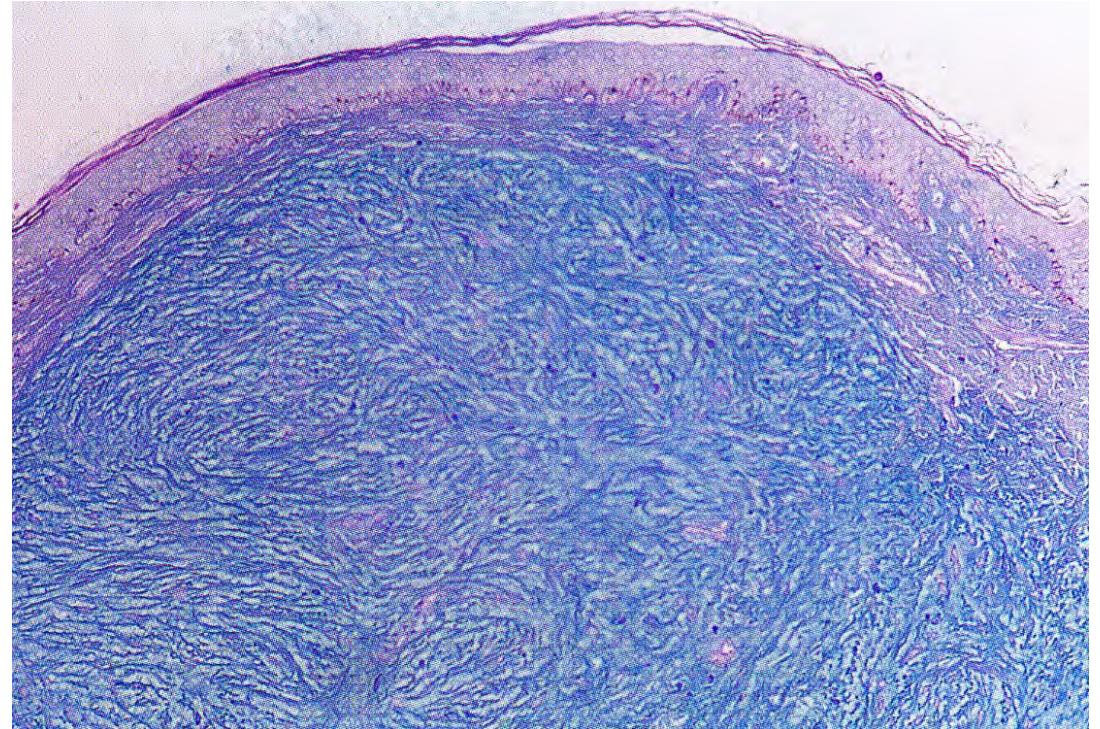
Rongioletti F. Uptodate. WoltersKluwer 2017

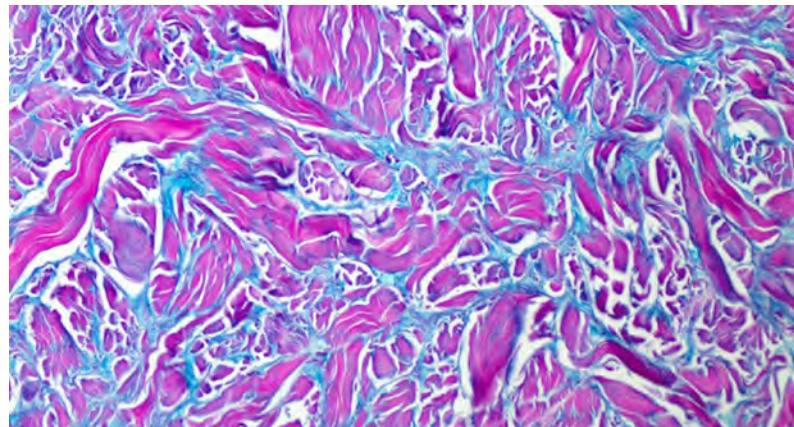
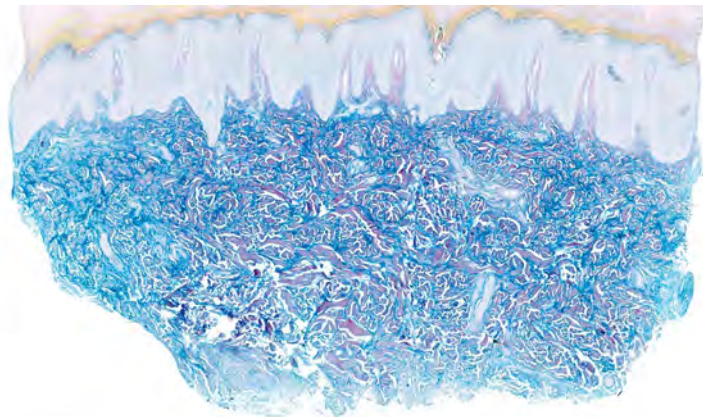
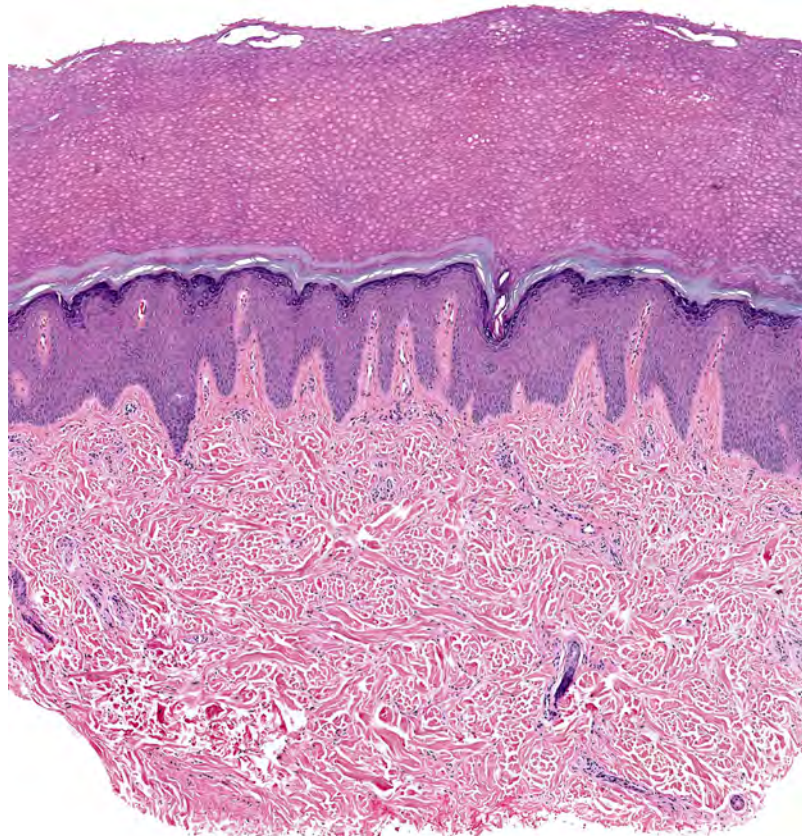
Mitteldorf C, Rongioletti F, J Eur Acad Dermatol Venereol 2017

# Nodular lichen myxedematosus



- Multiple, asymptomatic nodules larger than 1 cm distributed on the trunk and limbs





EXTRAORDINARY CASE REPORT

## Nodular-Type Lichen Myxedematosus: A Rare Variant With Exclusive Involvement of the Hands—Report of Two Cases With a Comprehensive Review of the Literature

Lorenzo Cerroni, MD\* and Franco Rongioletti, MD†

### CASE REPORTS

**Abstract:** Lichen myxedematosus (LM) is an uncommon cutaneous mucinosis characterized by the deposition of mucin and fibroblast proliferation in the dermis. This condition can be classified into 2 forms: a diffuse/generalized LM, also known as scleromyxedema, associated with monoclonal gammopathy and systemic implications, and a localized form, primarily affecting the skin. Within the localized form, nodular-type LM is a rare variant presenting as firm, skin-colored to pinkish mucinous nodules. In this article, we report 2 new cases of nodular-type LM with exclusive involvement of the hands and provide a comprehensive review of the diagnosis, histopathological aspects, and therapeutic considerations of this rare condition.

**Key Words:** lichen myxedematosus, cutaneous mucinosis, nodular-type lichen myxedematosus, pachydermodactyly

(*Am J Dermatopathol* 2024;46:36–39)

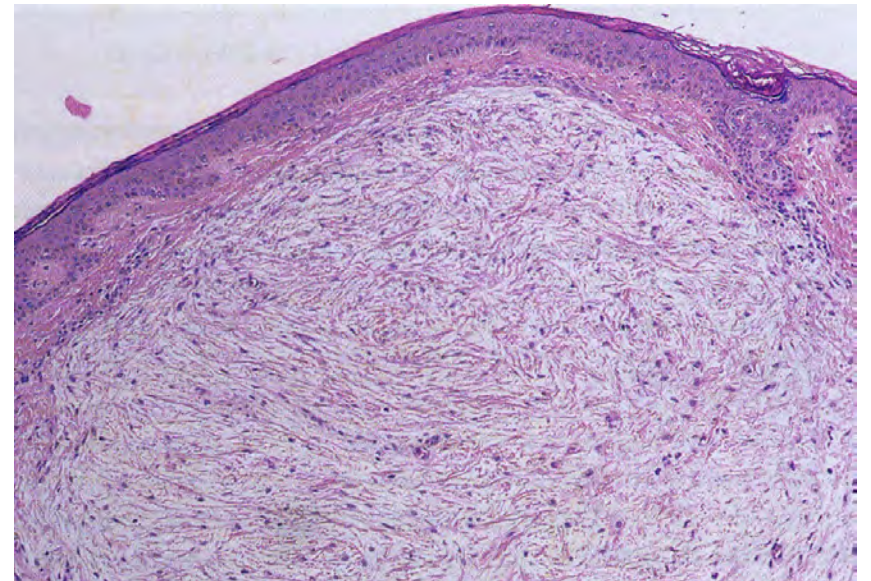
#### Case 1

A 29-year-old black man presented with asymptomatic, skin-colored nodules, and swelling on the extensor side of his fingers and back of the right hand (Fig. 1A). He had no significant medical history. There was no history of friction or rubbing. Laboratory tests, including thyroid function and gammopathy markers, were all within normal limits. Histopathology revealed abundant mucin deposition throughout all the dermis separating the thickened collagen bundles (Fig. 1B) in the absence of fibroblast proliferation (Fig. 1C). No inflammatory infiltrate was present. Colloidal iron stain confirmed interstitial mucin deposition (Fig. 1C). A diagnosis of nodular-type LM was established. Treatment of lesions with topical corticosteroids and topical calcineurin inhibitor was unsuccessful. Local injection of triamcinolone acetonide or hyaluronidase was proposed but given that his lesions were asymptomatic, further treatment was deferred.

# Nodular lichen myxedematosus




# Nodular lichen myxedematosus with exclusive hand involvement



Courtesy of D.Bessis

# Lichen Myxedematosus (Papular mucinosis)

Rongioletti & Rebra, JAAD, 2001

- **A distinction between scleromyxedema and localized lichen myxedematosus is important for prognosis and therapy**
  - **Localized lichen myxedematosus needs no therapy (“wait and see” approach)**
  - **Scleromyxedema is a disease with substantial morbidity/mortality that needs to be treated (IVIg)**
- 

# Scleredema(Buschke)

Rongioletti F.Mucinoses. In J. Bologna et al. Dermatology, Elsevier, 5th Ed. 2021

- Described by Pitford in 1876
- Symmetrical diffuse non-pitting induration of the upper part of the body
- Hands and feet spared
- Rare internal organ involvement
- Restriction of movements



# Scleredema



# Scleredema



# Classification of scleredema

(EDF/EADV S1-Guidelines of Sclerosing Diseases of the Skin )

1

**Type 1 associated  
with febrile  
illness/infections**

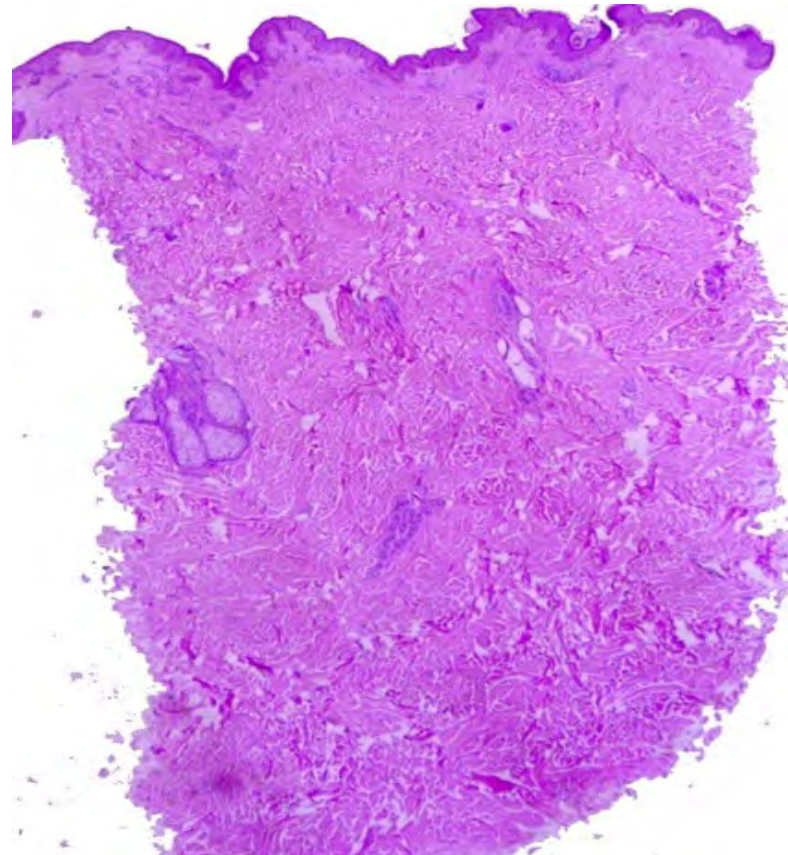
2

**Type 2 associated  
with  
paraproteinemias**

3

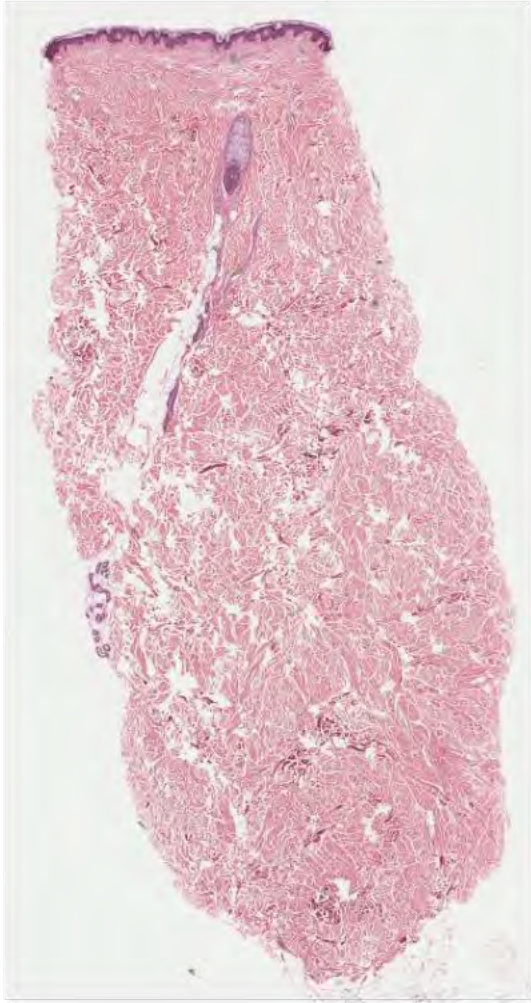
**Type 3 associated  
with diabetes  
(diabetic  
scleredema)**

# Scleredema

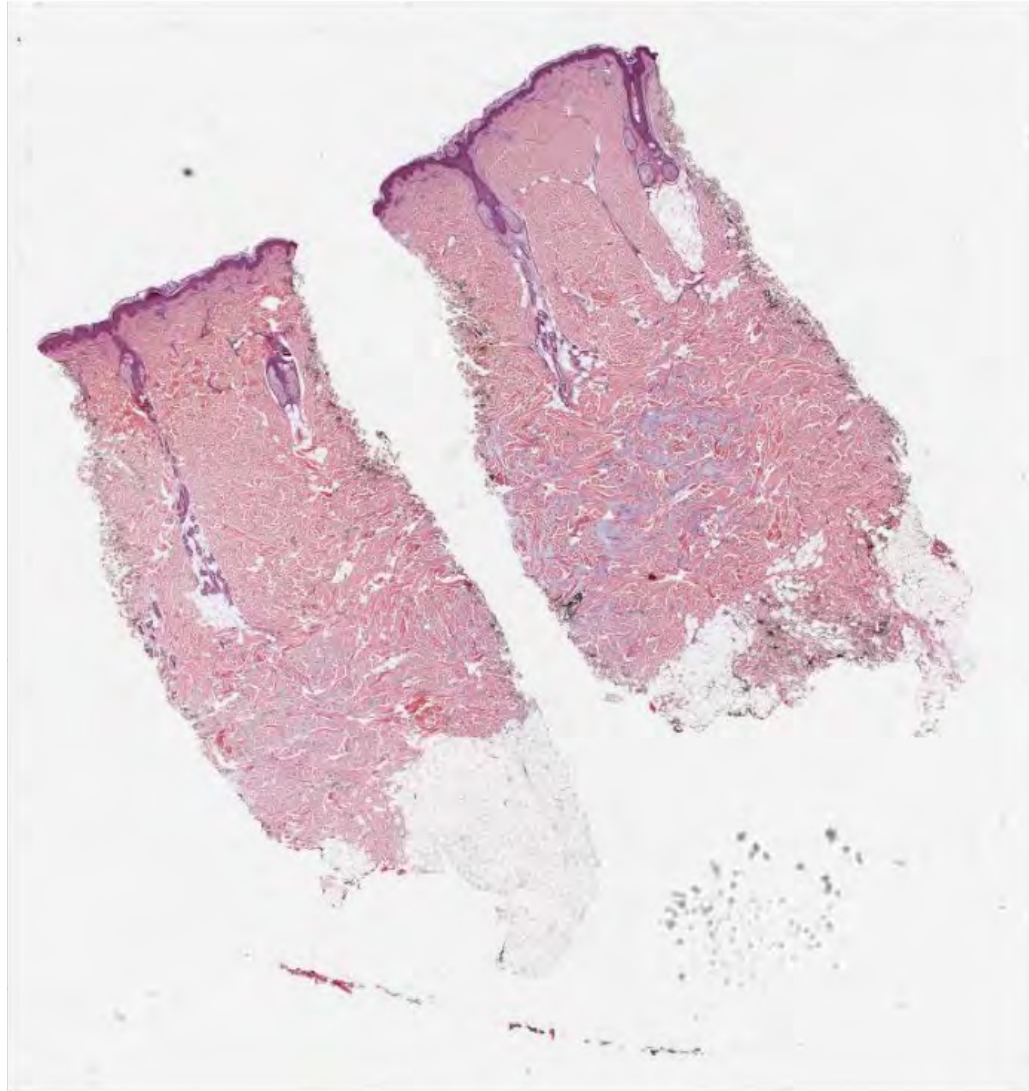


**The dermis is 3-4 times thicker than normal**

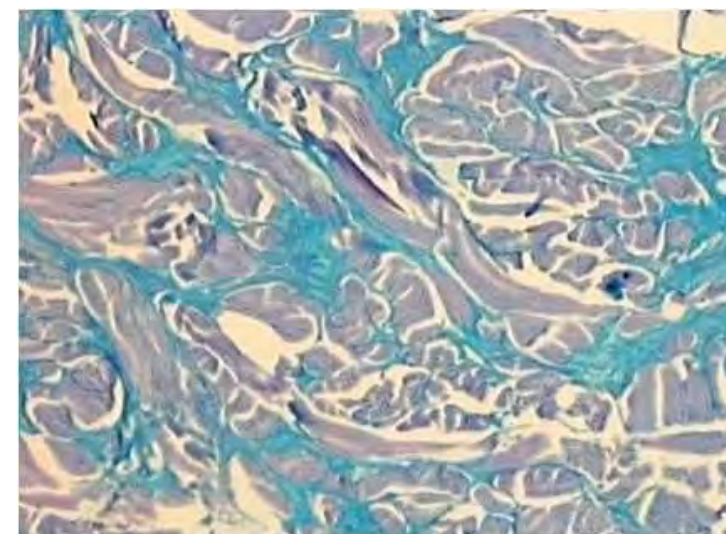
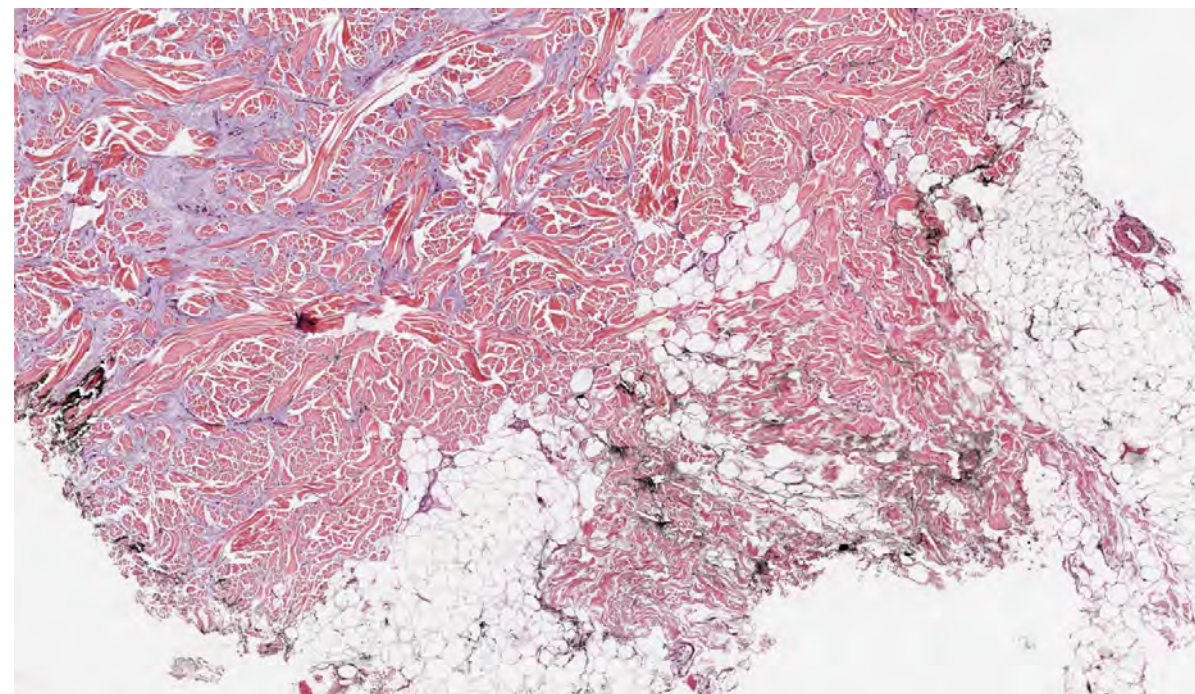
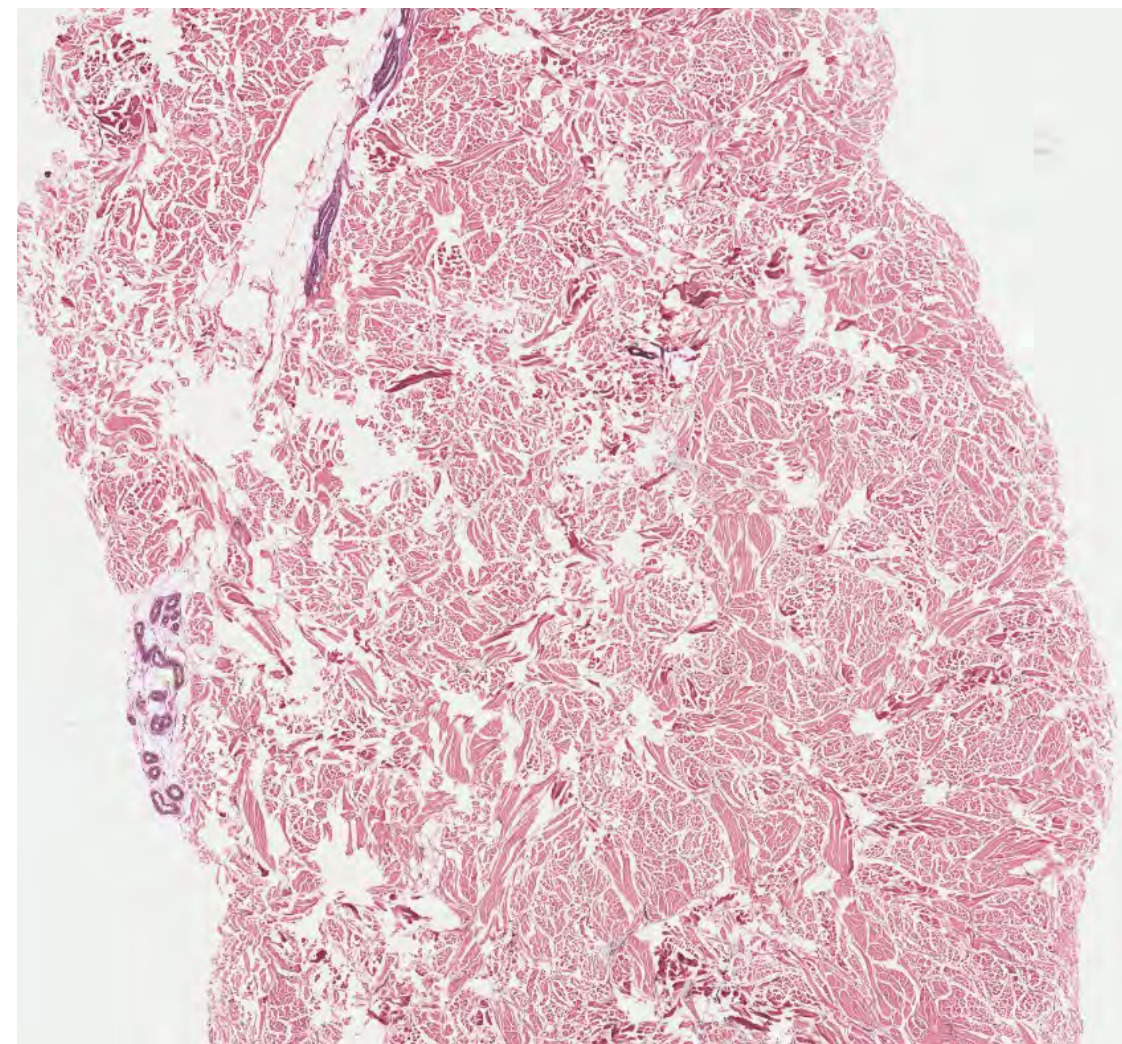
# Scleredema



**Dermis is thickened at the expense of the subcutis**



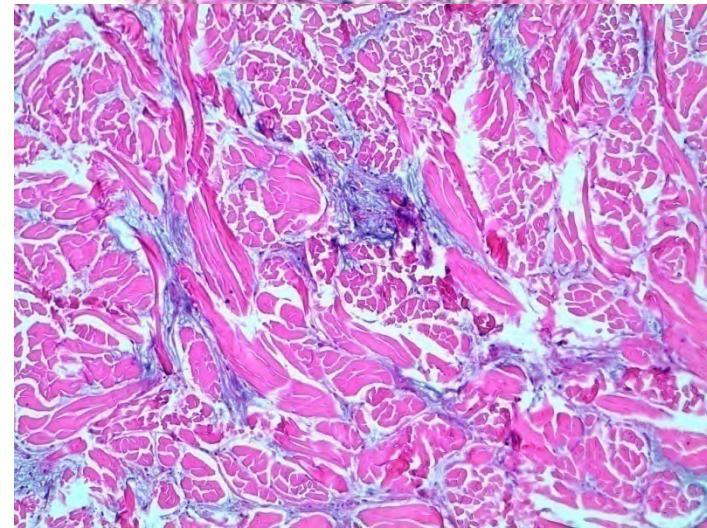
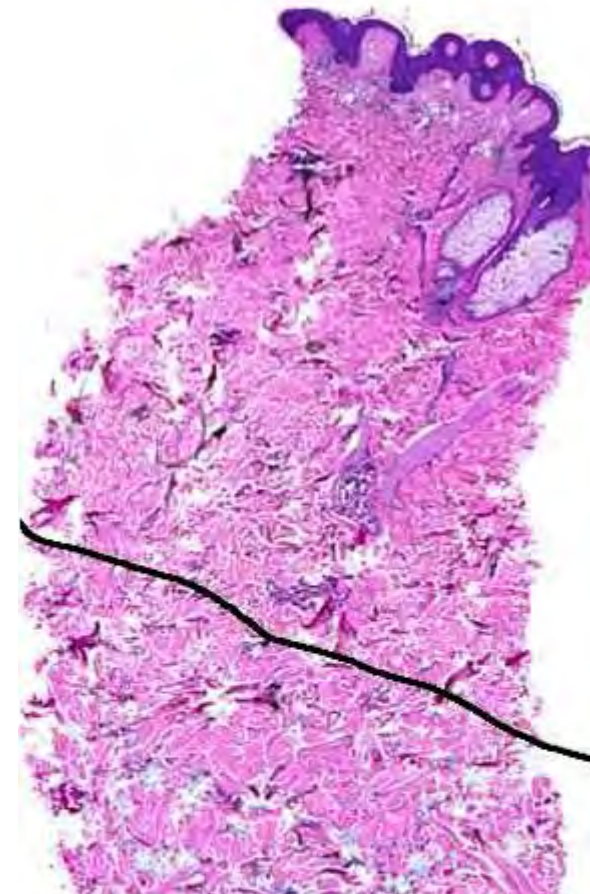
# Scleredema



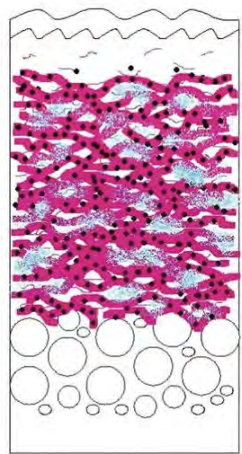
- Increased interstitial mucin between fenestrated collagen bundles in deep dermis

# Scleredema

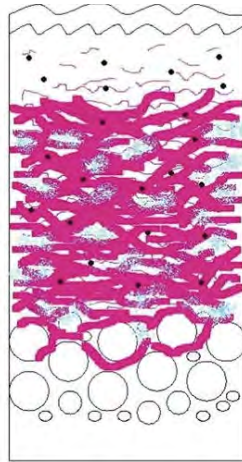
- Epidermis is normal
- The reticular dermis is thickened (a sweat gland above the black line)
- Increased interstitial mucin between fenestrated collagen bundles in deep dermis
- A superficial biopsy would not demonstrate the abnormality
  - No fibroblast proliferation
  - No inflammatory infiltrate
  - No vascular alteration



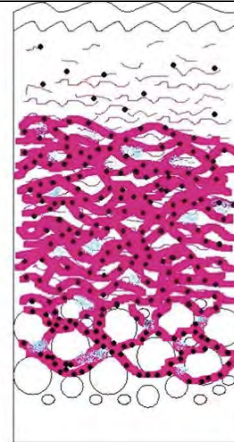
Disease	CLINICAL MANIFESTATION/PATHOLOGICAL FEATURES
 <p><b>SCLERO MYXEDEMA</b></p>	 
 <p><b>SCLEREDEMA</b></p>	 
 <p><b>NEPHROGENIC SYSTEMIC FIBROSIS</b></p>	 






Scleromyxedema



Scleredema



Nephrogenic  
systemic fibrosis

	<b>Collagen bundles</b>
	<b>Mucin deposits</b>
	<b>Fibroblasts</b>

# Localized (pretibial) myxedema (Thyroid dermopathy)

- Indurated waxy plaques on the shins with peau d'orange appearance
- Sign of hyperthyroidism (Graves' disease)
- Often following treatment of thyroid
- Frequent association with exophthalmos and thyroid acropachy
- Role of TSH receptor antibodies



# Localized (pretibial) myxedema

1. non-pitting edema (43%)



2. plaque (27%)



3. nodular (18%)



4. elephantiasis (5%)



# “Monster”elephantiasis-like (pretibial)myxedema



Courtesy B.Cribier, Strasbourg

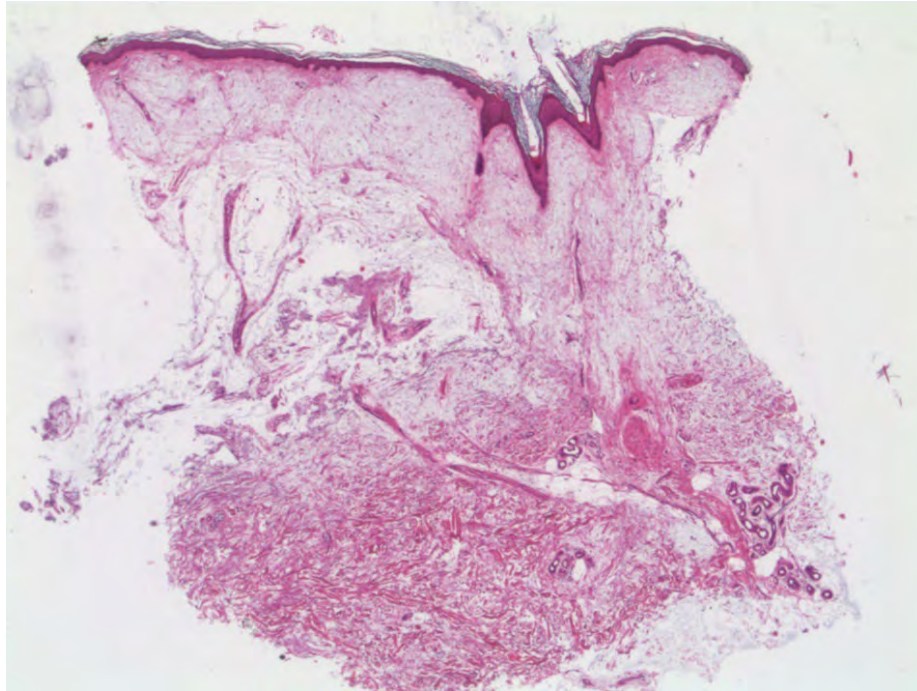


# Thyroid dermopathy



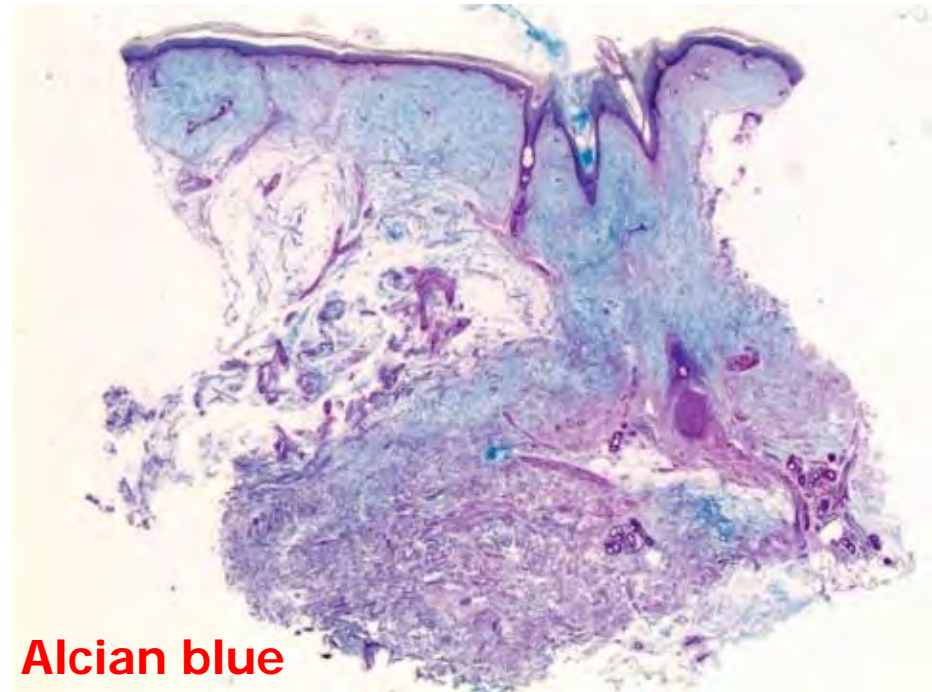
Courtesy of Shyam Verma

# Localized (Pretibial) myxedema



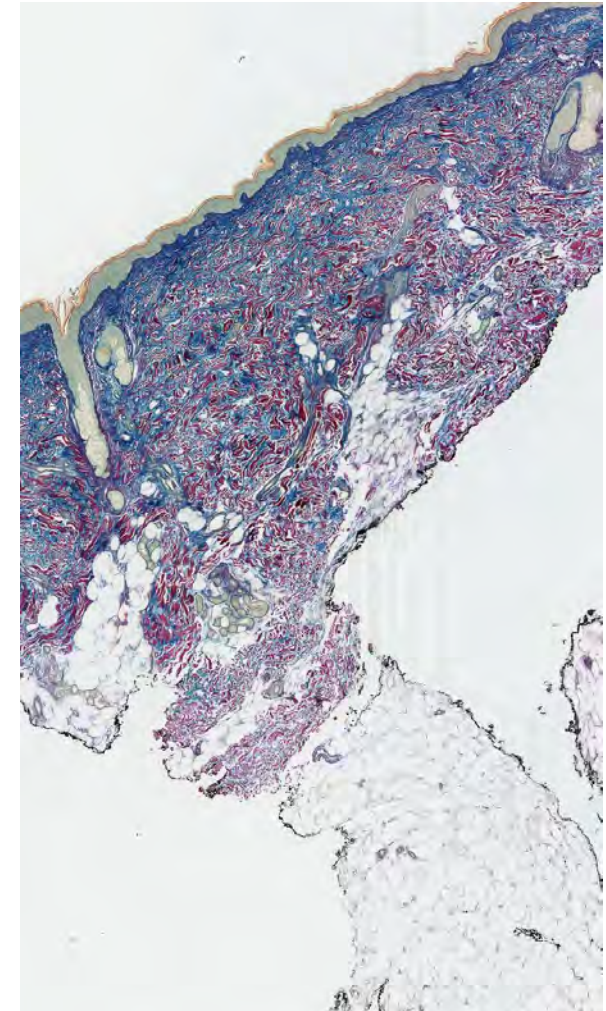
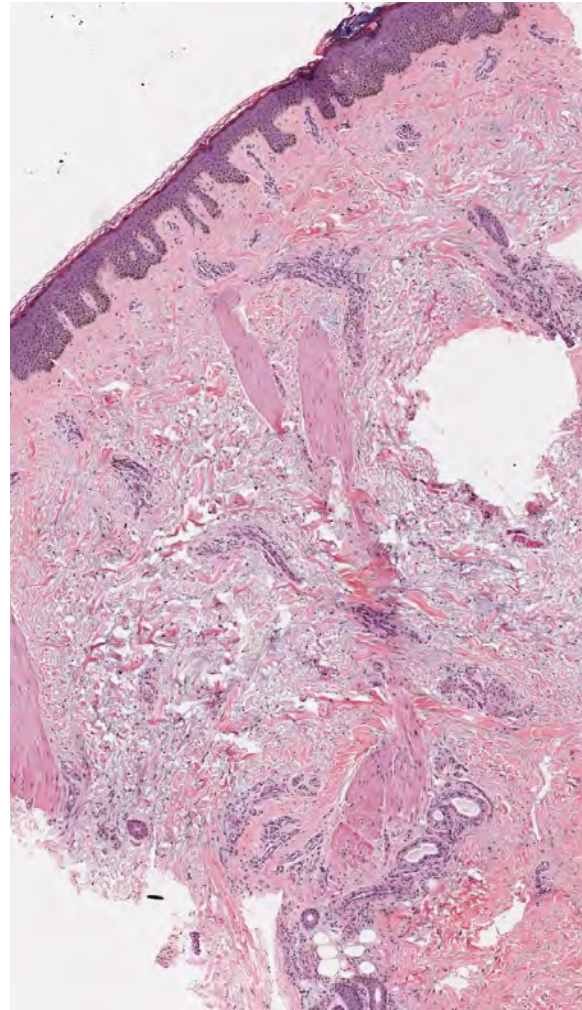
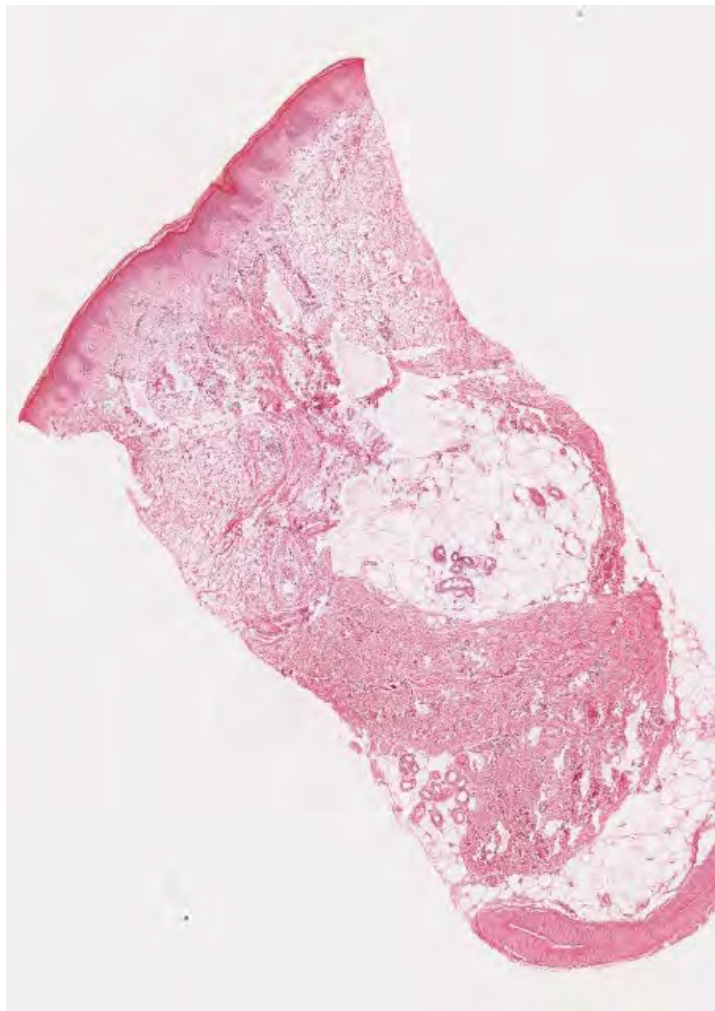
Diffuse deposit of mucin throughout the entire reticular dermis , sometimes in subcutis

Associated findings:  
Orthohyperkeratosis  
Acanthosis  
Follicular plugging  
> Mast cells

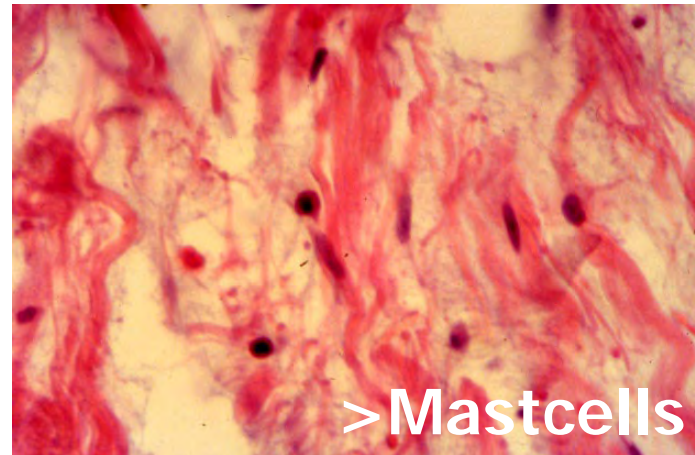
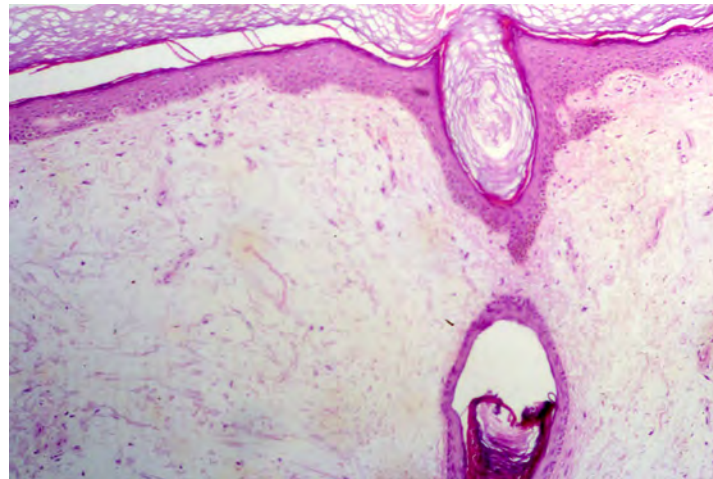
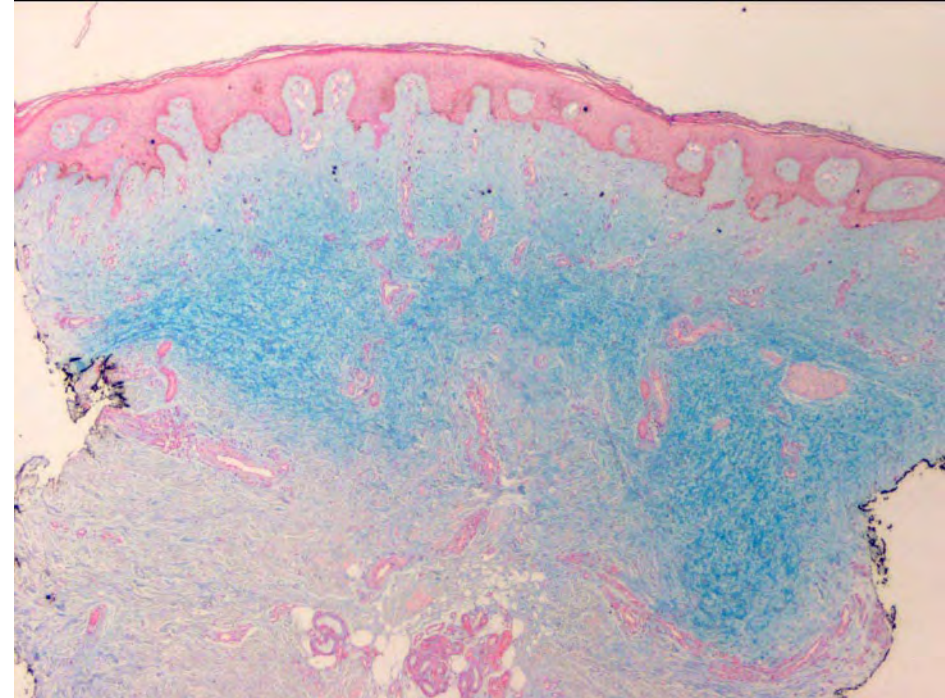
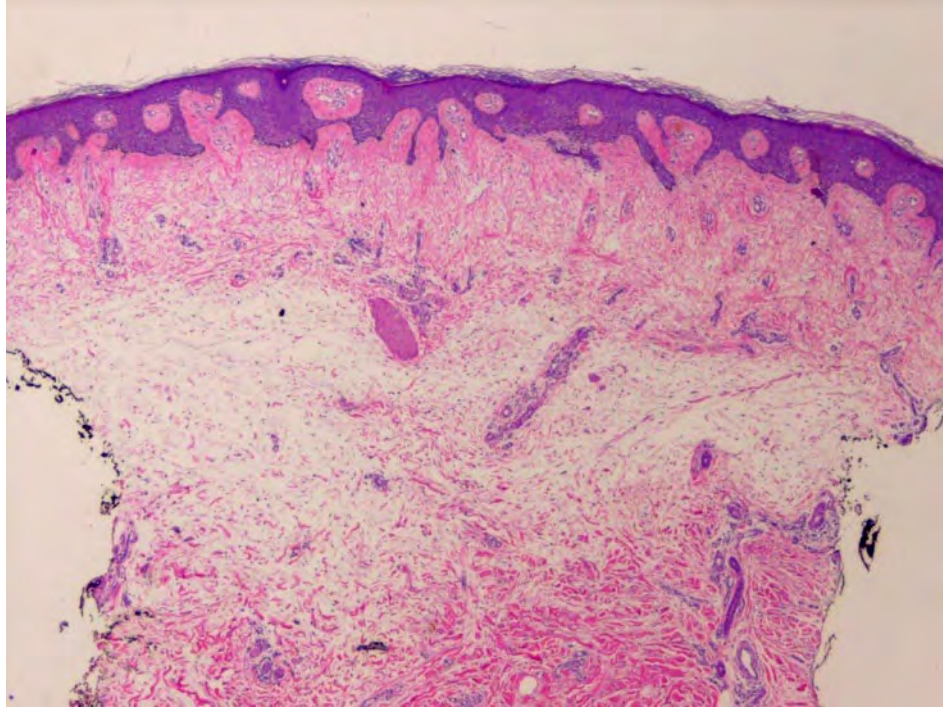


Alcian blue

# Localized (pretibial) myxedema



Diffuse mucin deposition throughout all reticular dermis with only slight fibroblast proliferation



**Diffuse deposit  
of mucin in the  
mid/lower  
dermis**

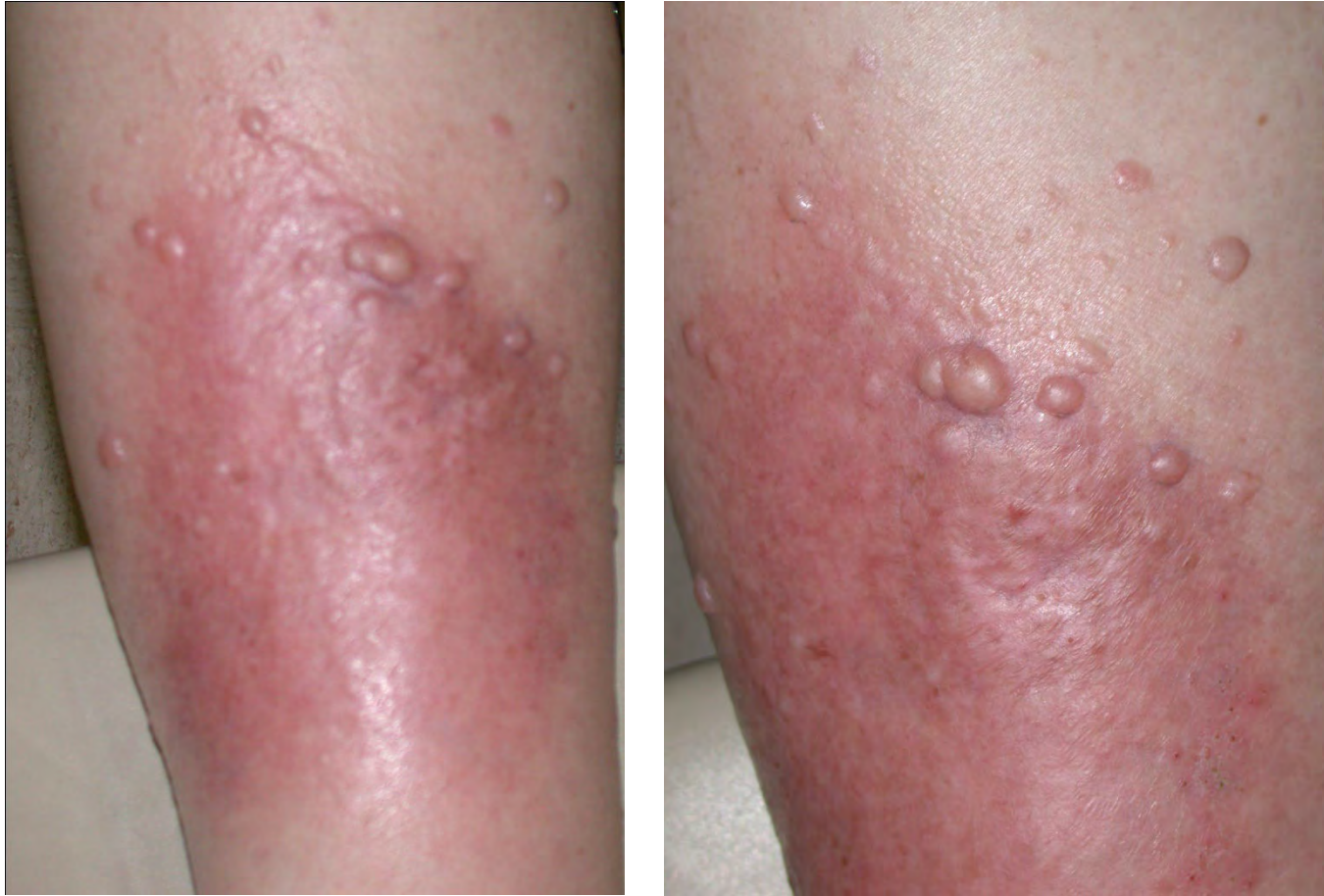
**Associated  
findings:  
hyperkeratosis  
follicular plugging  
> mast-cells**

# Pitfalls



# Obesity-associated lymphedematous mucinosis

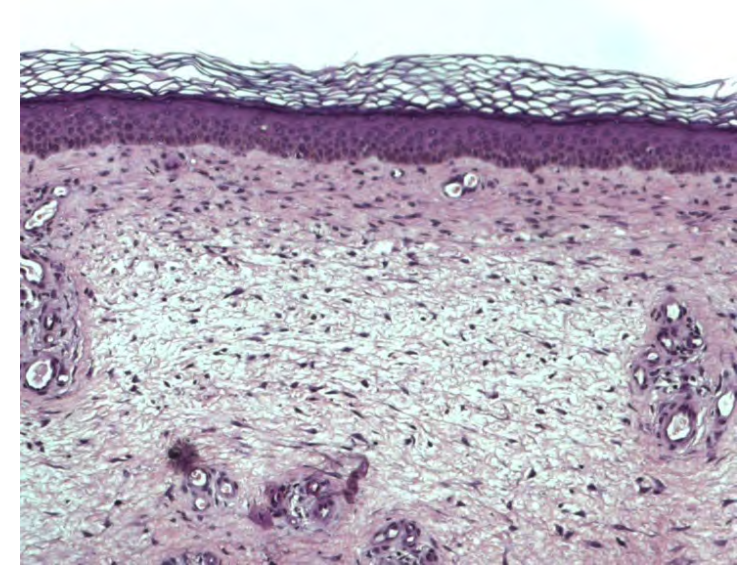
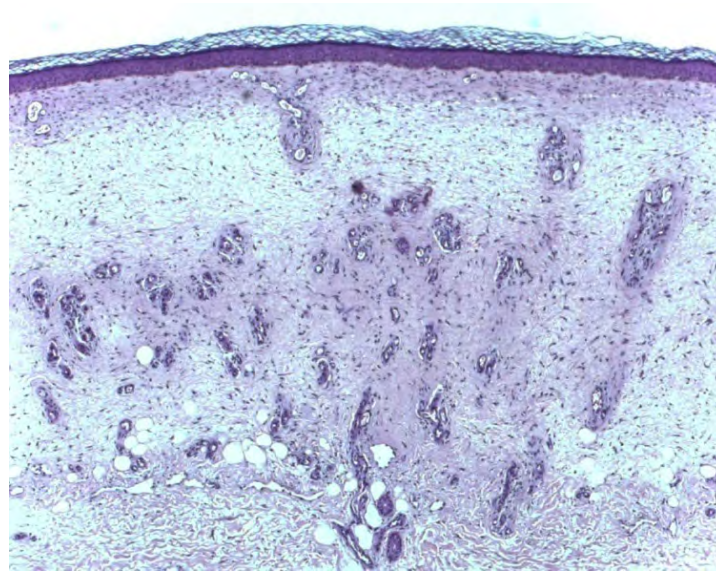
Rongioletti F, et al. J Cutan Pathol. 2009;36



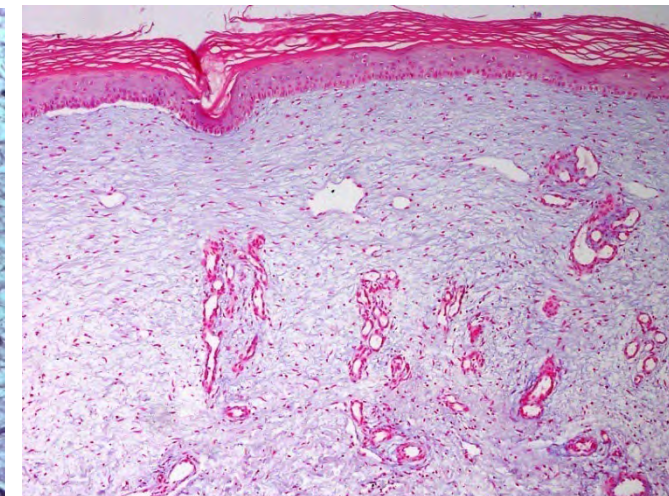
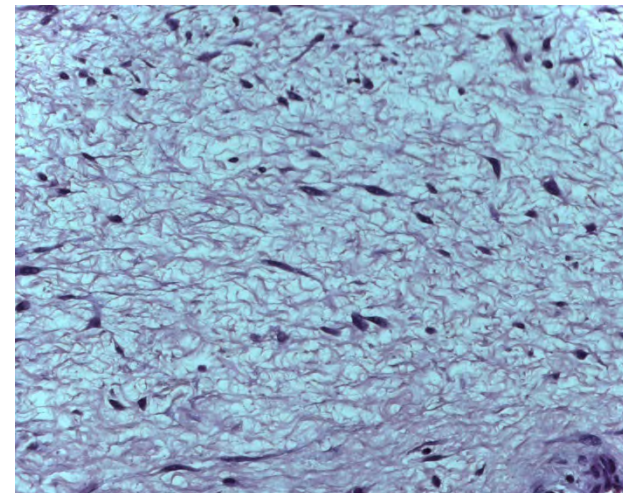
**Bilateral semitranslucent papules and nodules on the shin  
of obese euthyroid patients with swollen pitting oedema of the legs**

# Obesity-associated lymphoedematous mucinosis

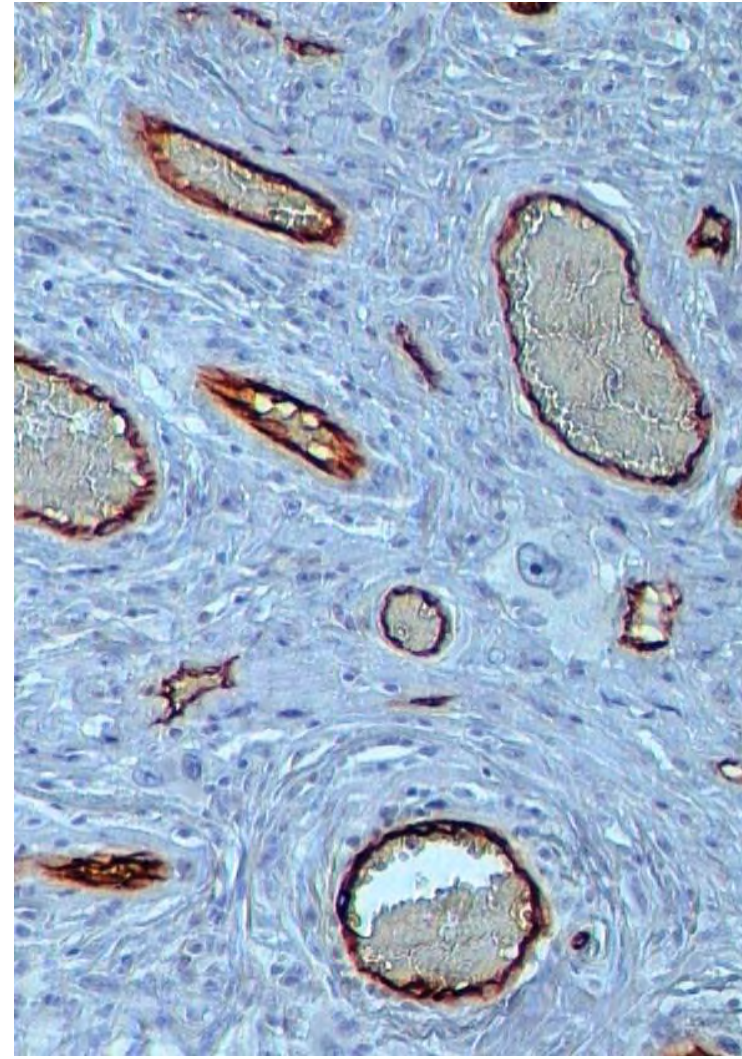
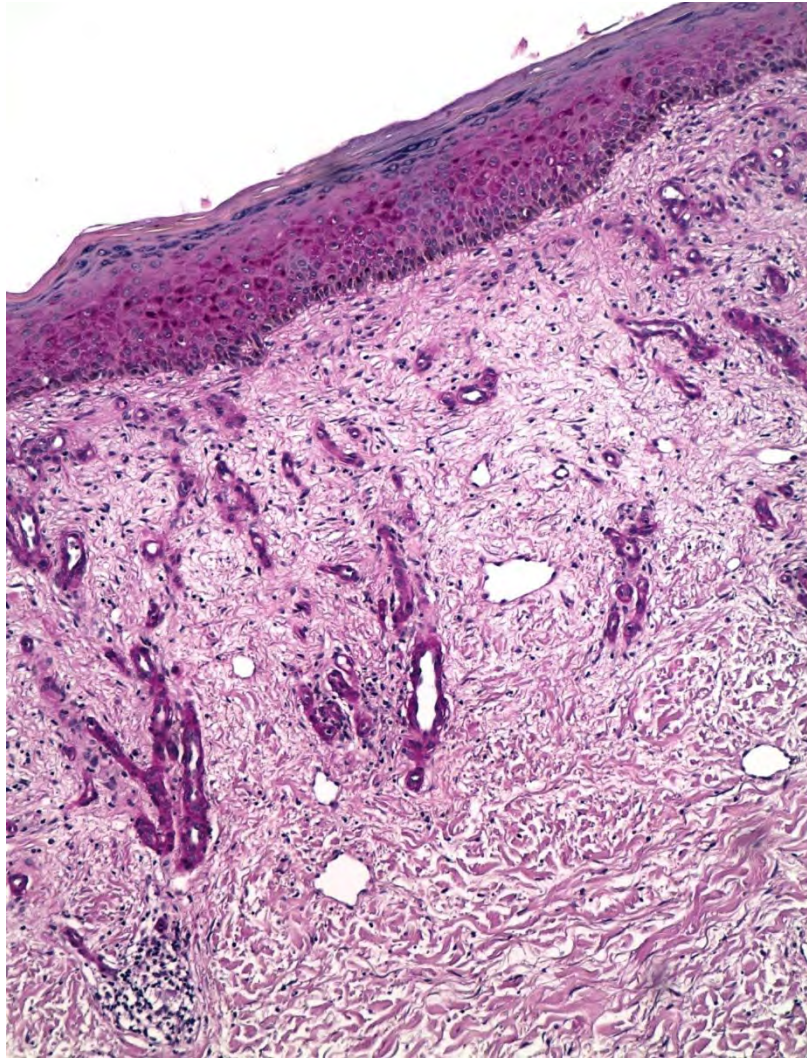
Ferrelli C, Pinna AL, Pilloni L, Rongioletti F. Dermatopathology (Basel). 2018



**Mucin (oedema) in the superficial dermis**  
**Epidermal atrophy with effacement of the rete ridge**  
**Angioplasmia with vertical running of vessels**  
**Stellate or linear fibroblasts**



# Increase of lymphatic vessels

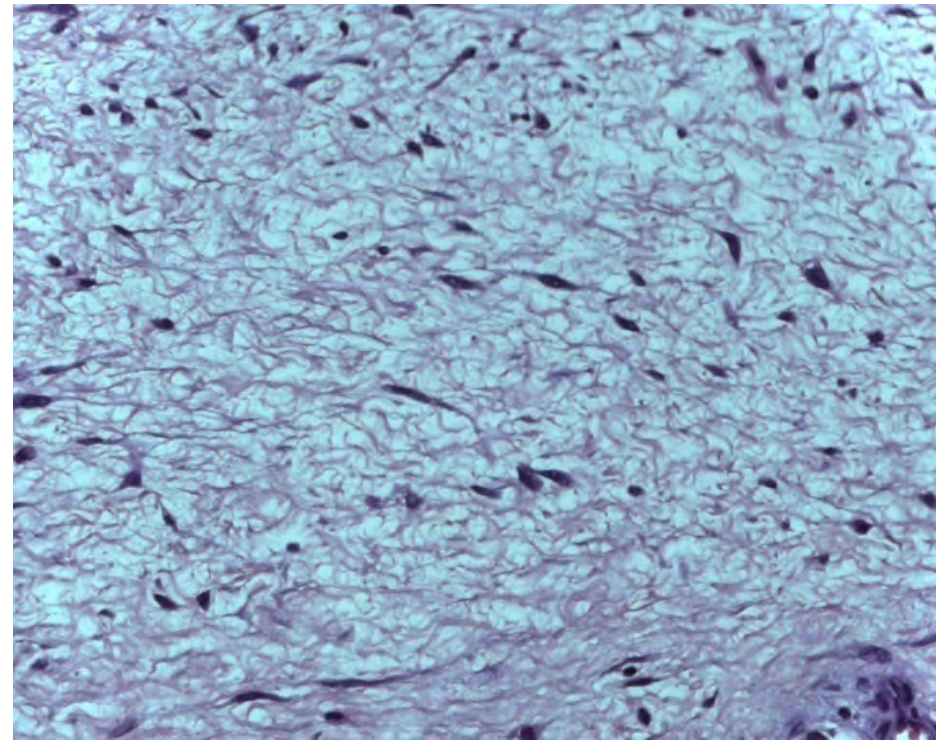
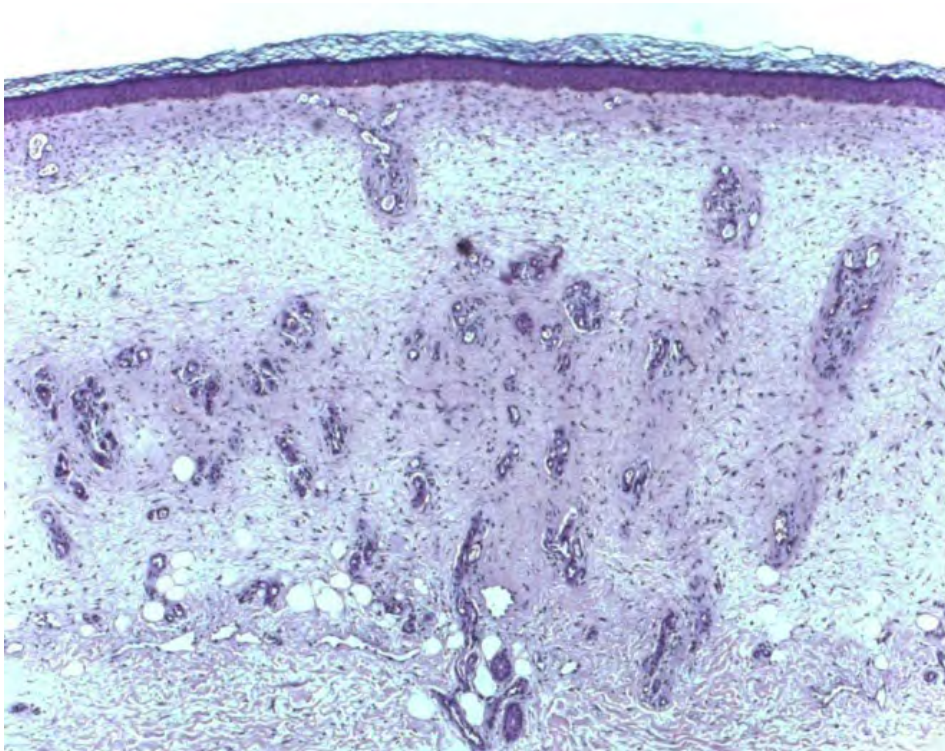


**D2-40**

# Pathogenesis of dermal mucin deposition

Rongioletti F. J Cutan Pathol 2009; Pugashetti R et al J Cutan Pathol 2010.

- **Accumulation of lymphatic fluid and extravascular plasma protein can stimulate fibroblasts to synthesize and deposit glycosaminoglycans**



# Differential diagnosis

- Obesity-associated lymphoedematous mucinosis in euthyroid

*Epidermal atrophy*

*Angioplasmia*

*Oedema with Mucin in superficial dermis*

*Stellate or linear fibroblasts*

*Hemosiderin*

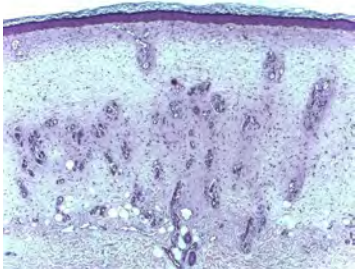
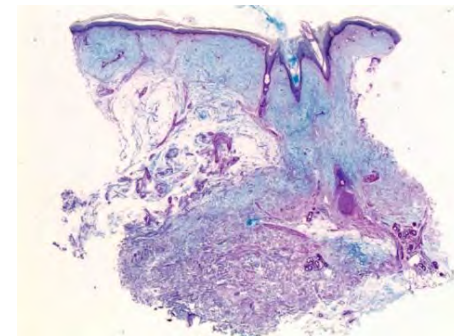
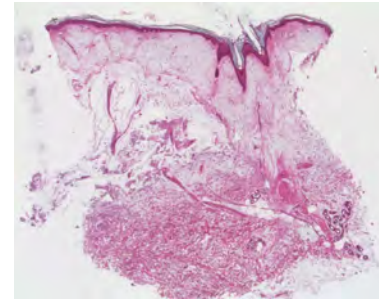
- "Pretibial myxedema" in Graves disease

*Acanthosis,*  
*hyperkeratosis*

*No angioplasmia or hemosiderin*

*Mucin throughout the reticular dermis*

*Mastcells*



## Obesity-Associated Lymphedematous Mucinosis: Two Further Cases and Review of the Literature

Caterina Ferrelli<sup>a</sup> Anna Luisa Pinna<sup>a</sup> Luca Pilloni<sup>b</sup> Marialuisa Corbeddu<sup>a</sup>  
Franco Rongioletti<sup>a</sup>

<sup>a</sup>Section of Dermatology, Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy; <sup>b</sup>Section of Pathology, Department of Surgery, University of Cagliari, Cagliari, Italy

- Pretibial mucinosis is associated with morbid obesity (IBM>40) and lymphoedematous features of the legs
- A low-calorie diet coincided with a clinical improvement and partial resolution of the vesicles, papules and nodules of pretibial mucinosis.



Before diet



After diet

# Reticular erythematous mucinosis (REM) (Plaque-like cutaneous mucinosis)

Rongioletti F Br J Dermatol 2013;169.



Erythematous, papular, or plaque-like eruption in the midline of the back or chest with net-like configuration in middle-aged women

# Reticular erythematous mucinosis (REM) (Plaque-like cutaneous mucinosis)

Rongioletti F. Br J Dermatol 2013;169.



# Main characteristics of REM

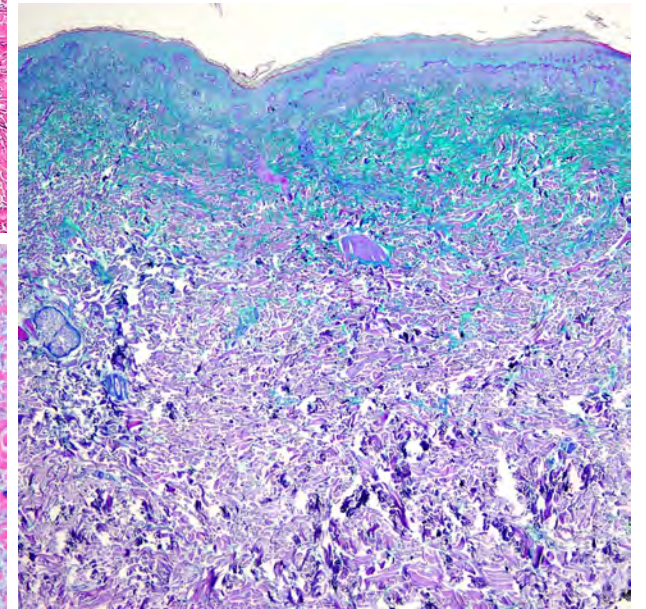
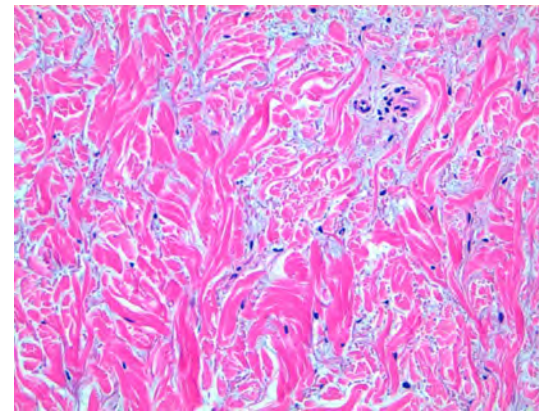
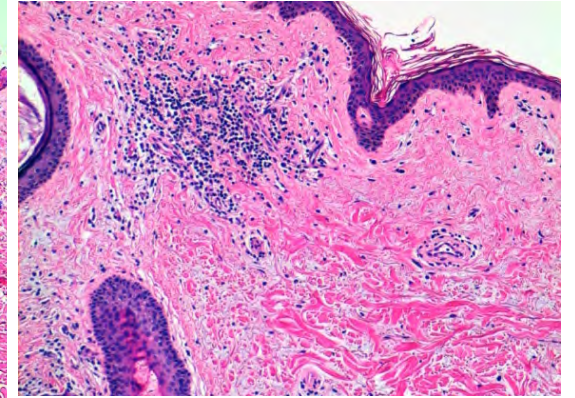
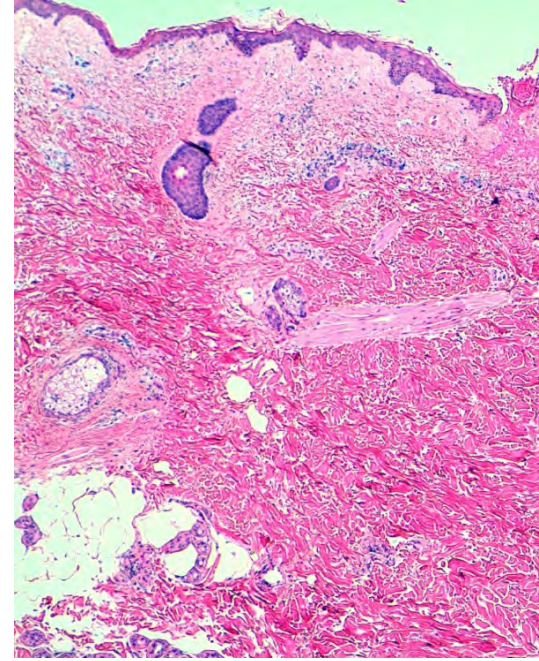
- Reticular pattern with involvement of the midline of the chest and back
- Predilection for middle-aged women
- Controversial relationship with photosensitivity
- Possible association with other conditions such as malignancies and thyroid dysfunctions



REM in breast cancer (Personal collection)

# Histopathology of REM

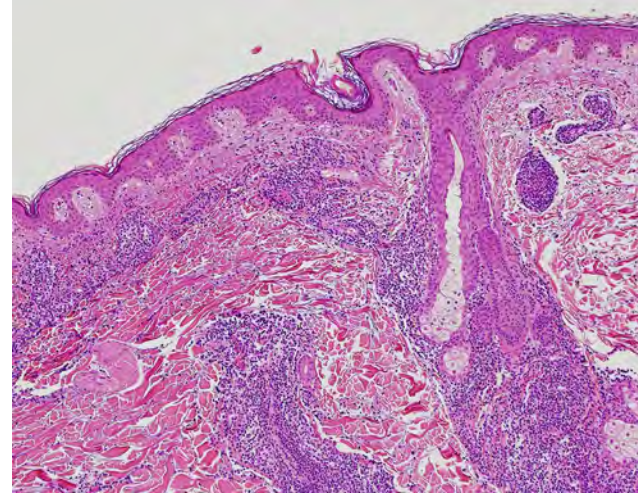
- Interstitial, diffuse mucin deposition in the upper/mid dermis
- Superficial and mid-dermal perivascular and sometimes perifollicular T-lymphocytic infiltrate
- No interface changes



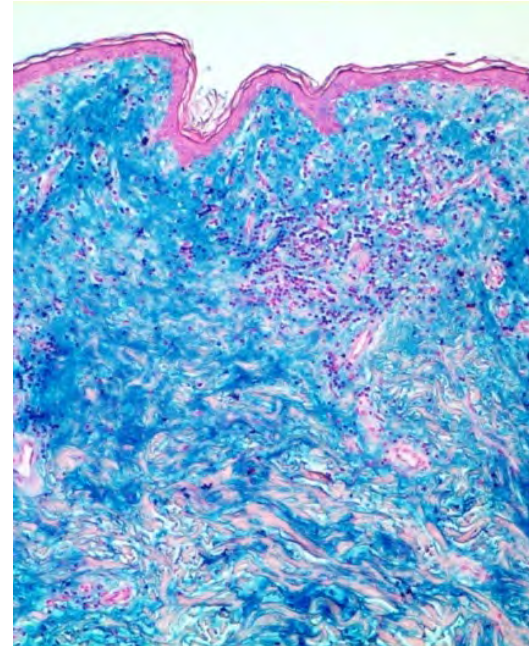
# Differential with lupus erythematosus tumidus



Annular plaques with a succulent appearance on face and less frequently on trunk



More dense infiltrate



More diffuse mucin

ORIGINAL ARTICLE

**Reticular erythematous mucinosis: histopathological and immunohistochemical features of 25 patients compared with 25 cases of lupus erythematosus tumidus**

E. Cinotti,<sup>1,2\*</sup> V. Merlo,<sup>3</sup> W. Kempf,<sup>3</sup> C. Carli,<sup>4</sup> J. Kanitakis,<sup>5</sup> A. Parodi,<sup>1</sup> F. Rongioletti<sup>1-4</sup>

<sup>1</sup>Section of Dermatology, Department of Health Sciences (DISSAL), University of Genoa and IRCCS San Martino-IST University Hospital, Genoa, Italy

<sup>2</sup>Section of Dermatology, University Hospital of Saint-Etienne, Saint-Etienne, France

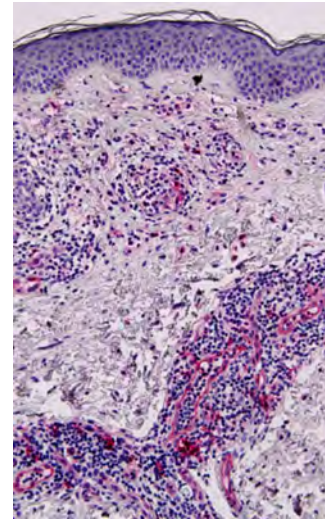
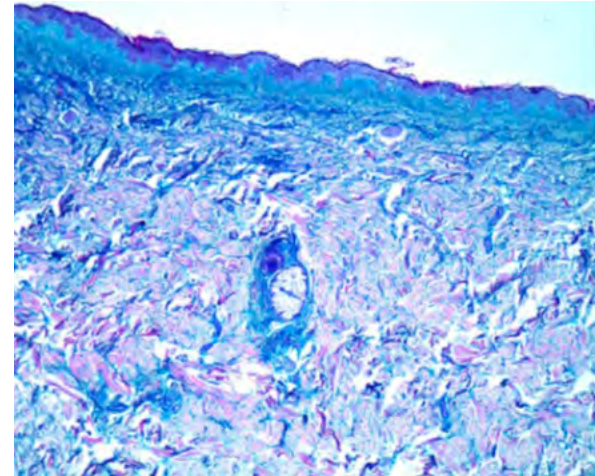
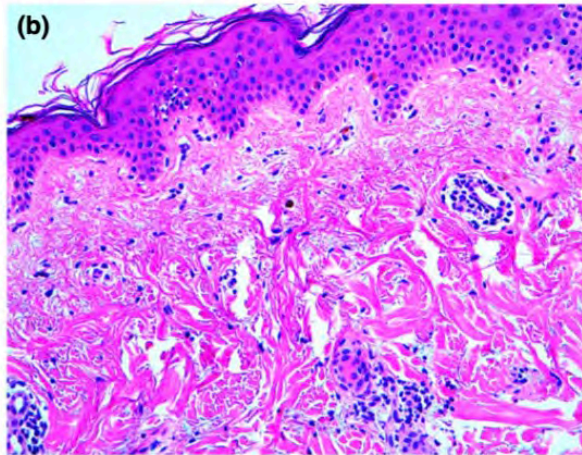
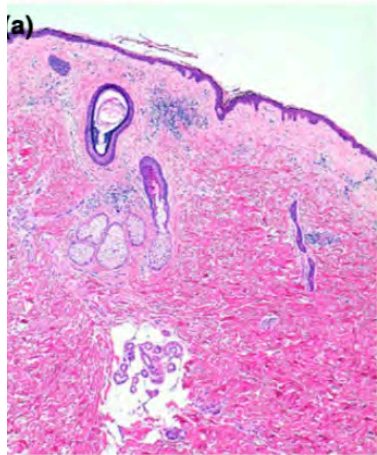
<sup>3</sup>Kempf and Plätz, Histological Diagnostics and Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

<sup>4</sup>Department of Surgical and Diagnostic Sciences (DISC), Pathology Unit University of Genoa and IRCCS San Martino-IST University Hospital, Genoa, Italy

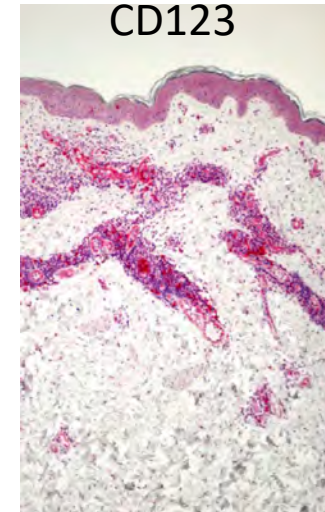
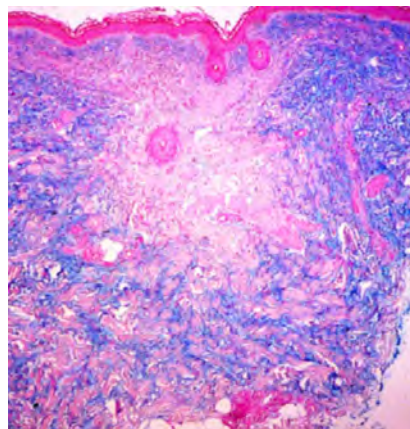
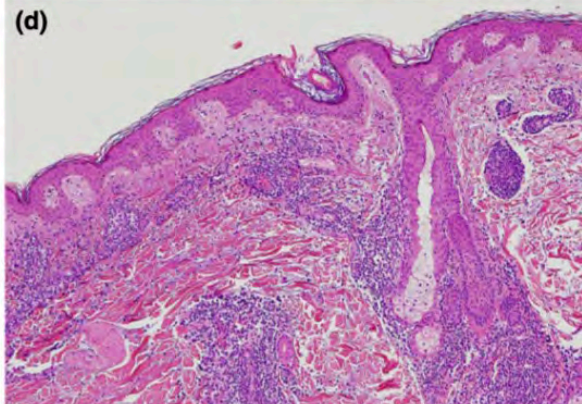
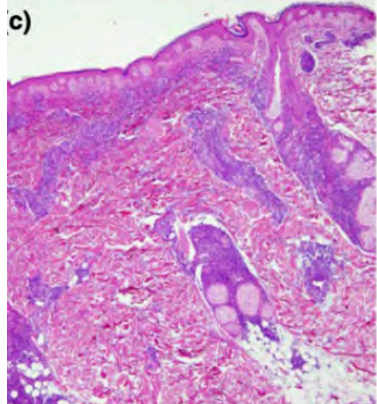
<sup>5</sup>Department of Dermatology, Ed. Hemot Hospital Group, Lyon, France

\*Correspondence: E. Cinotti. E-mail: [eliascinotti@gmail.com](mailto:eliascinotti@gmail.com)

# REM and lupus tumidus



REM



Lupus tumidus

# REM

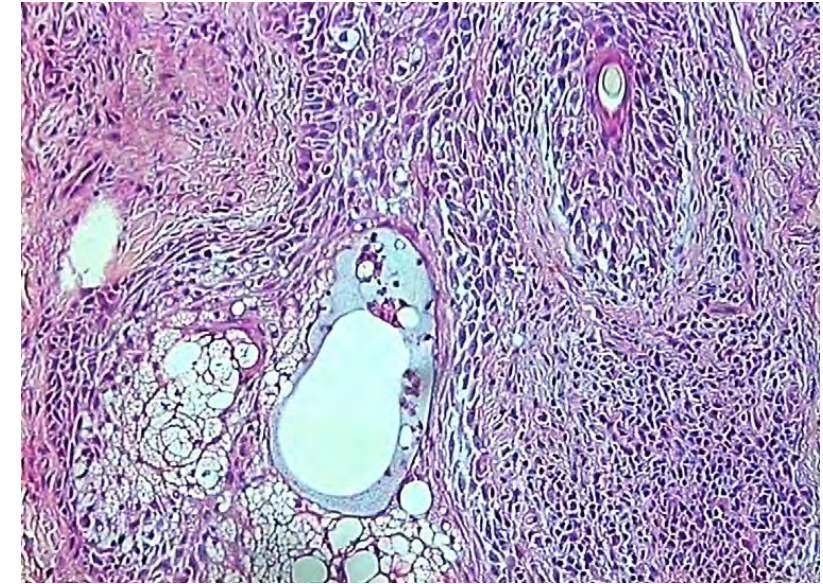
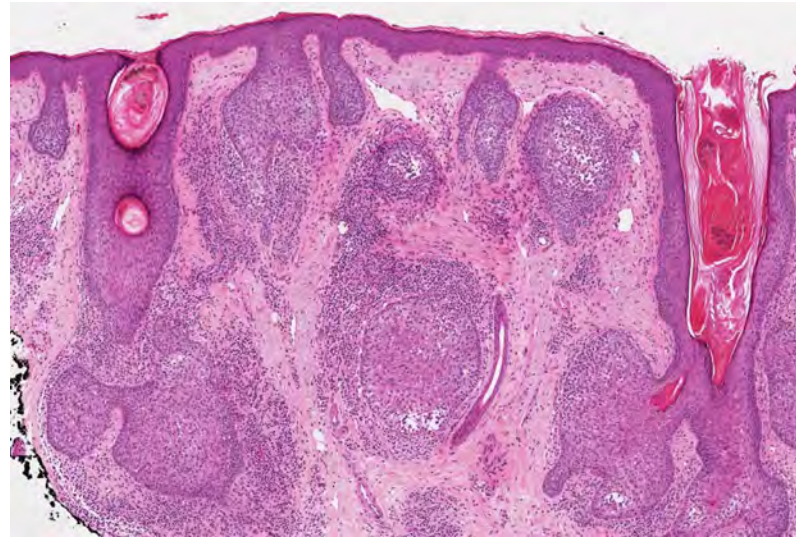
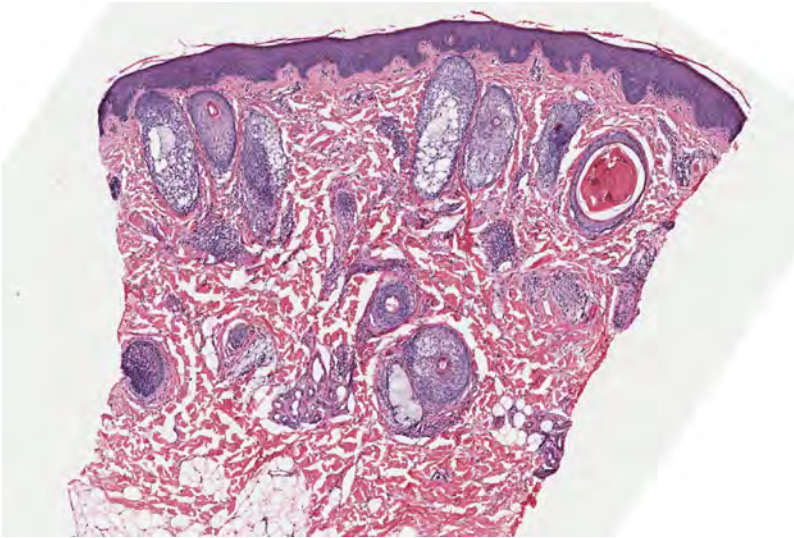
Primary mucinosis  
or variant of lupus  
erythematosus  
tumidus?

Different  
pathogenesis or  
same spectrum of  
disease?

# The Truth

- **The Japanese eat very little fat and suffer fewer heart attacks than the British and the Americans**
- **The French eat a lot of fat and suffer fewer heart attacks than the British or Americans**
- **The Chinese drink very little red wine and suffer fewer heart attacks than the British and the Americans.**
- **The Italians drink excessive amounts of red wine and also suffer fewer heart attacks than the British or Americans.**
- **Conclusion: Eat & drink what you like. It's speaking English that kills you.**

# Follicular mucinosis



**Epithelial reaction pattern characterized by mucin accumulation in the follicle and sebaceous glands**

# Origin of follicular mucin





- Mucin originate from follicular epithelial cells and CD8+ T-cells

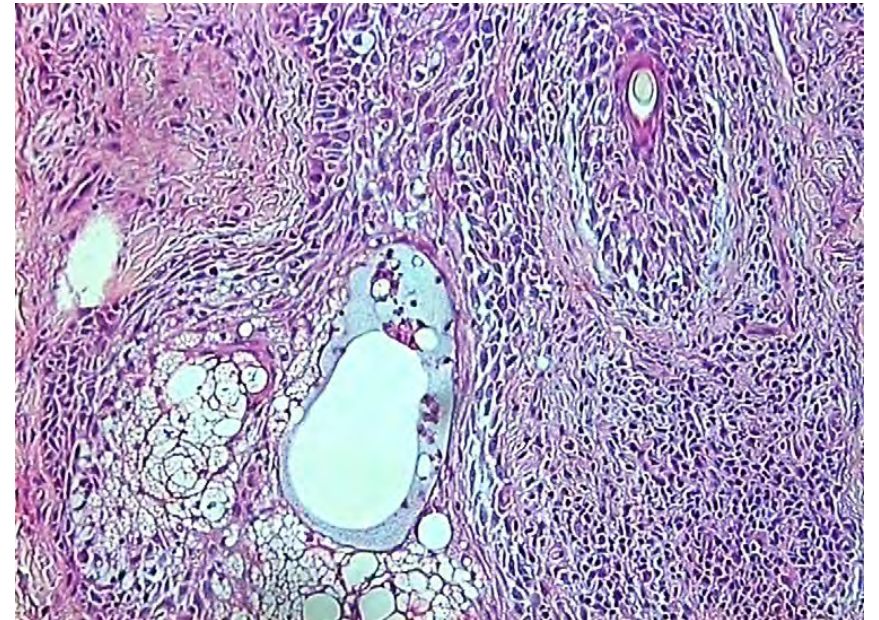
Received: 30 June 2022 | Accepted: 27 January 2023  
DOI: 10.1111/jdv.18992

ORIGINAL ARTICLE

 **EADV** 

**Identifying the potential origin of mucin in primary cutaneous mucinoses—A retrospective study and analysis using histopathology and multiplex fluorescence staining**

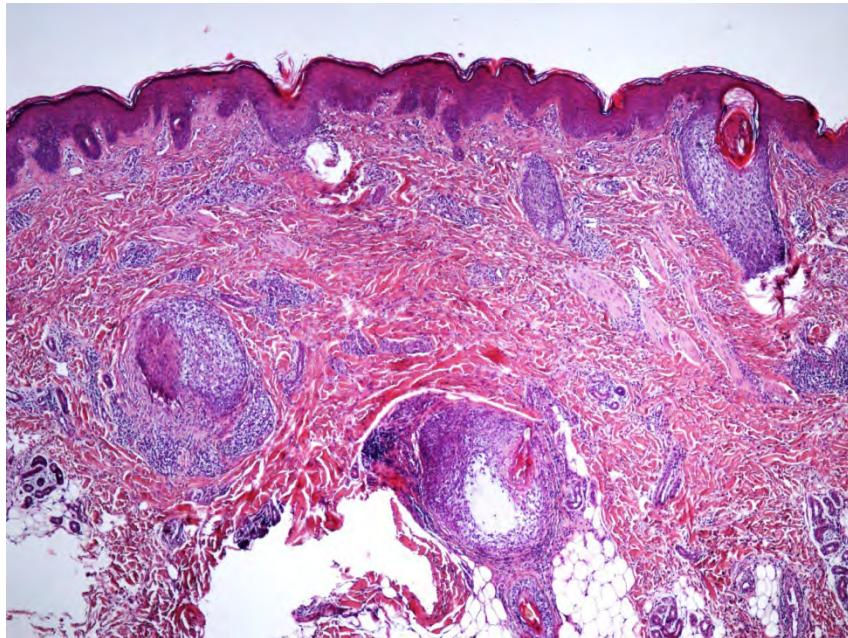
S. Steinmann<sup>1,2</sup>  | C. Guillet<sup>1,2</sup>  | P. F. Cheng<sup>1,2</sup> | M. P. Levesque<sup>1,2</sup> | R. Dummer<sup>1,2</sup>  |  
I. Kolm<sup>1,2</sup> | J. T. Maul<sup>1,2</sup> 



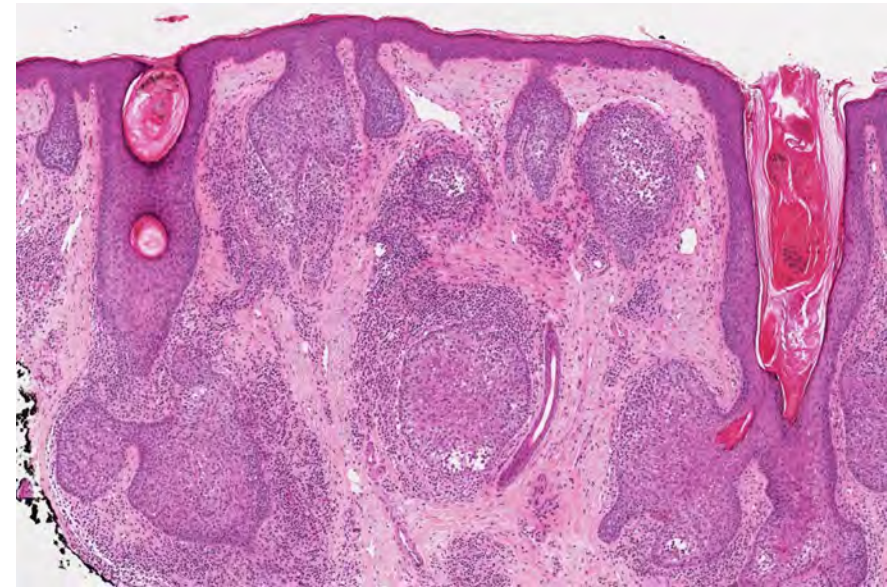
# Follicular mucinosis

Rongioletti F, Rebora A. Mucinoses. In Bologna J et al. Dermatology, Mosby, 2004)

■ **Primary (Pinkus)  
(Idiopathic)**



■ **Secondary**  
associated with  
many disorders,  
mainly mycosis  
fungoides



1. May primary FM represent a benign sui generis condition or a form of localized cutaneous T-cell lymphoma?
2. Is it possible to distinguish a primary FM from a secondary FM associated to MF?

# Primary follicular mucinosis (alopecia mucinosa) (Pinkus)

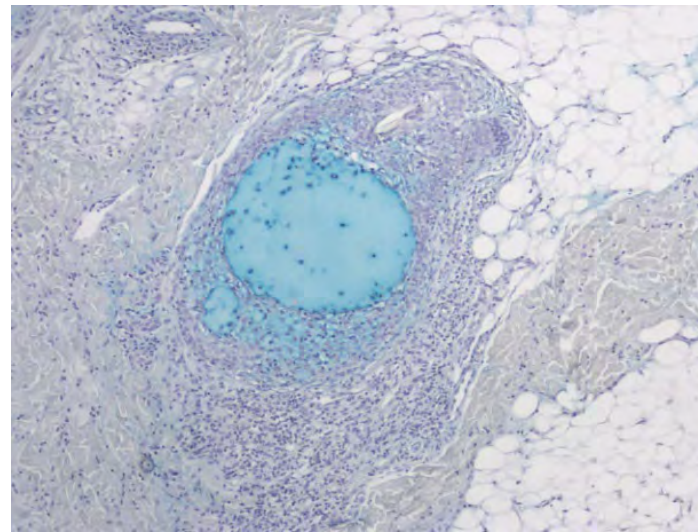
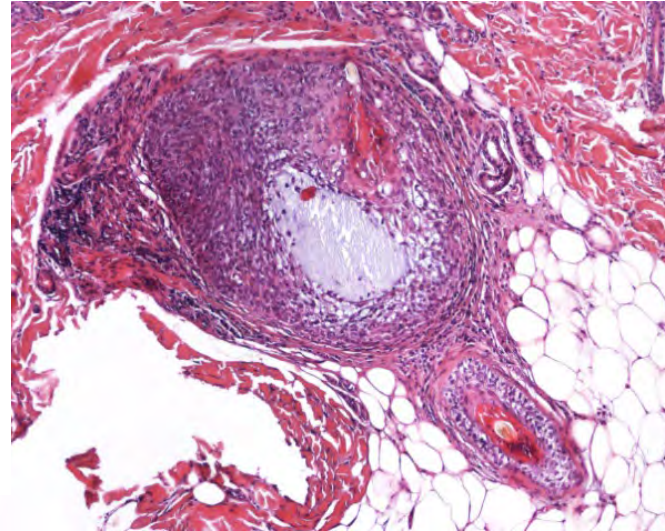
(Rongioletti F, Rebora A. Mucinoses. In Bologna J et al. Dermatology, Mosby, 2004)

- Most pediatric cases with the remainder of patients being younger than 40 years
- Focal cutaneous lesions characterized by grouped follicular papules or plaques with alopecia limited to the head and the neck
- Most lesions spontaneously resolve between 2 months and 2 years.



# Primary Follicular mucinosis

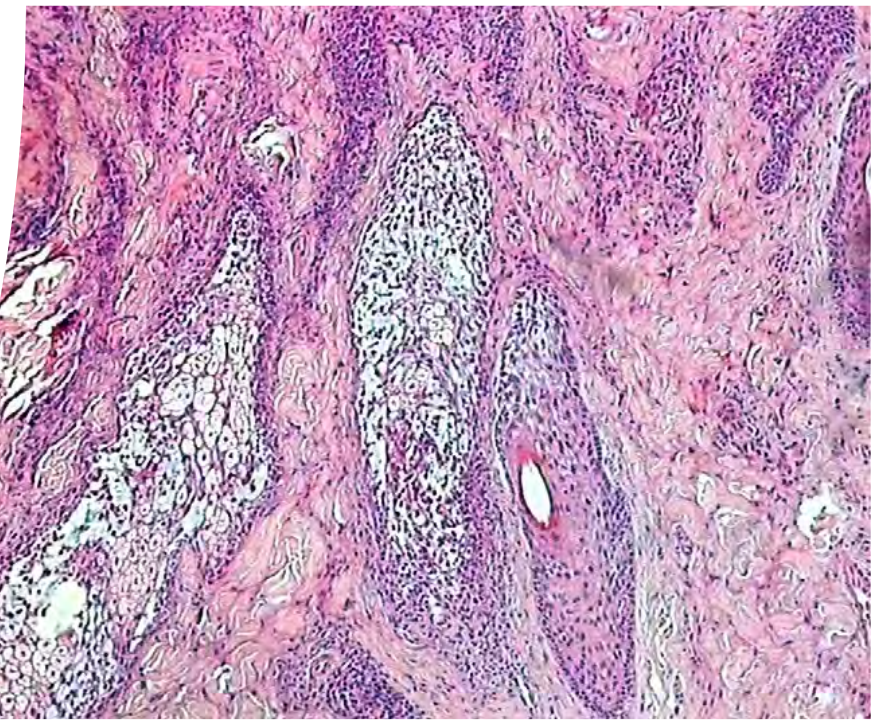
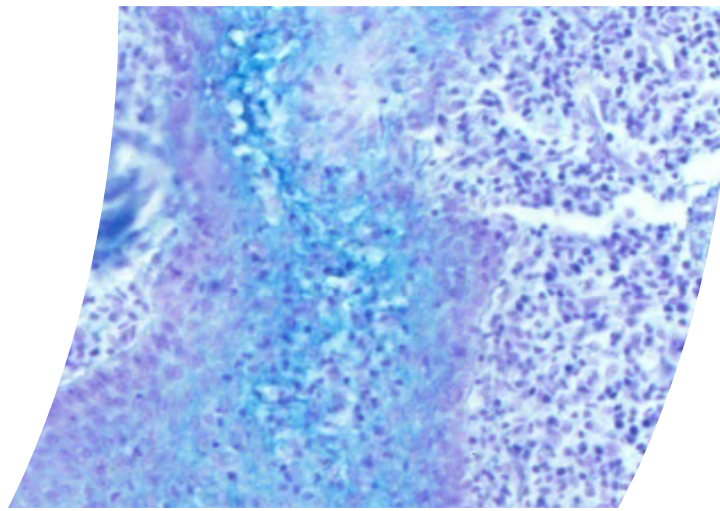
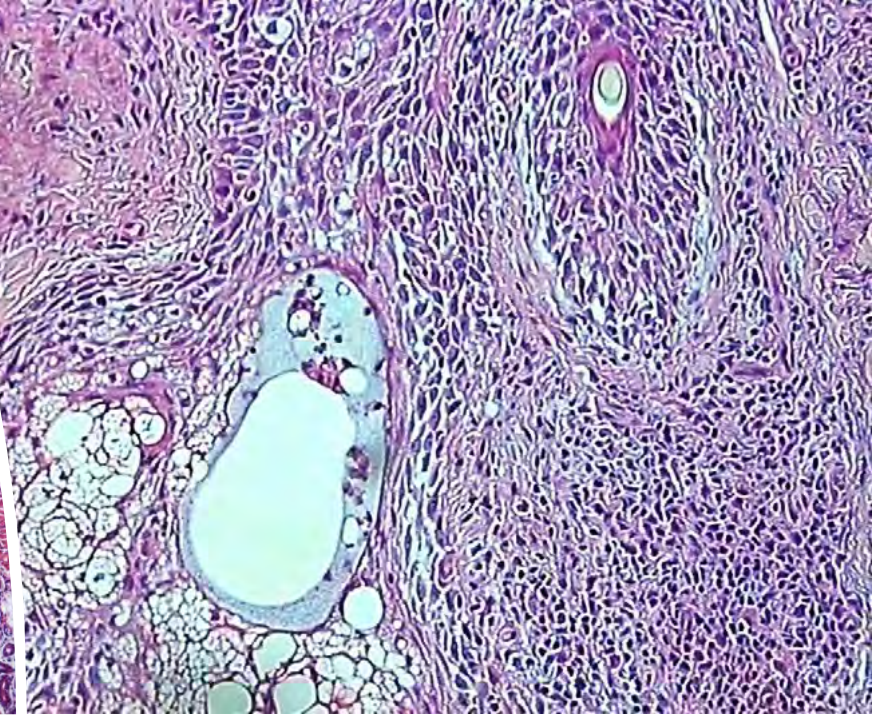
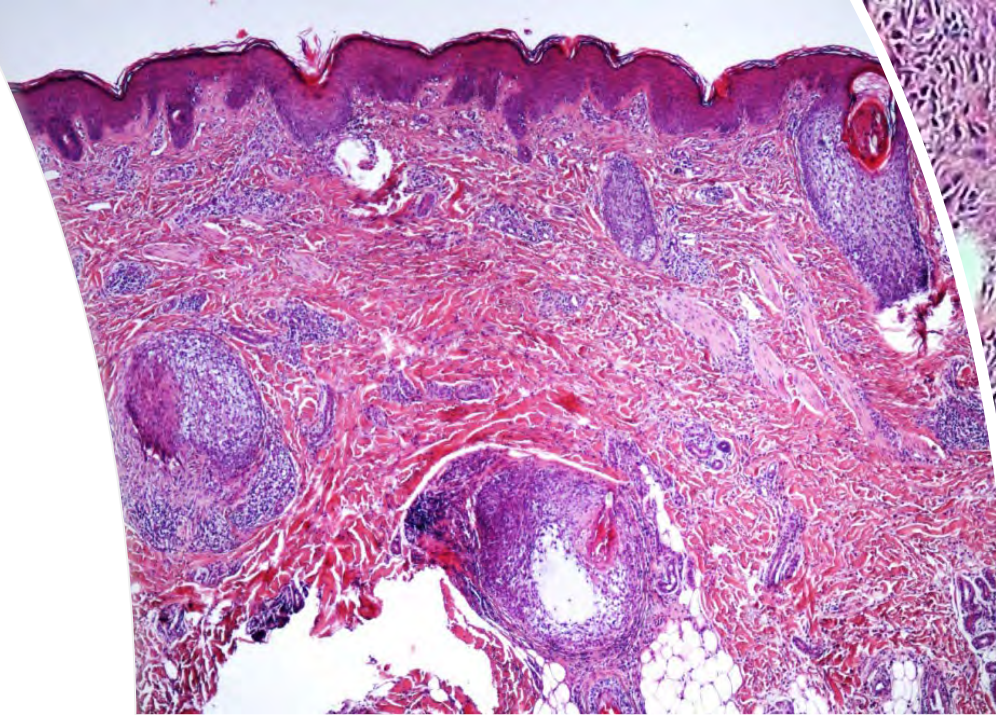
(Rongioletti F, Rebora A. Mucinoses. In Bologna J et al. Dermatology, Mosby, 2004)



- **Mucin within dilated follicles causing keratinocytes to disconnect**
- **Large cystic space with slight/moderate lymphocytic infiltrate with some eosinophils**

# Primary follicular mucinosis

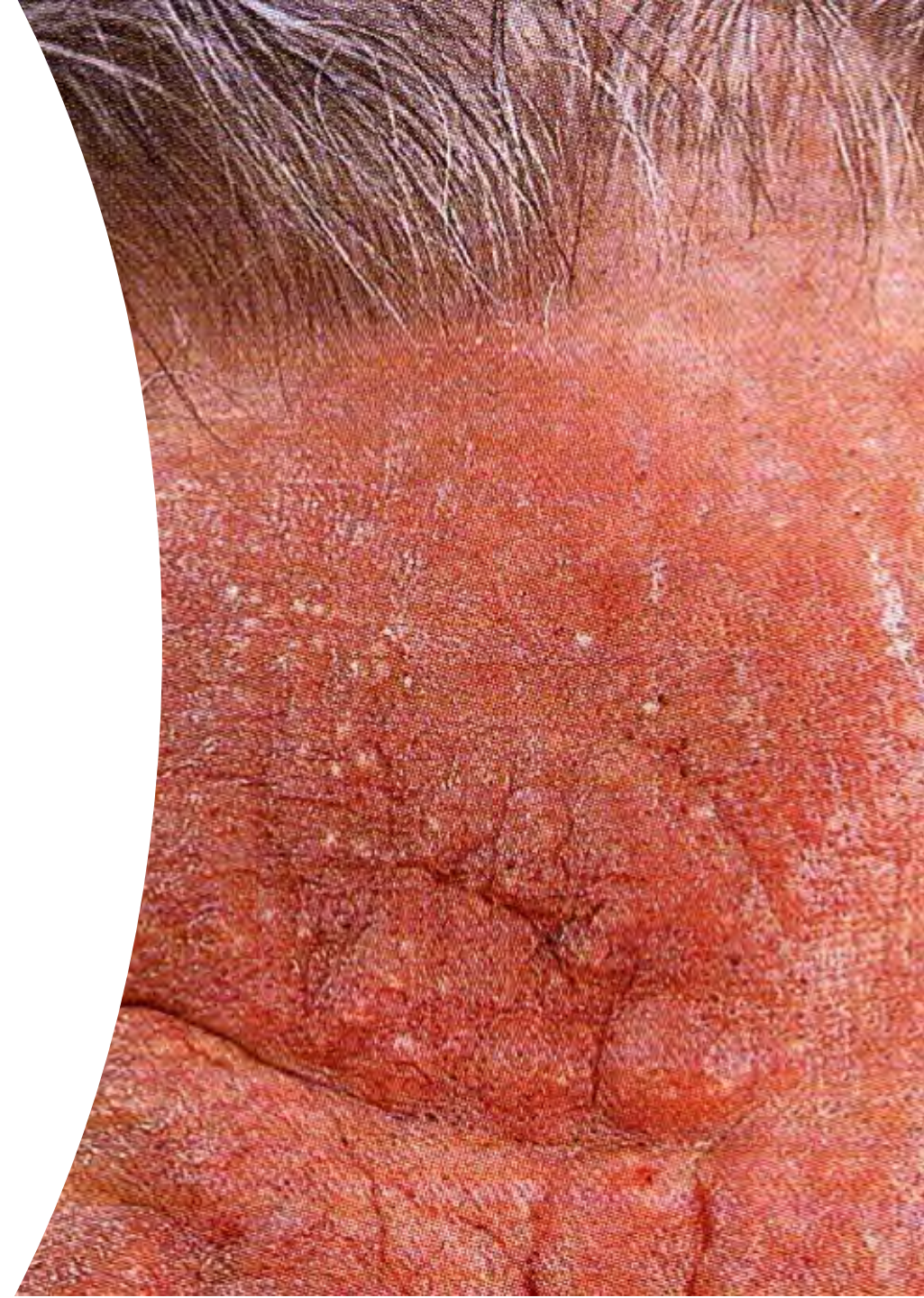
- Mucin within dilated follicles causing keratinocytes to disconnect
- Large cystic space with slight/moderate lymphocytic infiltrate with some eosinophils



# Secondary Follicular mucinosis

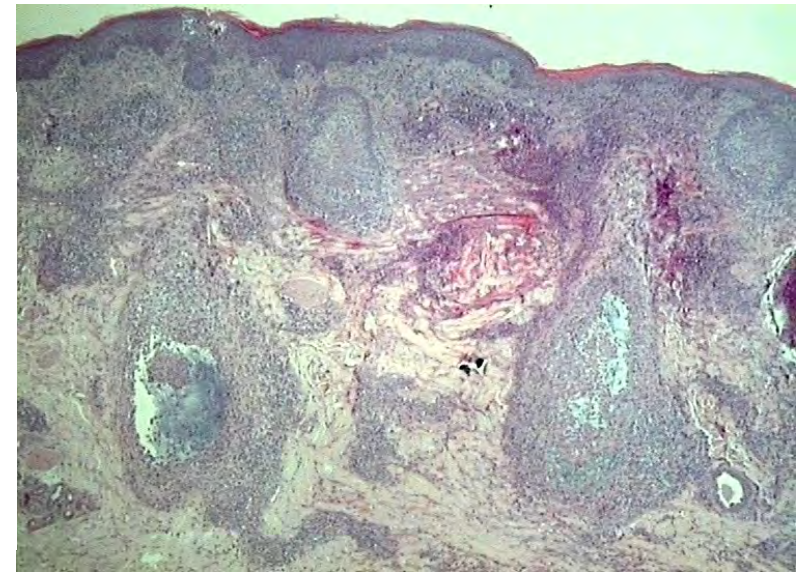
(Rongioletti F, Rebora A. Mucinosis. In Bologna J et al. Dermatology, Mosby, 2004  
Cerroni L et al. Arch Dermatol 2002)

- **Patients aged 50-70 years**
- **Boggy plaques and nodules with prominent follicular orifices, a more generalized distribution and a chronic course**
- **Mostly associated with cutaneous T-cell lymphoma**

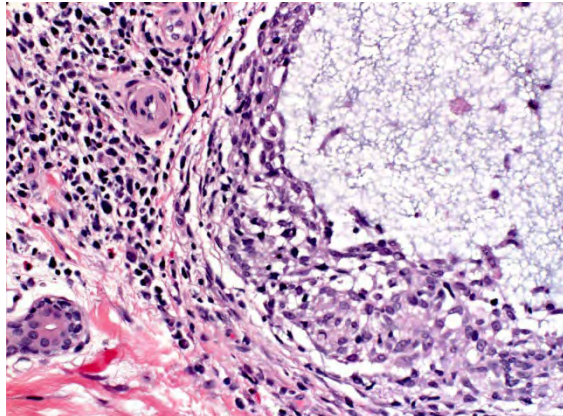
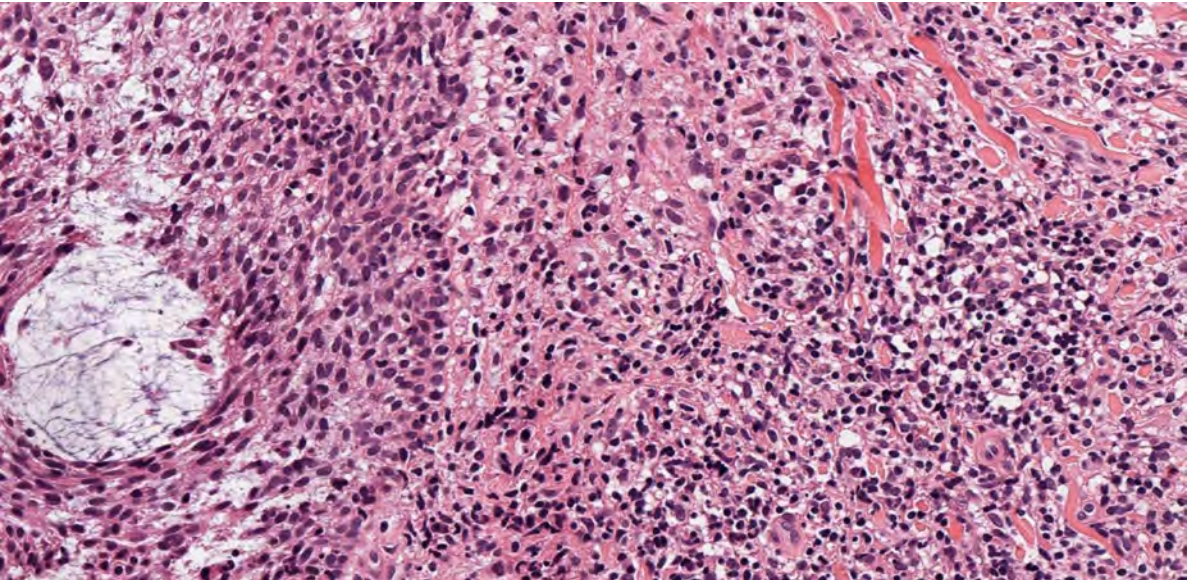
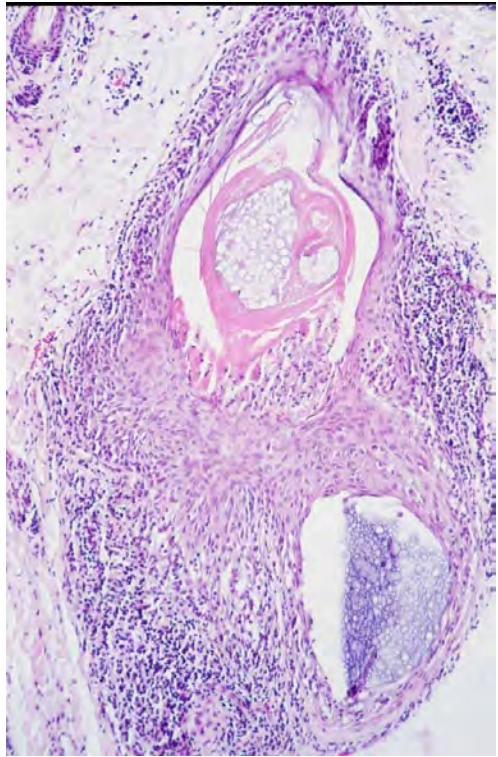
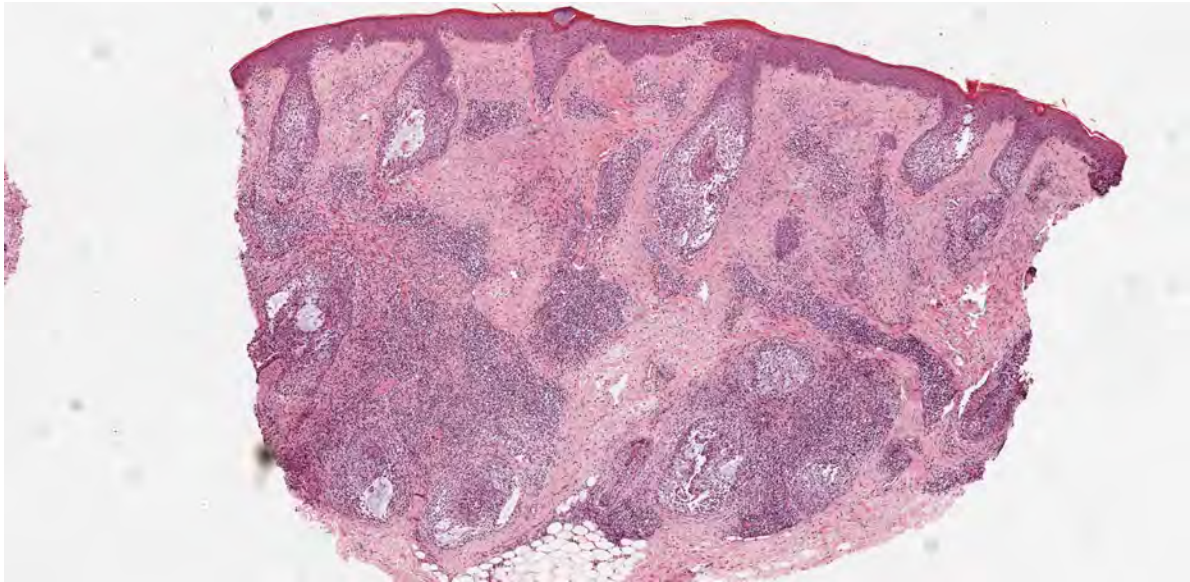


# Secondary FM associated with mycosis fungoides

- Mycosis fungoides is recognized at the time of diagnosis in approximately 15-30% of patients



# Follicular mucinosis associated with MF



## Feature

## Primary FM

## Secondary FM

**Typical age**

Young

Older

**Lesions**

Solitary or a few head 6 neck

Multiple, diffuse

**Self-limited?**

Yes

No

**Mucin deposition**

Prominent in outer root sheath

Less abundant

**Infiltrate**

Mild to moderate lymphocytic infiltrate

Atypical lymphocytes with cerebriform nuclei

**Epidermotropism**

Rare

Common, with atypical lymphocytes migrating into the epidermis

**CD4:CD8 ratio**

Normal or slightly elevated

Often markedly increased (e.g. > 10:1)

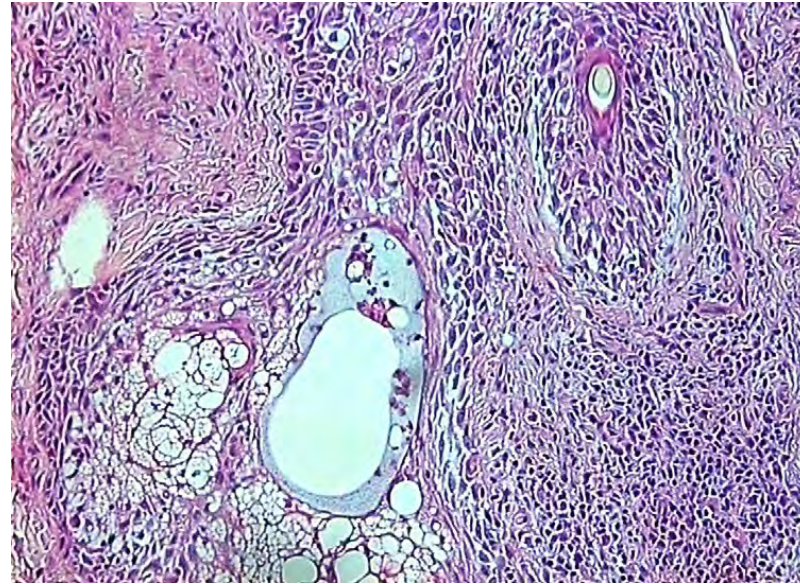
**T-cell clonality (PCR for TCR gene rearrangement)**

Polyclonal

Monoclonal T-cell population (suggesting lymphoma)

# Follicular mucinosis

- Diagnosis and classification of primary FM and secondary FM associated with MF continue to pose challenges for dermatologists and pathologists, and **no single diagnostic tool** is sufficient in providing diagnostic certainty
- A collective evaluation of pathologic, molecular, and clinical criteria is required




PRIMARY

Secondary with MF

SYSTEMATIC REVIEW

## **New and emerging conditions of acquired cutaneous mucinoses in adults**

F. Rongioletti<sup>1,2,\*</sup> 

<sup>1</sup>Dermatology Clinic, IRCCS San Raffaele Scientific Institute, Milan, Italy

<sup>2</sup>Vita-Salute San Raffaele University, Milan, Italy

\*Correspondence: F. Rongioletti. E-mail: franco.rongioletti@me.com

### **Three new clinical-pathologic entities**

- 1. Obesity associated lymphedematous mucinosis and pretibial stasis mucinosis**
- 2. Nodular mucinosis of the breast**
- 3. Aesop**

# Nodular mucinosis of the breast

Described in 1998 by Michal

Gradually enlarging, asymptomatic, soft or cystic nodular mass under the nipple in young women

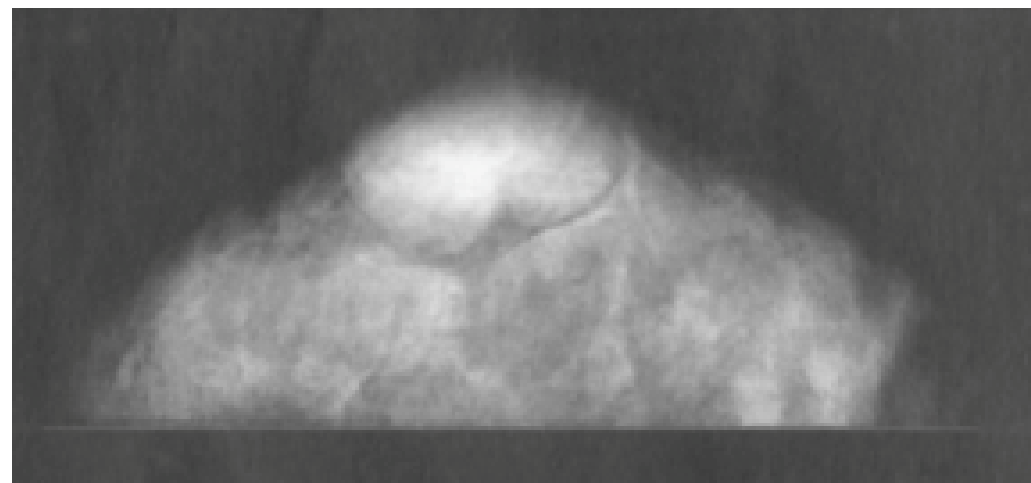
Occasionally nipple discharge or pain

Mimicker of mucinous carcinoma of breast

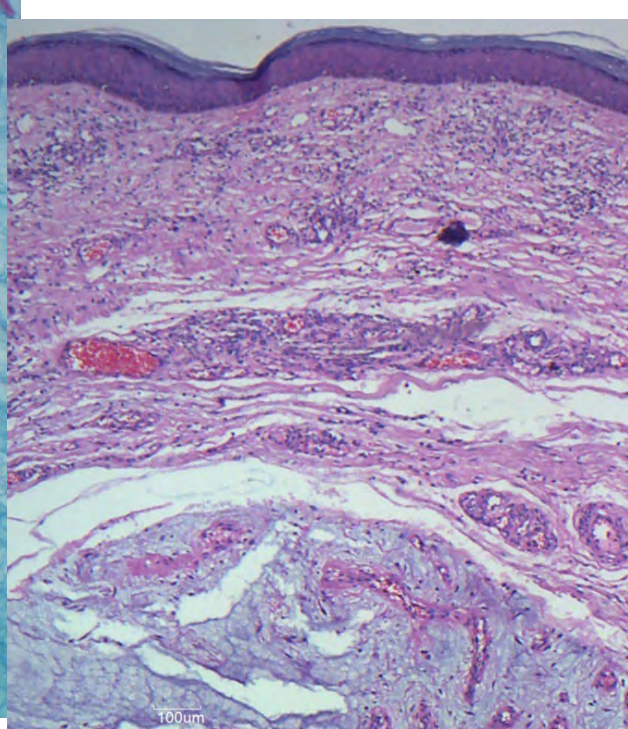
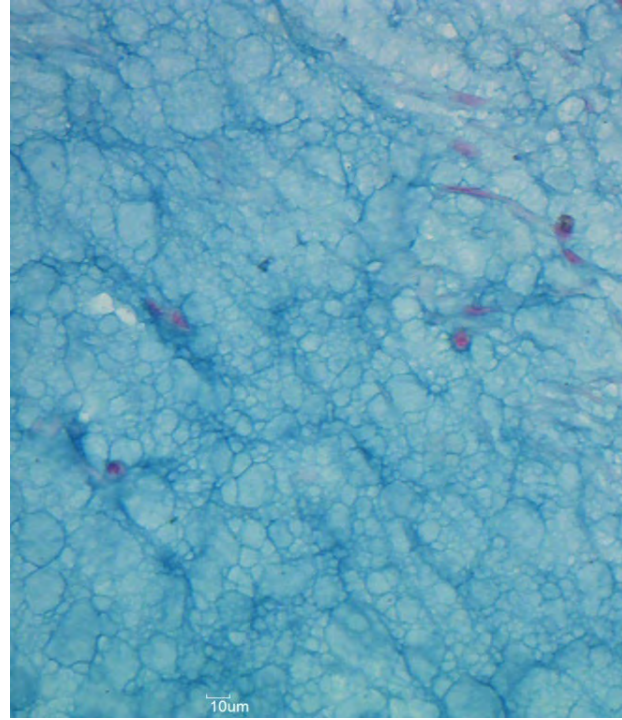
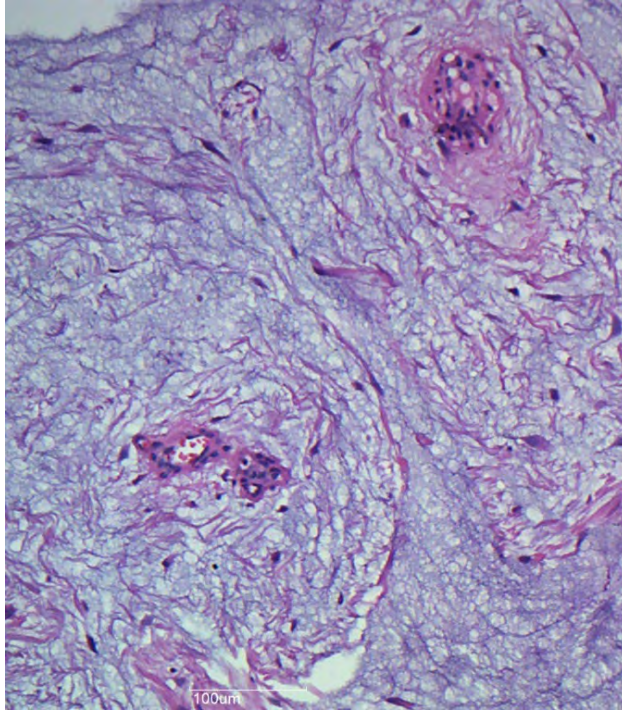
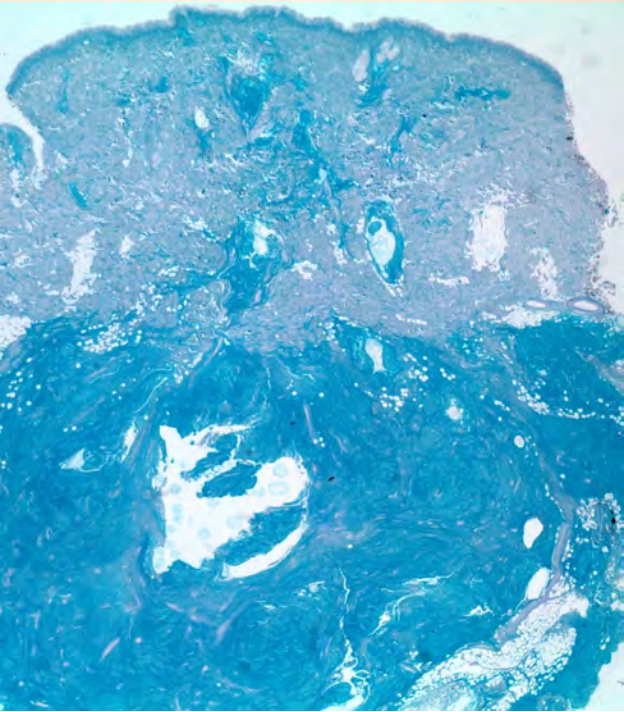
# Nodular mucinosis of the breast



Ultrasound sonography:  
Circumscribed lobulated  
hypoechoic lesion



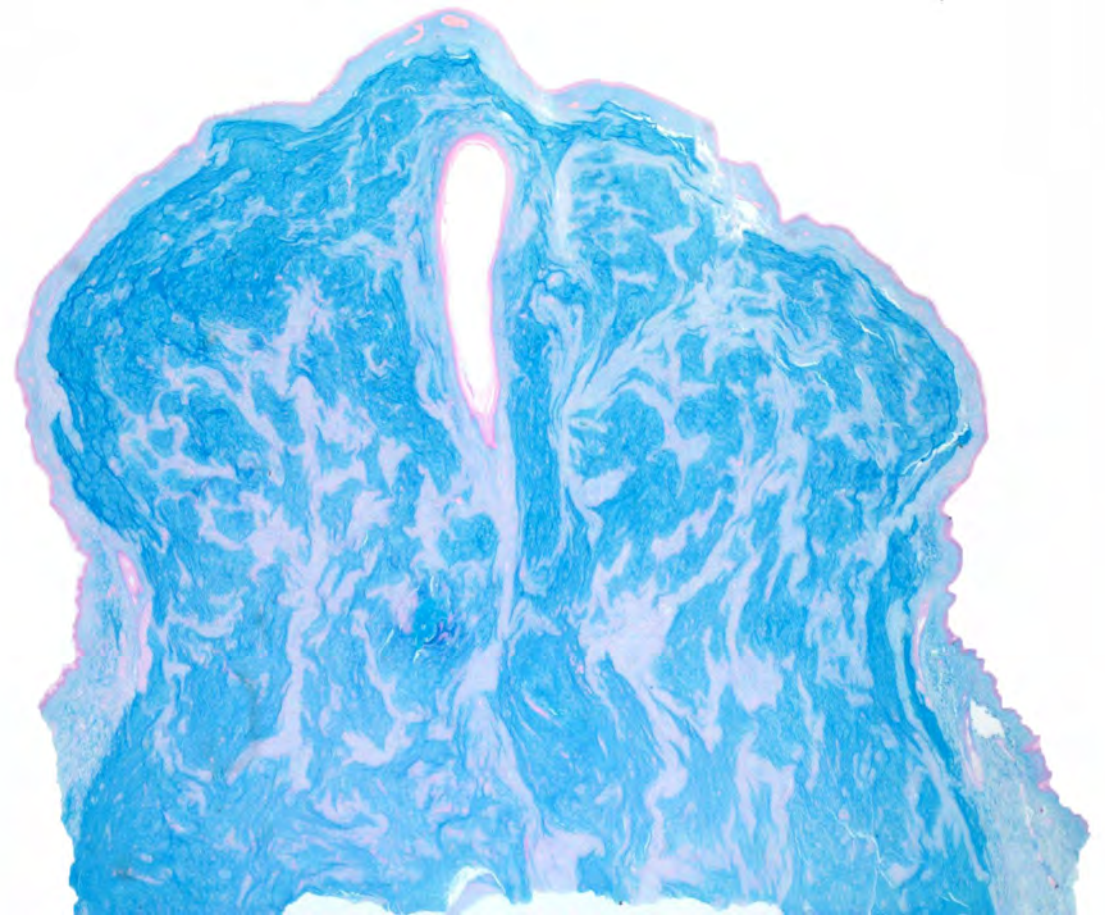
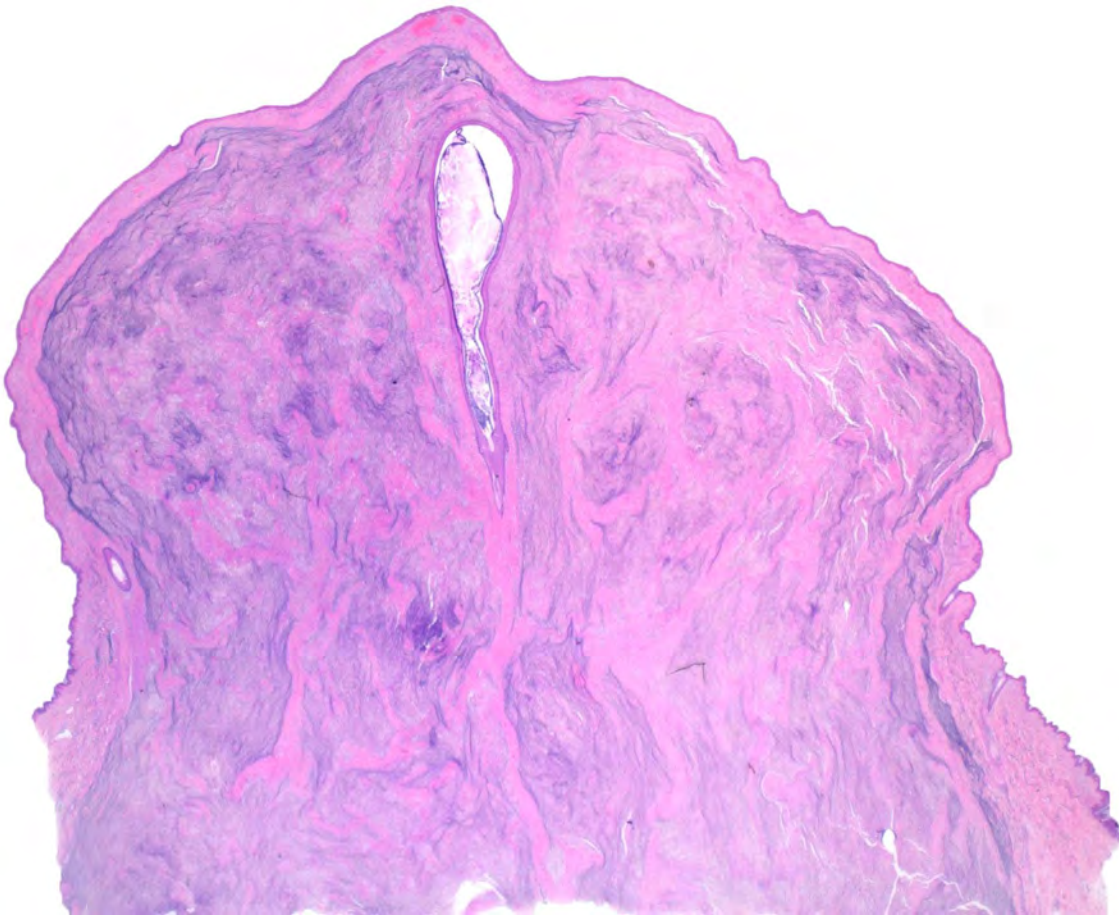
Mammography: Round-lobular shaped radiopaque  
mass without microcalcification



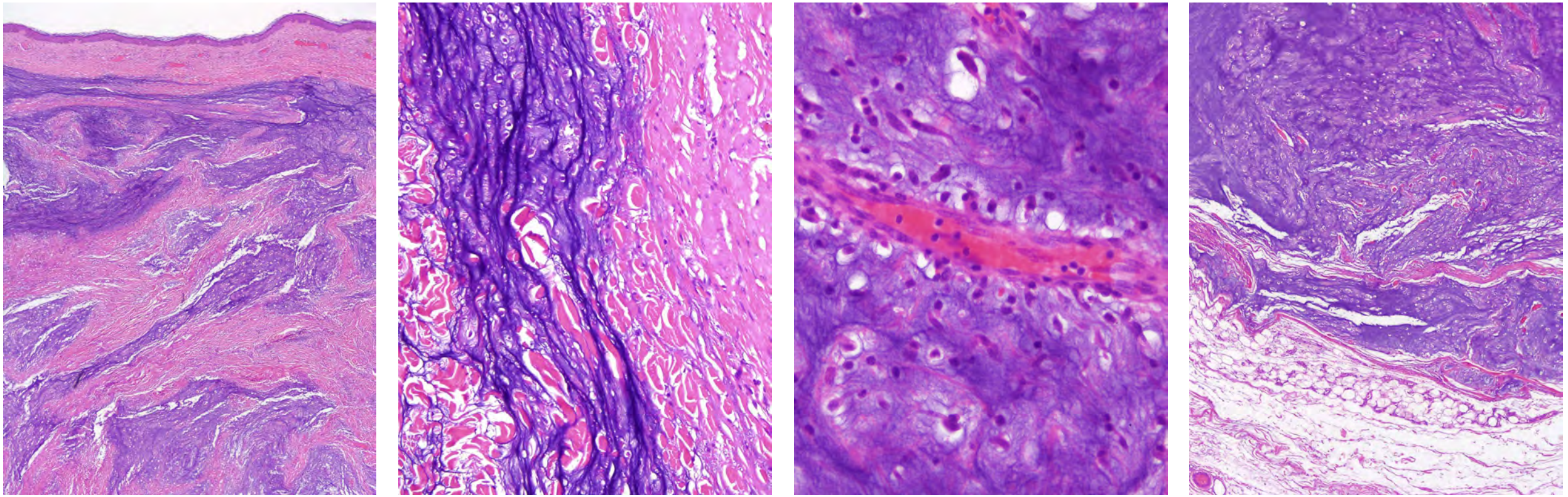
## Nodular mucinosis of the breast

- Abundant myxoid tissue with a multilobular appearance with fibrocollagenous stroma involving dermis and fat

# Nodular mucinosis of the breast



Courtesy of Maite Fernandez-Figueras

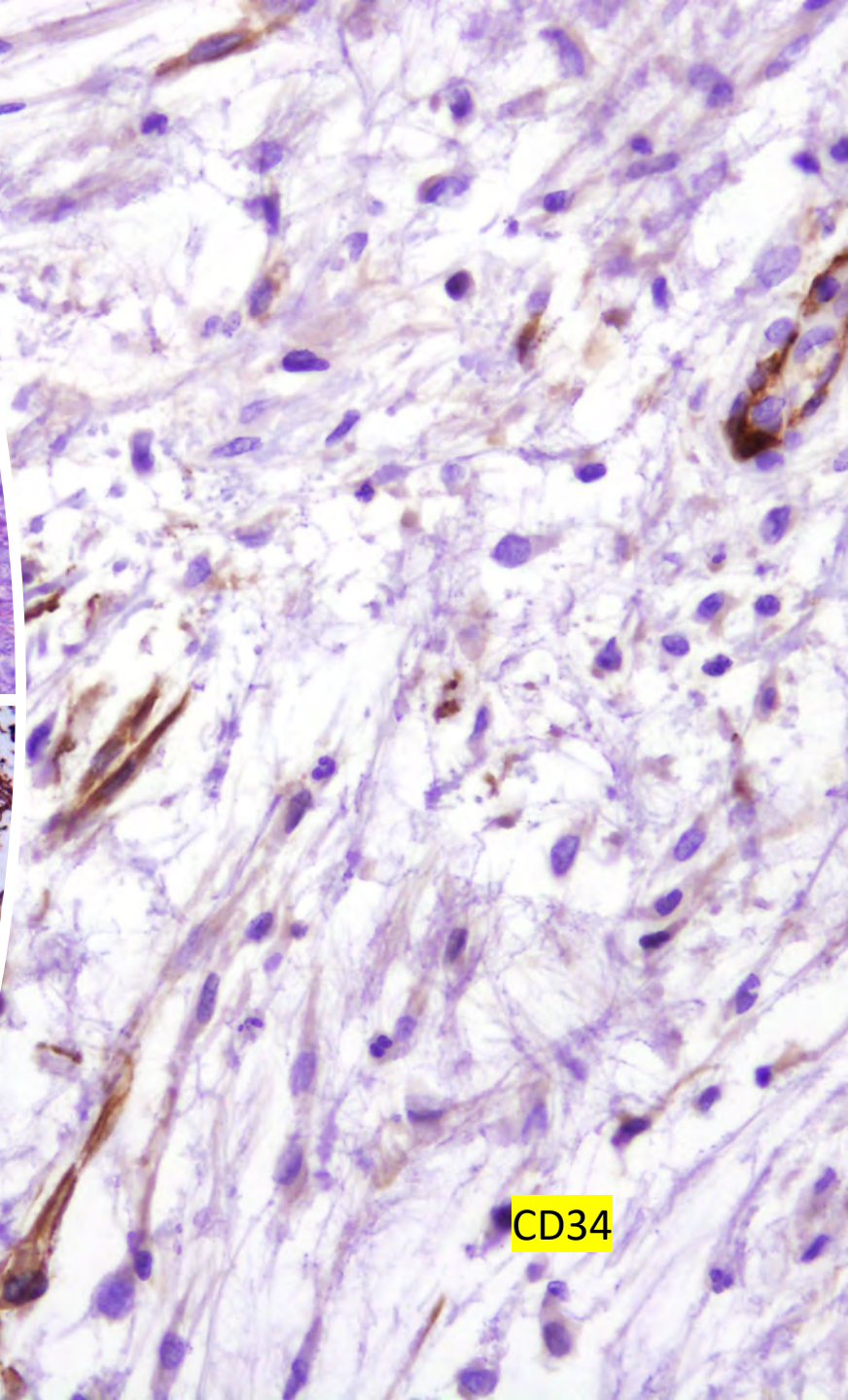
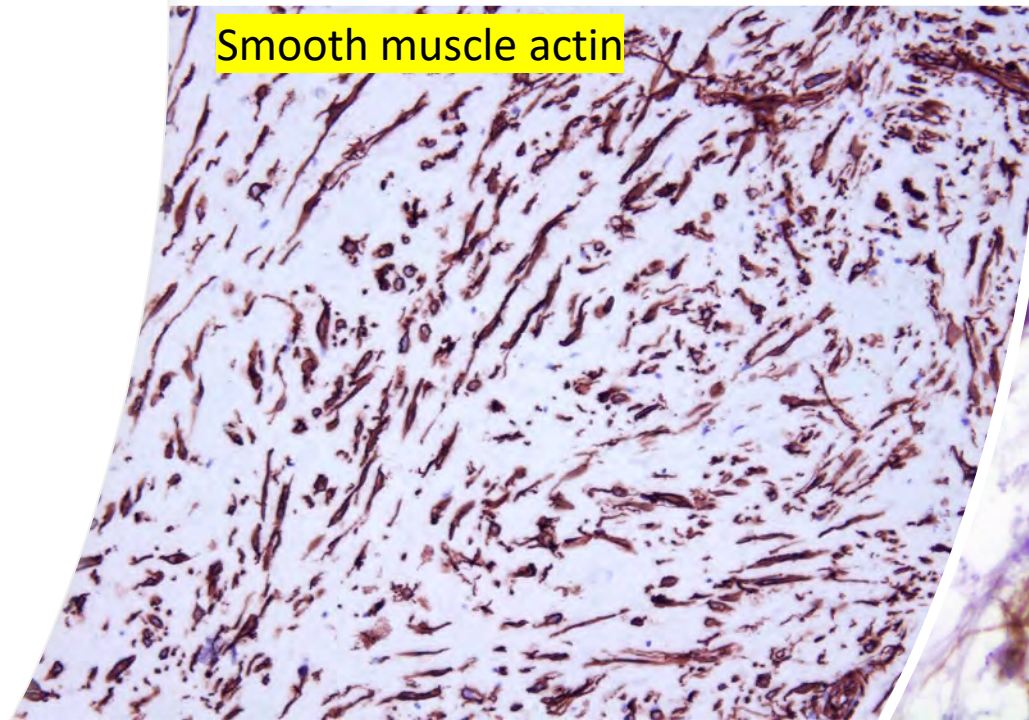
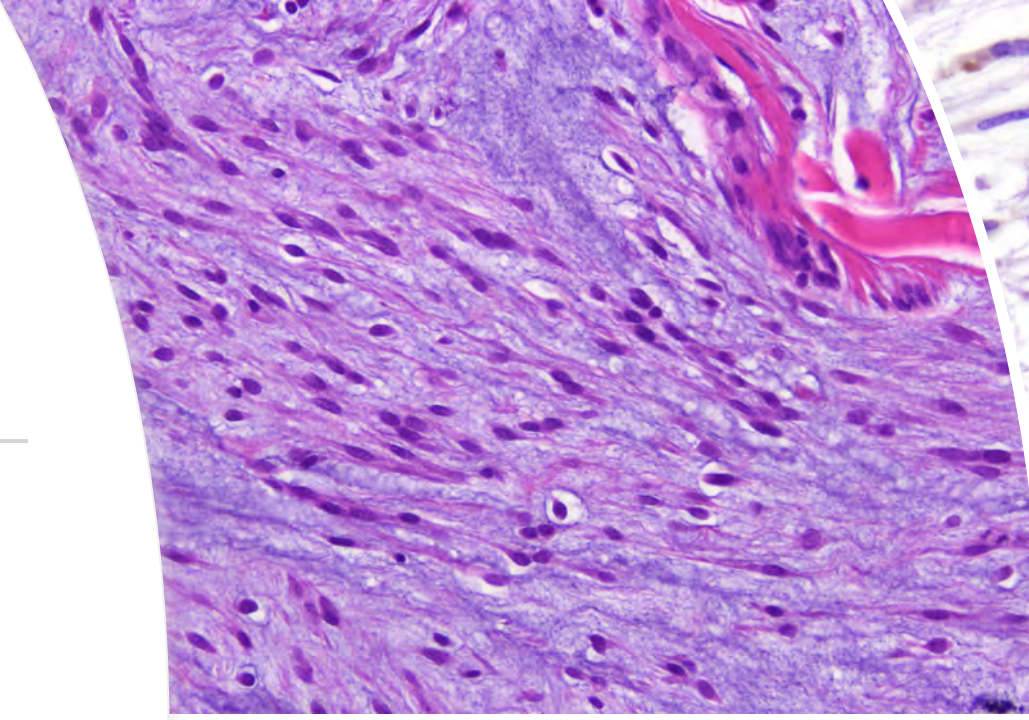


# Nodular mucinosis of the breast

Mucin deposition without epithelial cells or sign of malignancy to be differentiated from other myxoid lesions such as mucinous carcinoma

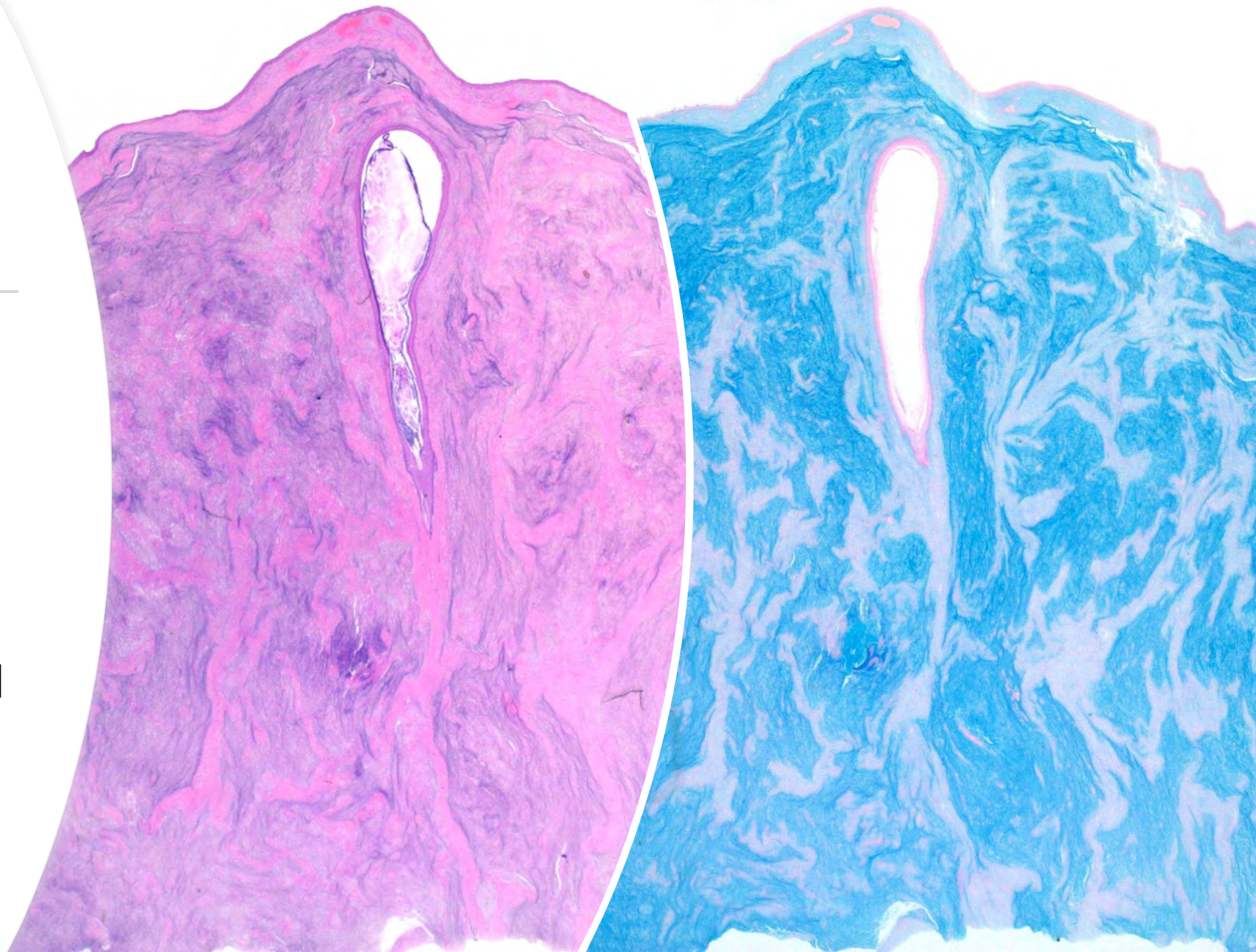
# Nodular mucinosis of the breast

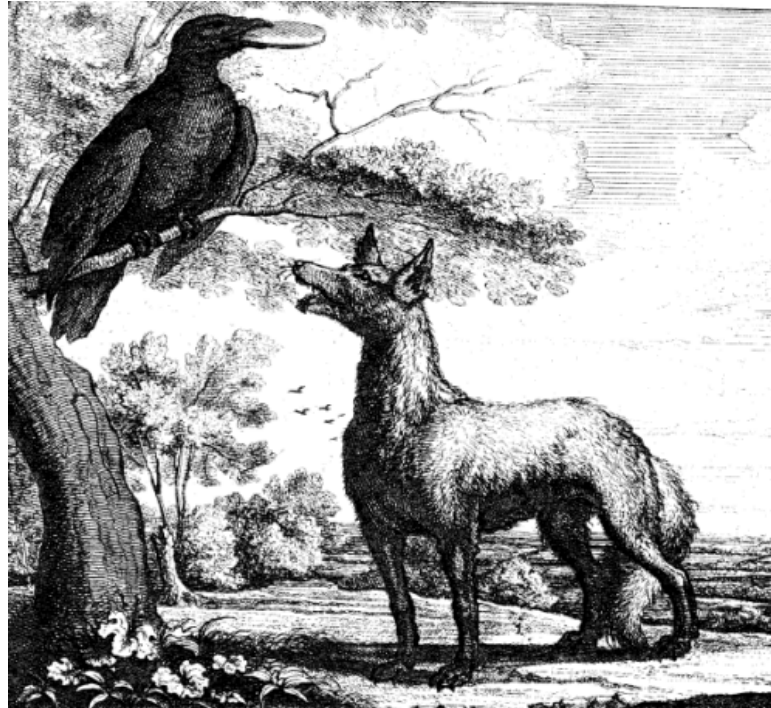
- Spindle cells with bland-looking nuclei and elongated amphophilic cytoplasm without atypia or mitosis
- Positive
  - Vimentin
  - Calponin
  - Smooth muscle actin
  - CD34
- Negative
  - Cytokeratin
  - S-100protein



# Nodular mucinosis of the breast

- Reactive lesion of a benign stromal neoplasm or a true neoplasm?
- Treatment of choice is surgical excision





# AESOP

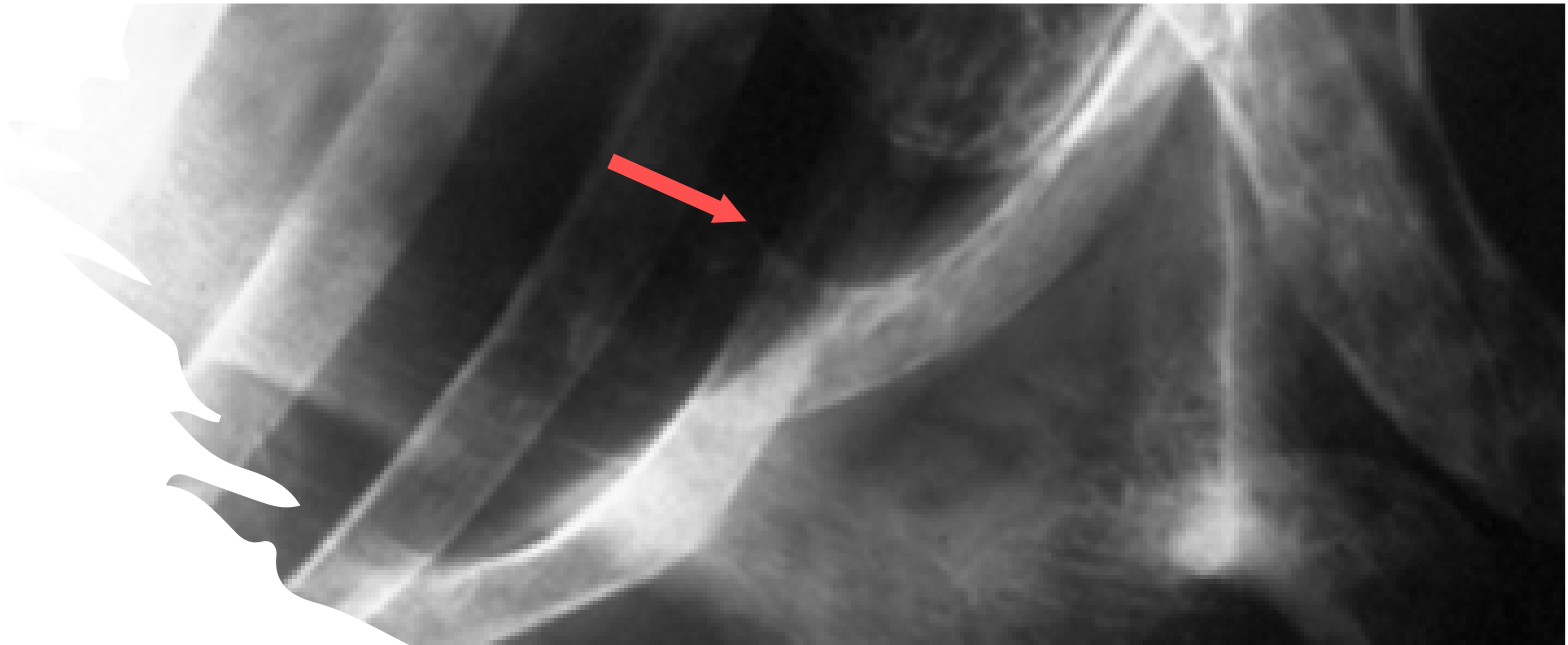
**Aesop** (620-564 BCE) was a [Greek](#) writer credited with a number of popular [fables](#)

# AESOP syndrome

Lipsker D. Medicine 2003

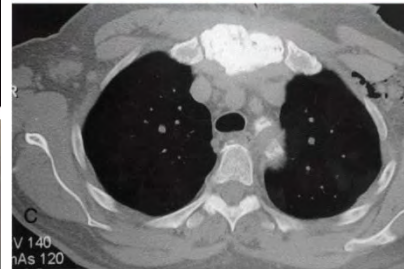
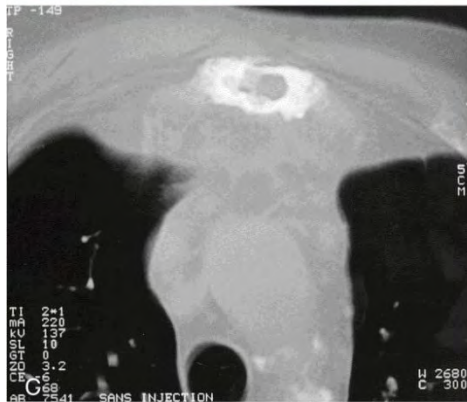
Rongioletti F, Romanelli P, Rebora A J Am Acad Dermatol. 2006

- **(Adenopathy)**
- **Extensive**
- **Skin patch**
- **Overlying**
- **Plasmocytoma**



# AESOP

Lipsker D. Medicine 2003; JAAD 2006



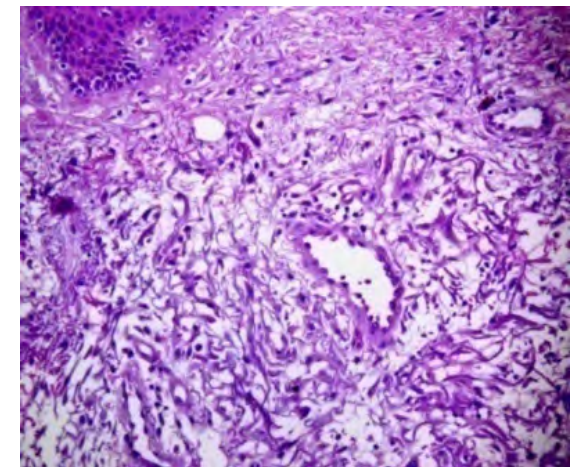
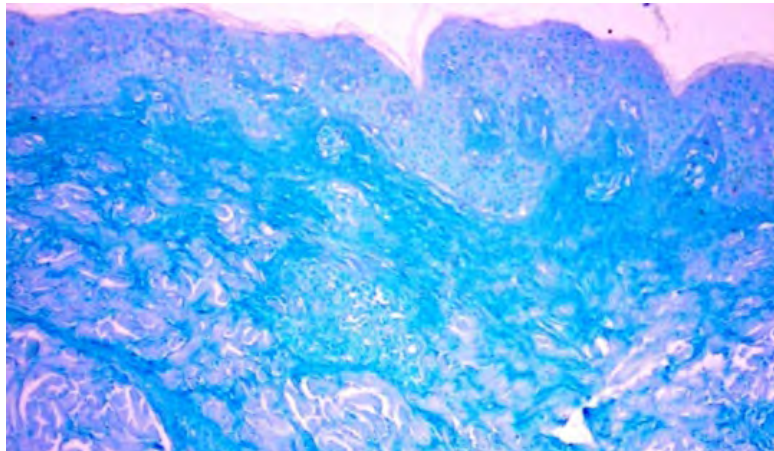
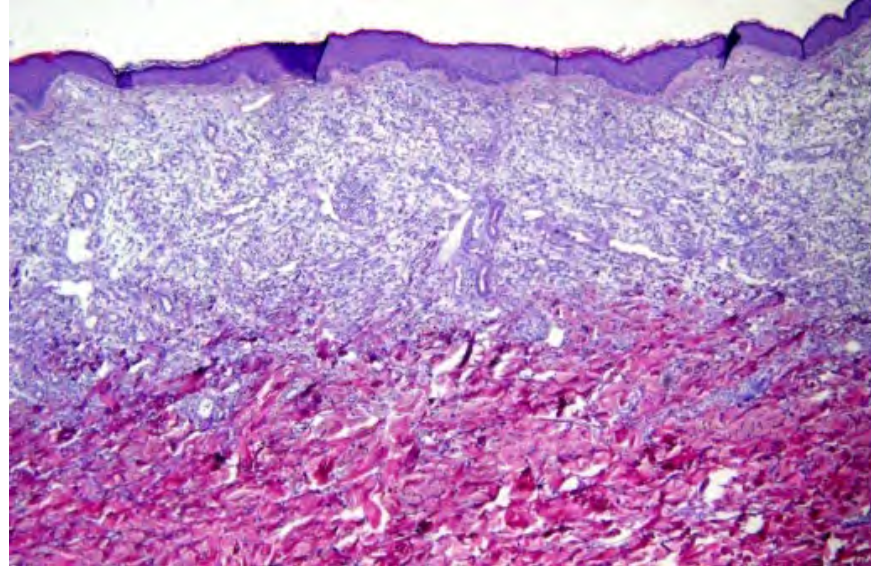
An enlarging red violaceous patch on the skin, usually on the thoracic region, which is the sign of an underlying solitary plasmacytoma of the ribs or sternum

# AESOP

(Adenopathy and extensive patch overlying a plasmocytoma)

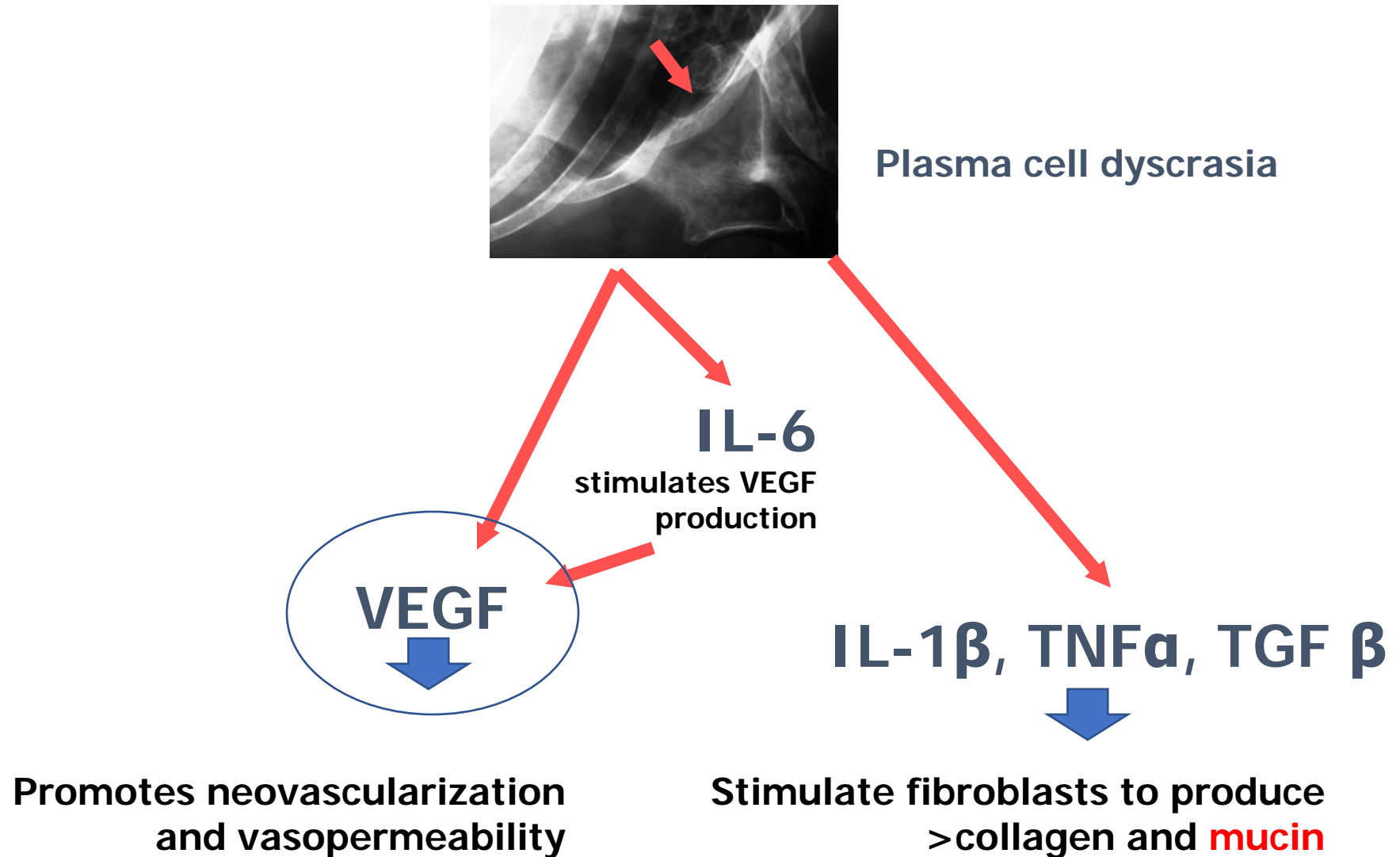
Medicine 2003,82

- Diffuse dermal mucin deposition in reticular dermis
- Vascular proliferation of small vessels with endothelial swelling (mucinous angiomatosis)



# Pathogenesis of AESOP


Rongioletti F J Am Acad Dermatol. 2006;55





# Cutaneous mucinosis in pediatric age

- **Rare (and sometimes controversial) diseases**
- **Mostly anecdotal cases**
- **No accepted classification**

**Primary paediatric cutaneous mucinoses\***F. Rongioletti 

Unit of Dermatology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

**Linked Comment:** Haber. *Br J Dermatol* 2020; 182:7–8.

- **Degenerative/  
Inflammatory:**

*Dermal*

- Cutaneous mucinosis of infancy
- Self-healing juvenile cutaneous mucinosis
- Scleredema

*Follicular***Pinkus' follicular mucinosis****Table 1** Classification of paediatric cutaneous mucinoses

I. Degenerative/inflammatory
A. Dermal/subcutaneous
a. Without systemic symptoms
1. Cutaneous mucinosis of infancy (localized lichen myxoedematosus)
b. May have systemic symptoms
1. Self-healing juvenile cutaneous mucinosis
2. Scleroedema (postinfectious)
c. Atypical papular mucinosis of infancy (cutaneous mucinosis of infancy/self-healing cutaneous mucinosis overlap)
B. Follicular
1. Pinkus follicular mucinosis
II. Hamartomatous/neoplastic
A. Dermal
1. Mucinous naevus
• Connective tissue naevus of proteoglycan type
• Combined epidermal–connective tissue naevus of proteoglycan type
• Perifollicular type
2. Mucinous eccrine naevus
3. Superficial angiomyxoma (cutaneous myxoma)
• Solitary
• In Carney complex
B. Follicular
1. Naevoid follicular mucinosis

# Cutaneous mucinosis of infancy (paediatric variant of localized lichen myxedematosus)

Podda M, Rongioletti F, Wolter M. Br J Dermatol 2001;144

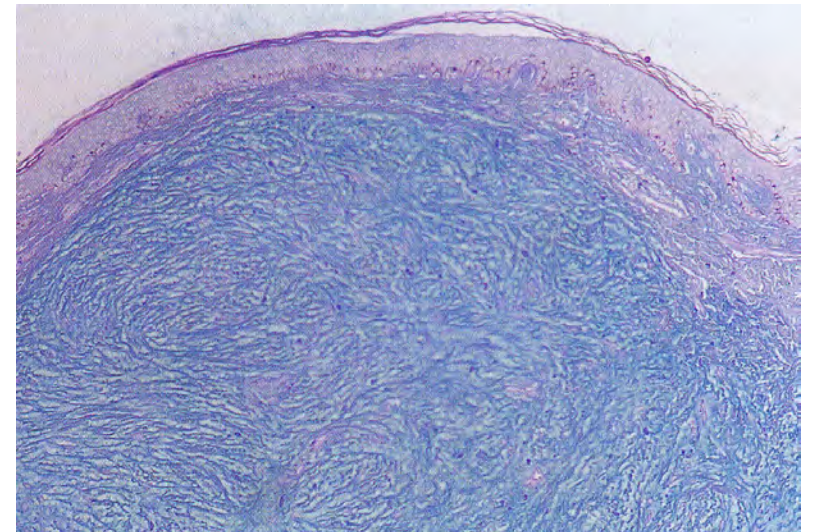
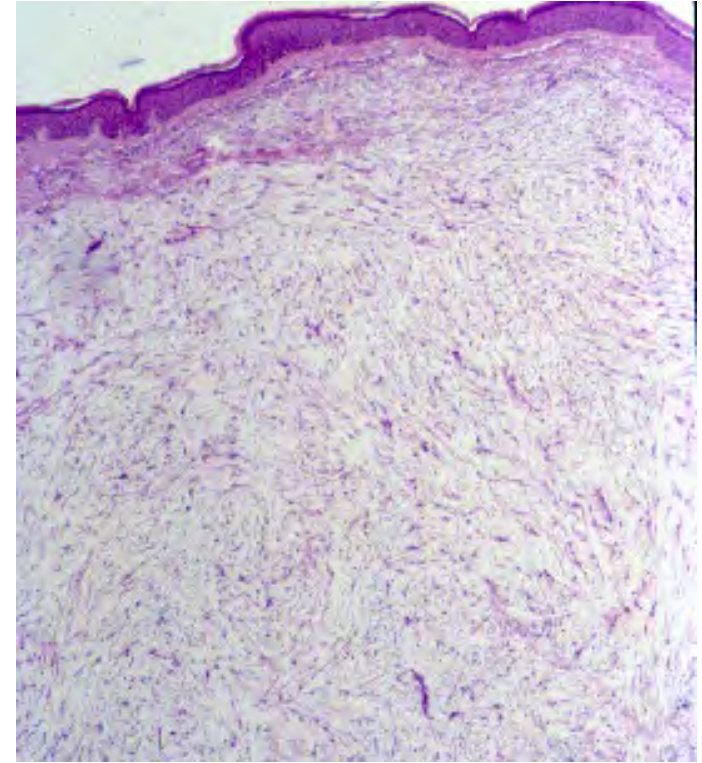


- Firm, opalescent, densely grouped but not coalescent papules (sometimes nodules) on upper arms and trunk
- Early infancy
- No systemic features ( no thyroid disease or paraproteinemia)
- No regression

# Cutaneous mucinosis of infancy

(paediatric variant of localized lichen myxedematosus)

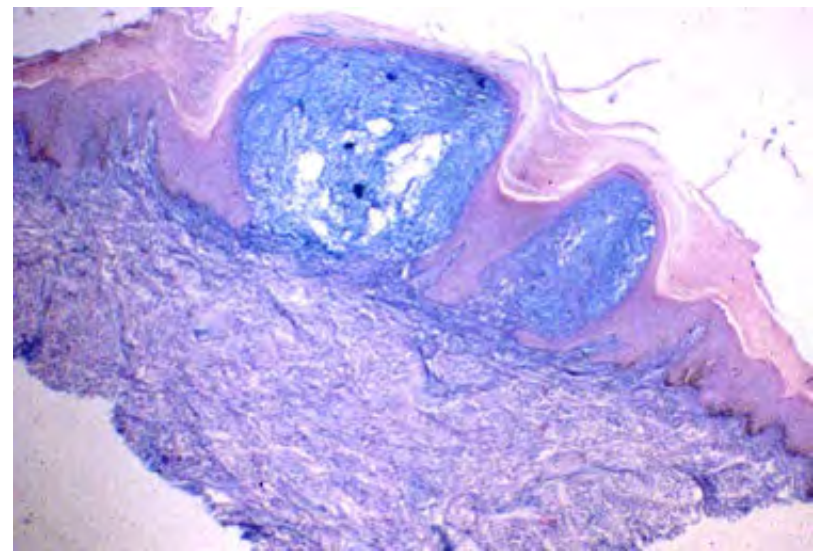
- **Focal well-circumscribed mucin deposits in the papillary/superficial dermis without any or with slight fibroblast proliferation**



# Cutaneous mucinosis of infancy

(paediatric variant of localized lichen myxedematosus)

- **Mucin so superficial as to look as if it is 'enclosed' by epidermis**



# Cutaneous Mucinoses in pediatric age

- **Degenerative/  
Inflammatory:**

## *Dermal*

- **Cutaneous mucinosis of  
infancy**
- **Self-healing juvenile cutaneous  
mucinosis**
- **Scleredema**

## *Follicular*

**Pinkus' follicular mucinosis**

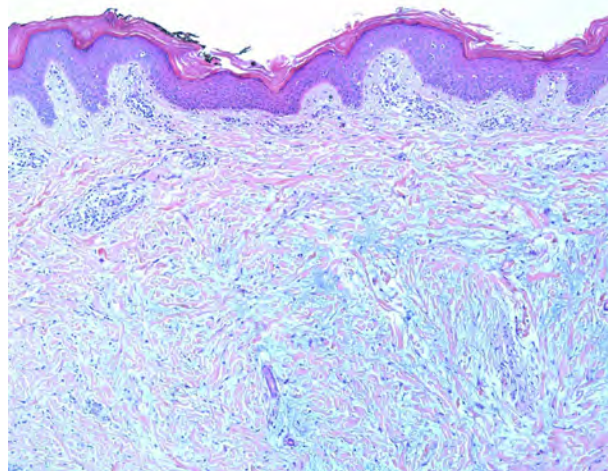
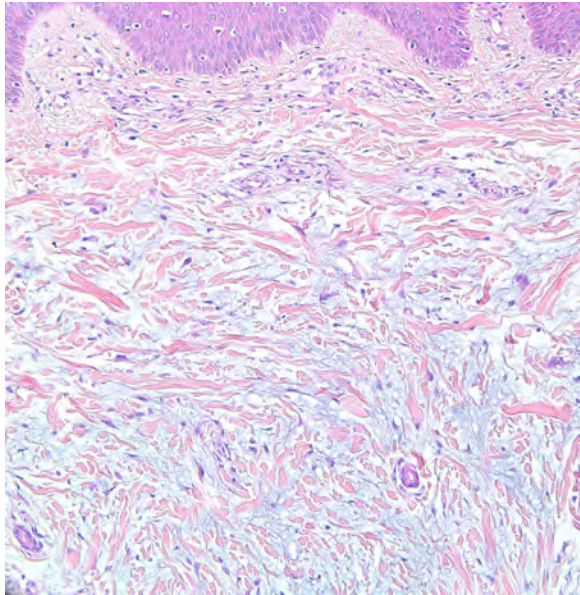
# Self-healing juvenile cutaneous mucinosis

Rongioletti F, Rebora A. Mucinoses in Bologna J. et al Dermatology, Mosby,2008

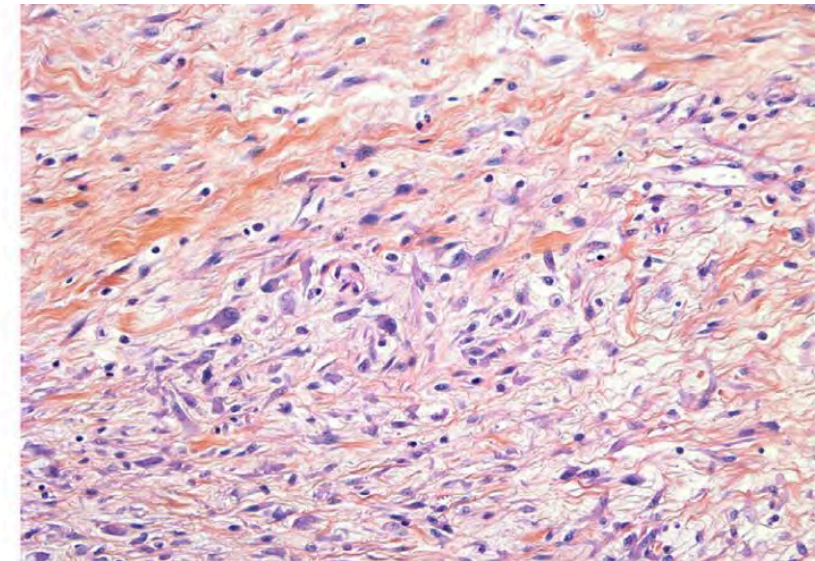
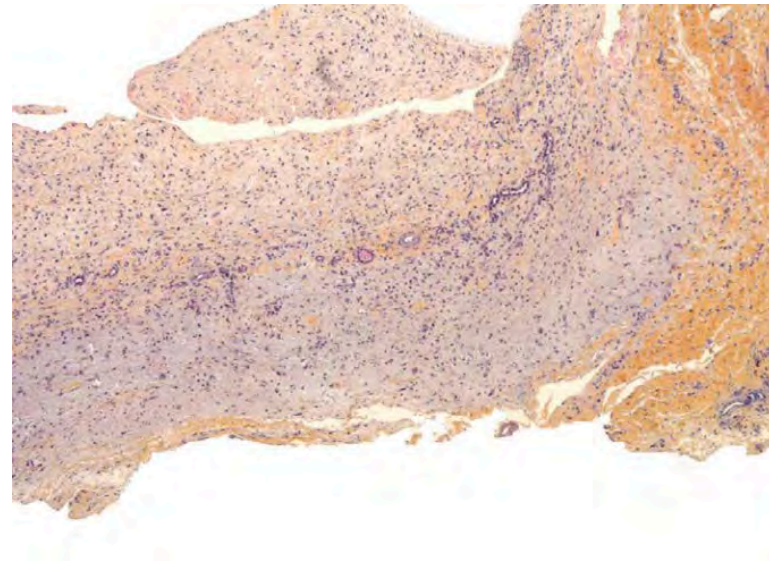
- **Acute eruption of papules, sometimes gathering in linear pattern, on the face, neck, scalp, abdomen and thighs**
- **Mucinous subcutaneous nodules on the face and on periarticular areas**
- **Systemic symptoms like fever, arthralgias, weakness and muscle tenderness in the absence of paraproteinemia and thyroid dysfunction**
- **Spontaneous resolution in a period ranging from a few weeks to many months (from 2 to 8)**



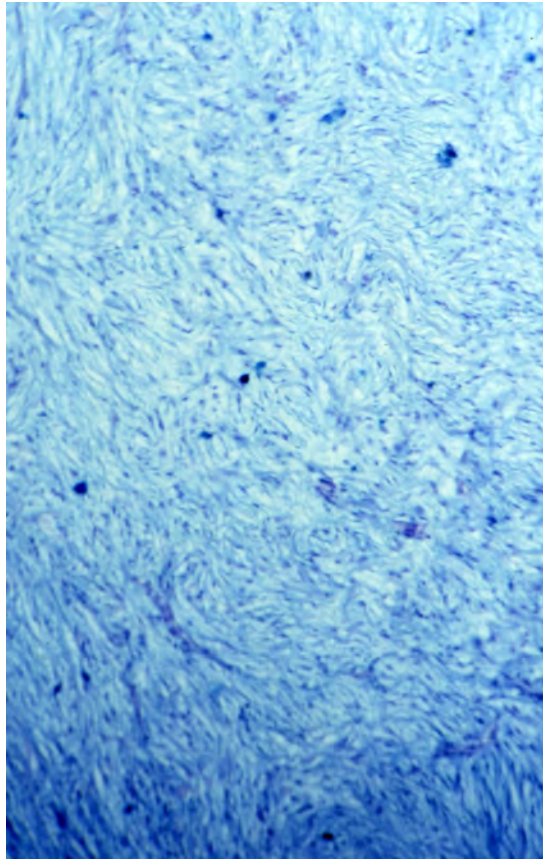
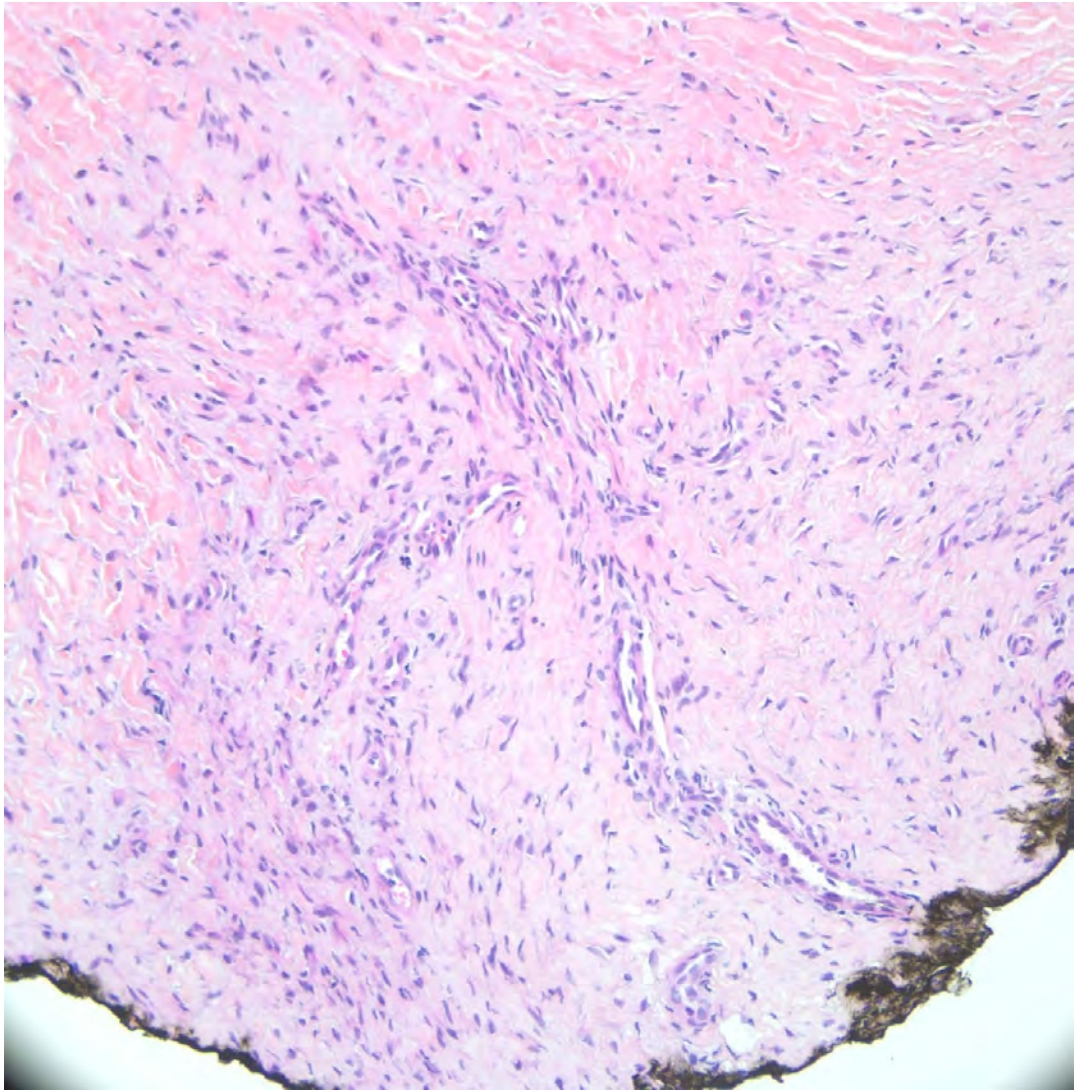
**Grouped, skin-colored, firm papules,  
sometimes in a linear fashion**



**Nodules on face  
and peri-articular, non painful nodules  
in both hands, adherent to the  
underlying tissue with arthralgias**



Fibroblasts and myofibroblasts associated with ganglion-like giant cells, a pattern resembling a proliferative fasciitis.



**Alcian blue pH 2.5**



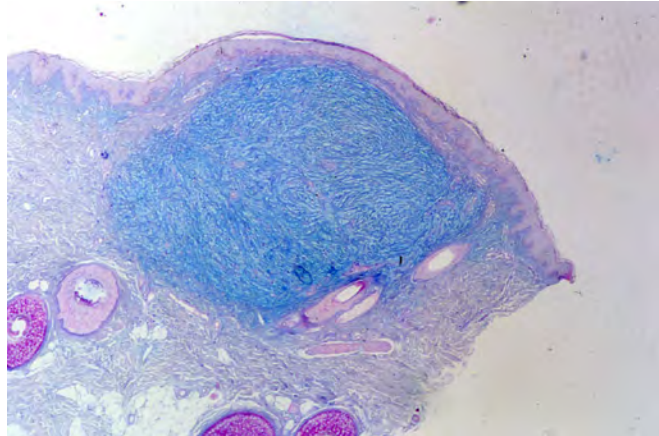
**Collagen fibers are dissociated by the presence of bluish material**

# Take-home pearls

- Mucinoses are a heterogeneous group of disorders divided into **dermal** and **follicular** forms
- They include the **adult** and **pediatric** forms
- **New mucinoses** should be considered
- Histopathologic diagnosis is hard for dermal mucinoses and requires **clinicopathologic correlation**
- Four histopathologic clues:
  1. The pattern of mucin distribution
  2. The level of mucin deposit
  3. Fibroblast proliferation
  4. Some additional findings

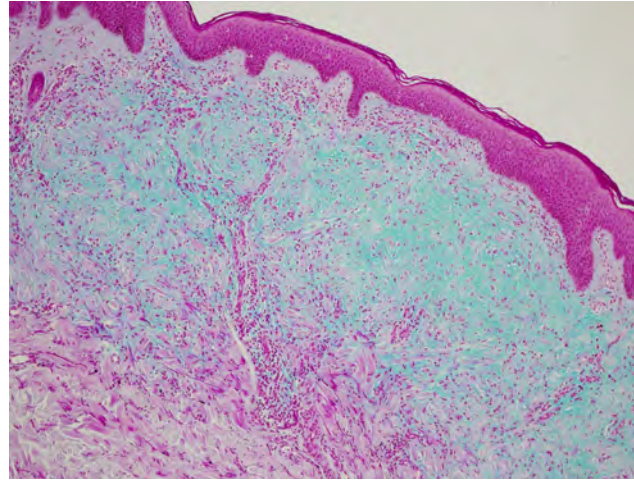
# 1. Pattern of mucin distribution

**Focal**



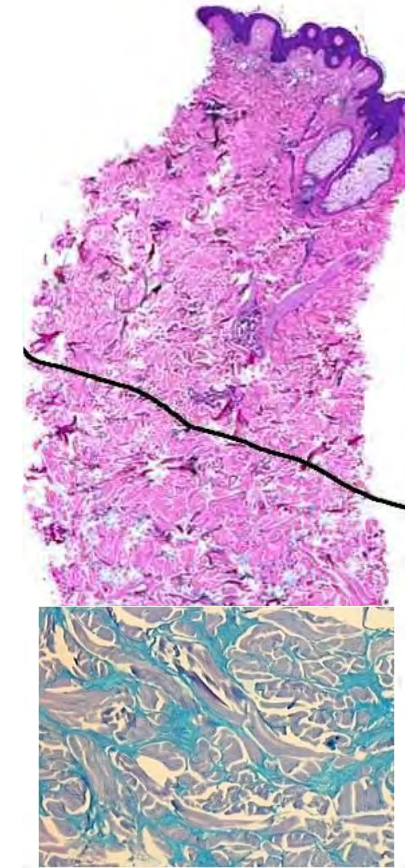
**Acral persistent  
papular mucinosis**

**Diffuse**



**Scleromyxedema**

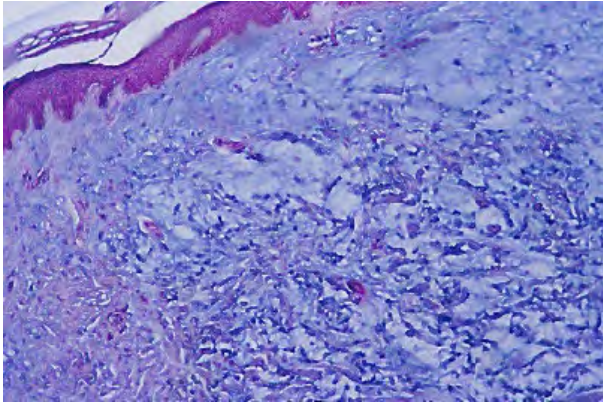
**Interstitial**



**Scleredema**

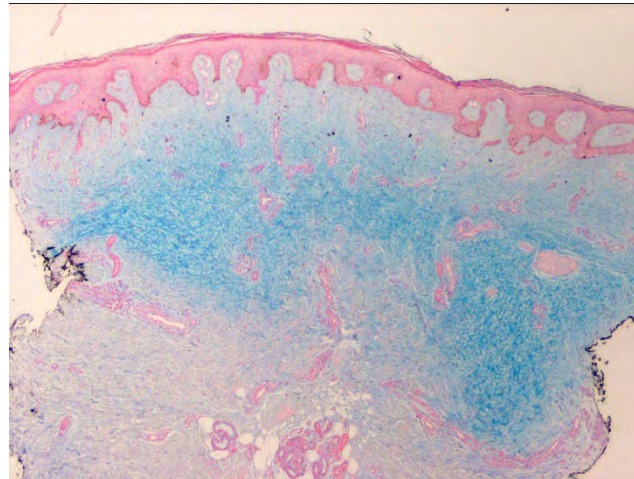
## 2. Level of mucin deposit

Superficial/upper dermis



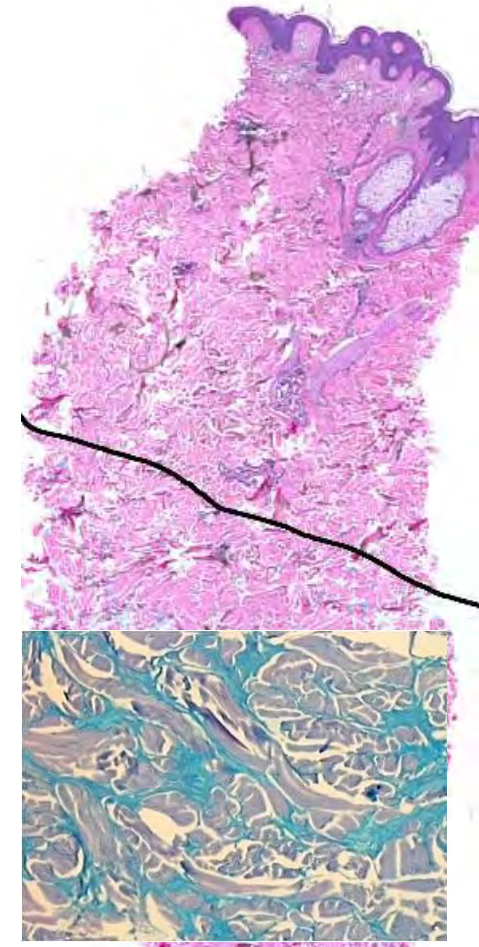
Localized  
lichen  
myxedematosus

Deep  
Mid/lower



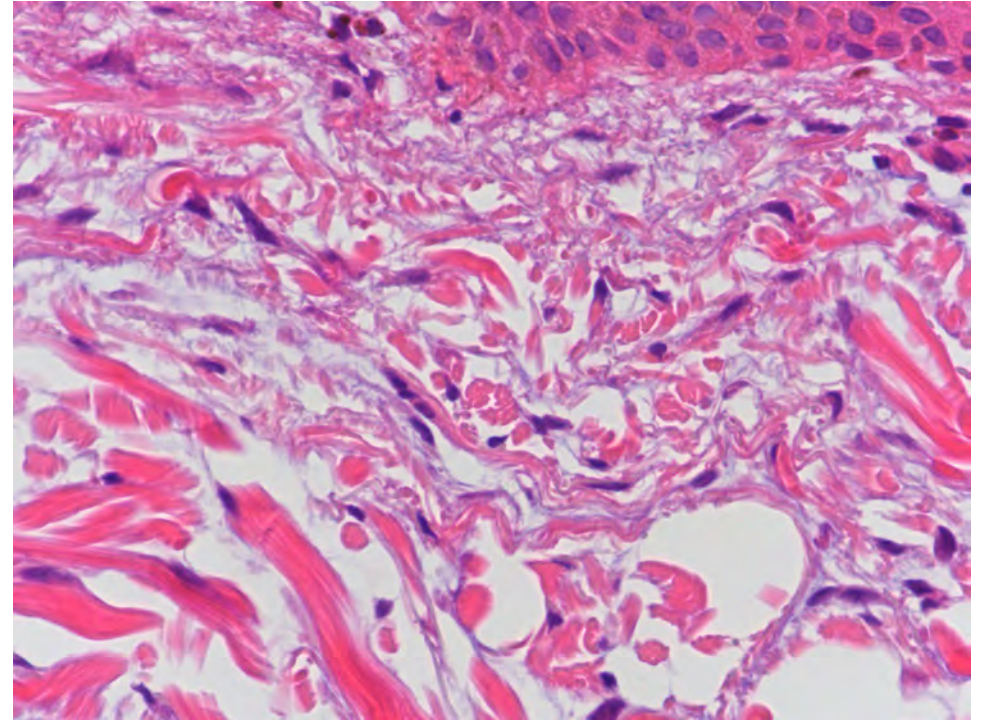
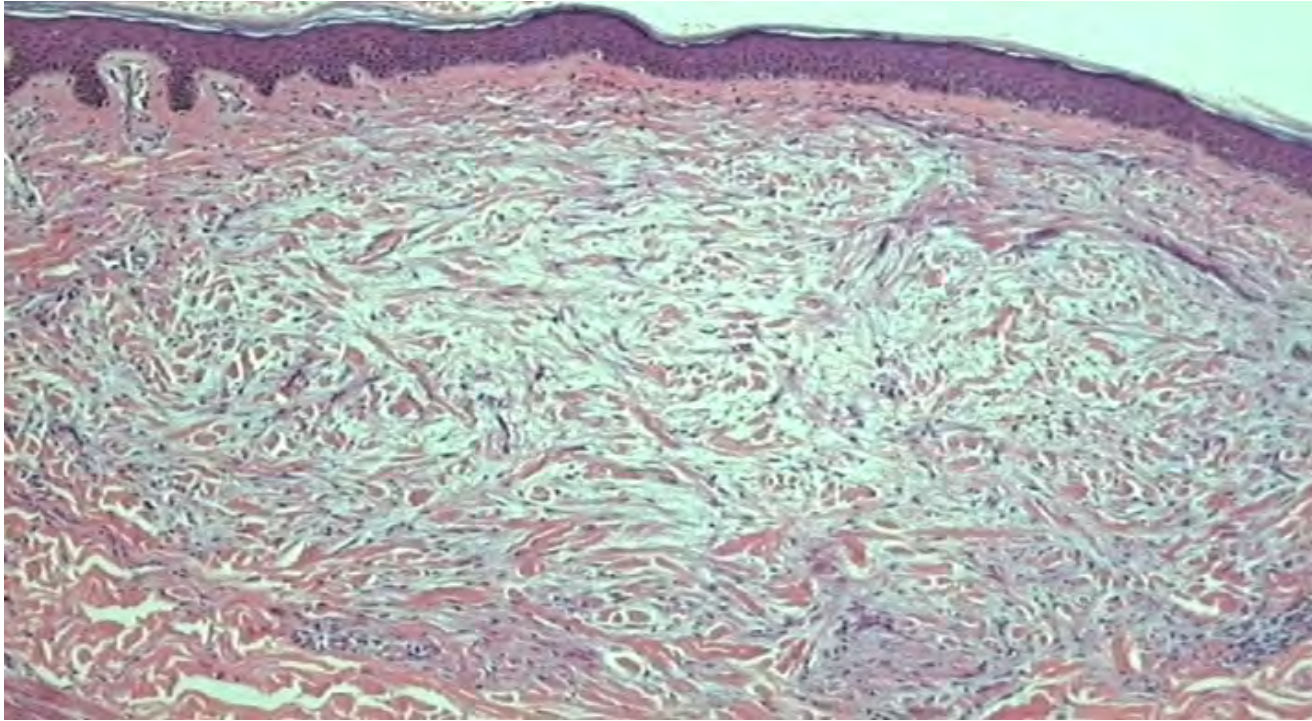
Pretibial myxedema

Reticular



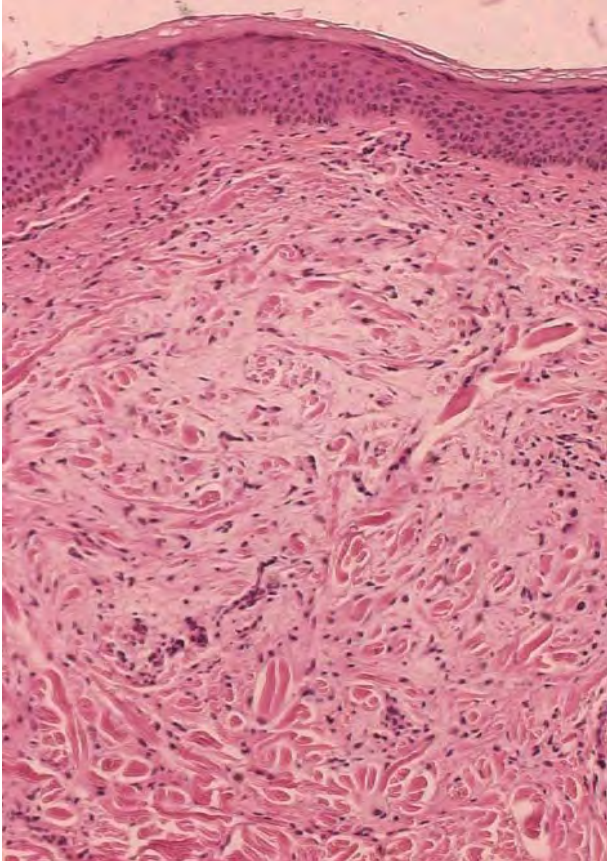
dema

### 3. Fibroblast proliferation



## 4. Additional findings

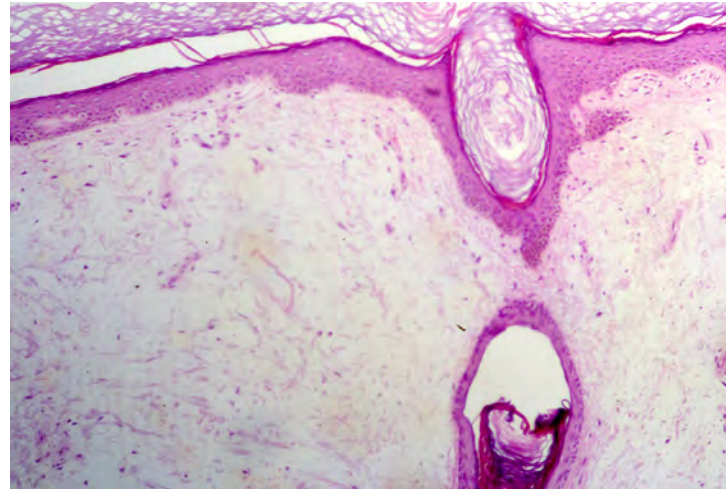
### Scleromyxedema



#### Triad:

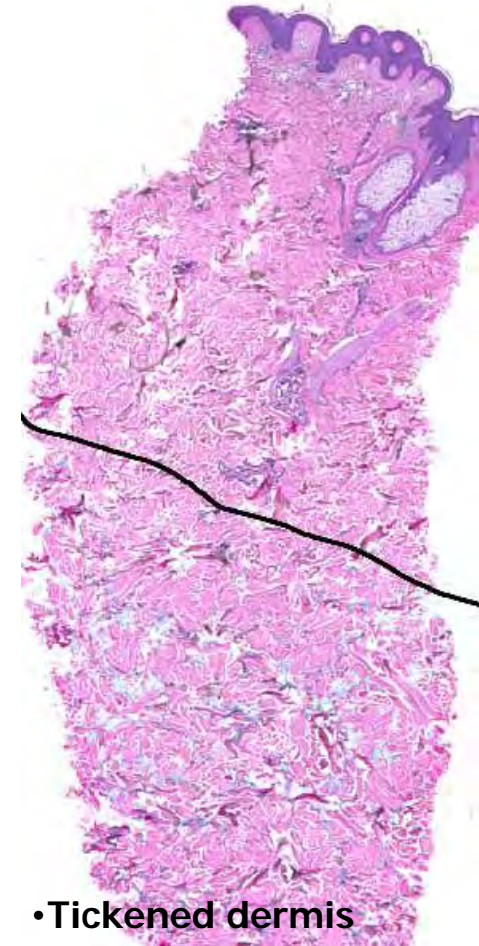
- mucin,
- fibroblast proliferation
- fibrosis

### Pretibial myxedema



- Hyperkeratosis
- Follicular plugging
- Mast-cells

### Scleredema



- Thickened dermis
- Fenestration of collagen
- No fibroblast proliferation

Be aware

Scleromyxedema vs scleredema

Reticular erythematous mucinosis vs  
lupus tumidus

Localized (pretibial) mucinosis vs obesity-  
associated lymphedematous mucinosis

Nodular mucinosis of the breast vs  
mucinous carcinoma

The eyes see what the mind  
knows

Johann Wolfgang Goethe





**GOT THE MESSAGE?**

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