Mucinous Disorders of the Skin-Don't GAG me!

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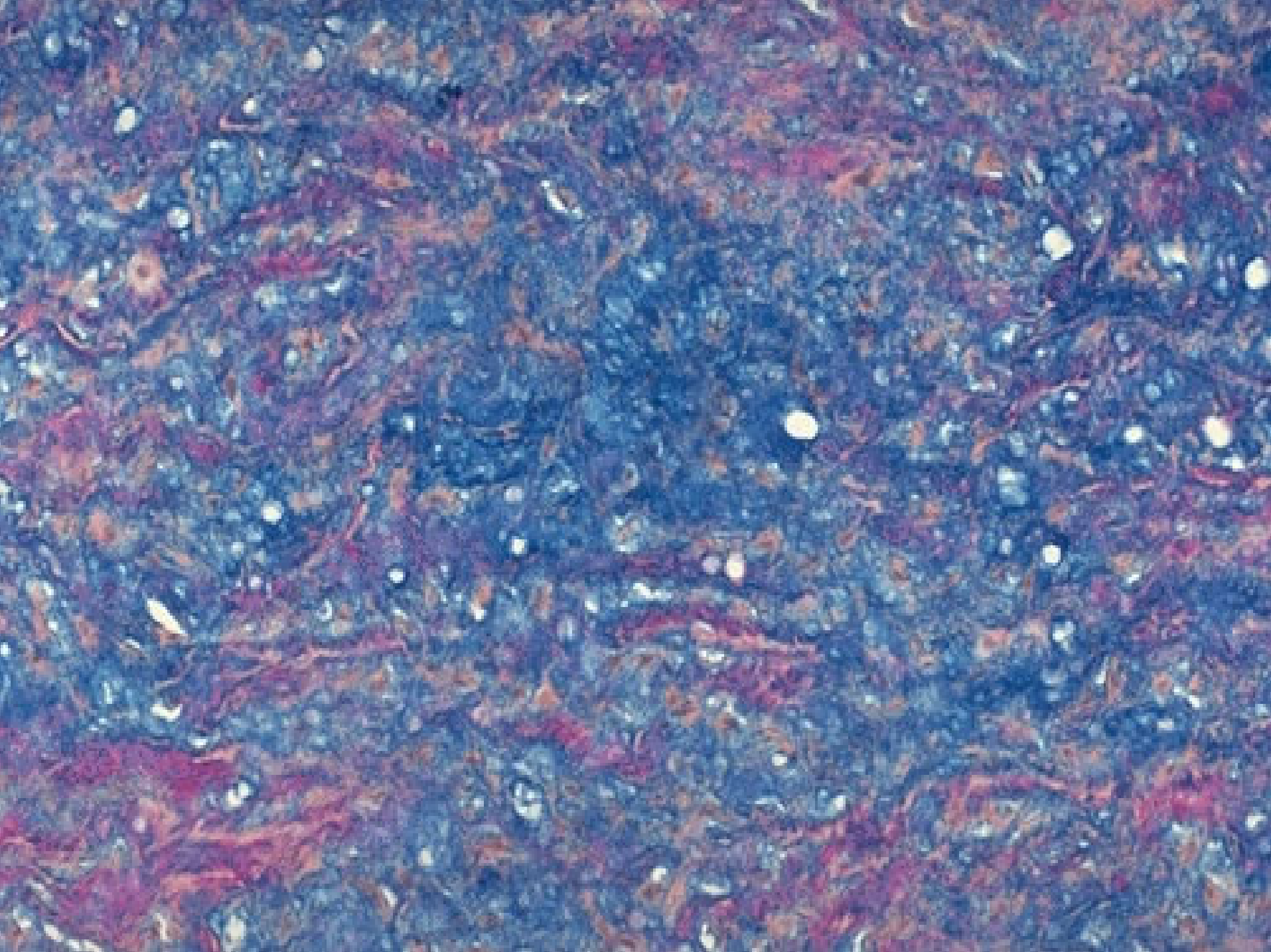
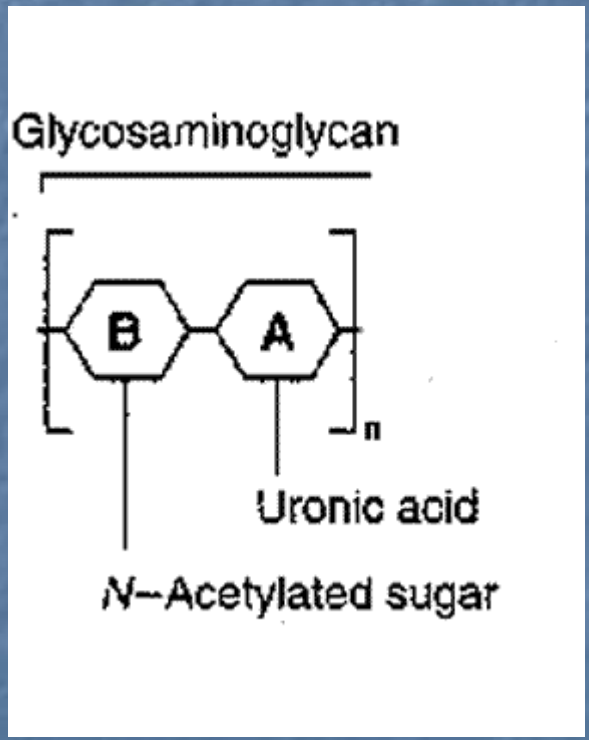
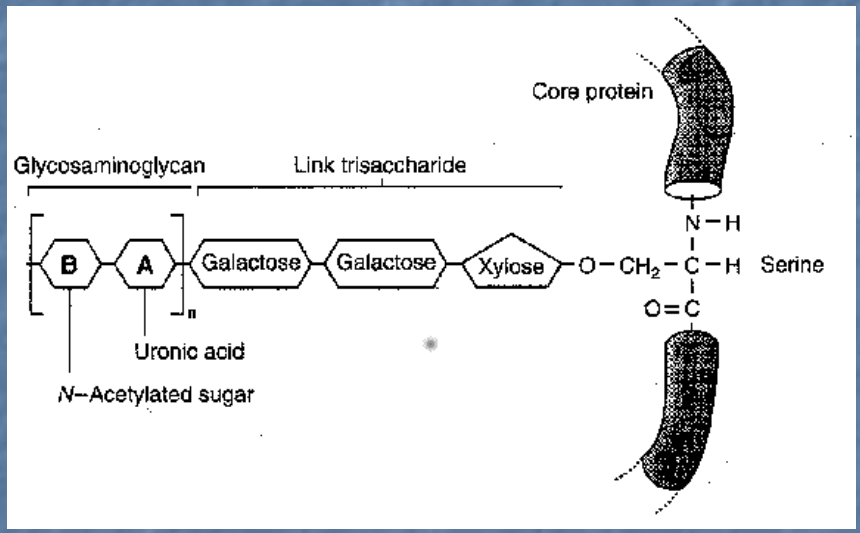


Glycosaminoglycans (GAGs)



- Unbranched polysaccharides containing a repeating disaccharide unit, either of two modified sugars--- N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc) and a uronic acid such as glucuronate or iduronate
- Imparts high viscosity to the solution and allows for lubrication and structural integrity for cells
- Specific GAGs of physiological significance
  - Hyaluronic acid
  - Dermatan sulfate
  - Chondroitin sulfate
  - Heparin
  - Heparan sulfate
  - Keratan sulfate

Proteoglycans (Mucopolysaccharides)



- Majority of GAGs in the body are linked to core proteins, forming proteoglycans
- GAGs extend perpendicularly from the core
- Linkage of GAGs to the protein core involves a specific trisaccharide composed of two galactose residues and a xylulose residue (GAG-GalGalXyl-O-CH2-protein)
- Trisaccharide linker is coupled to the protein core through an O-glycosidic bond to a *S* residue in the protein

MPS DISEASES (in alphabetical order)	CLINICAL PHENOTYPE	ENZYME DEFICIENCY
Mucolipidosis type I	Sialidosis types I and II	Neuaminidase
Mucolipidosis types II and III	I-Cell Disease Pseudo-Hurler Polydystrophy	Phosphotransferase
Mucolipidosis type IIIC	Pseudo-Hurler Polydystrophy	Phosphotransferase y-submit
Mucolipidosis type IV		Unknown
Mucopolysaccharidosis type I	Hurler Syndrome Scheie Syndrome Hurler-Scheie Syndrome	a-L-Iduronidase
Mucopolysaccharidosis type II	Hunter Syndrome	Iduronate-2-sulphatase
Mucopolysaccharidosis type IIIA	Sanfilippo Syndrome A	Heparan-N-sulphatase

MPS DISEASES (in alphabetical order)	CLINICAL PHENOTYPE	ENZYME DEFICIENCY
Mucopolysaccharidosis type IIIB	Sanfilippo Syndrome B	a-N-Acetylglucosaminidase
Mucopolysaccharidosis type IIIC	Sanfilippo Syndrome C	AcetylCoA:N-acetyltransferase
Mucopolysaccharidosis type IIID	Sanfilippo Syndrome D	N-Acetylglucosamine 6-sulphatase
Mucopolysaccharidosis type IVA	Morquio Syndrome	Galactose 6-sulphatase
Mucopolysaccharidosis type IVB	Morquio Syndrome	b-Galactosidase
Mucopolysaccharidosis type VI	Maroteaux-Lamy Syndrome	N-Acetylglucosamine 4-sulphatase
Mucopolysaccharidosis type VII	Sly Syndrome	b-Glucuronidase

Mucinous Dermal Disorders

- Considered Primary
  - Generalized myxedema
  - Pretibial myxedema
  - Reticular erythematous mucinosis
  - Scleredema
  - Scleromyxedema
  - Papular mucinosis
  - Acral persistent papular mucinosis
  - Focal mucinosis
  - Digital mucous cyst
  - Mucocele
  - Cutaneous myxoma
  - Cutaneous mucinosis of infancy
  - Nevus mucinosis
  - Alopecia mucinosa (Follicular mucinosis)
  - Mucopolysaccharidoses

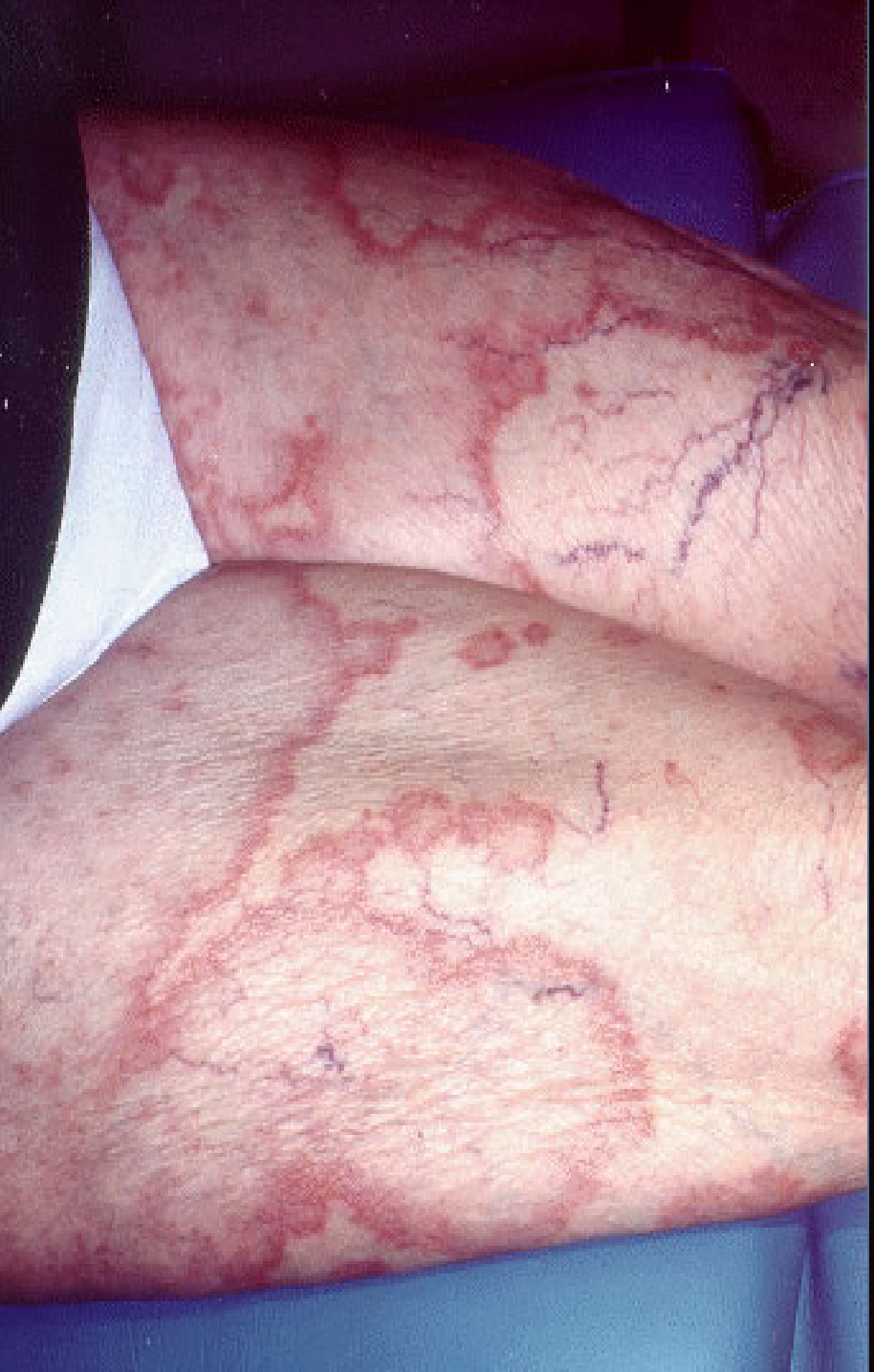
Mucinous Dermal Disorders

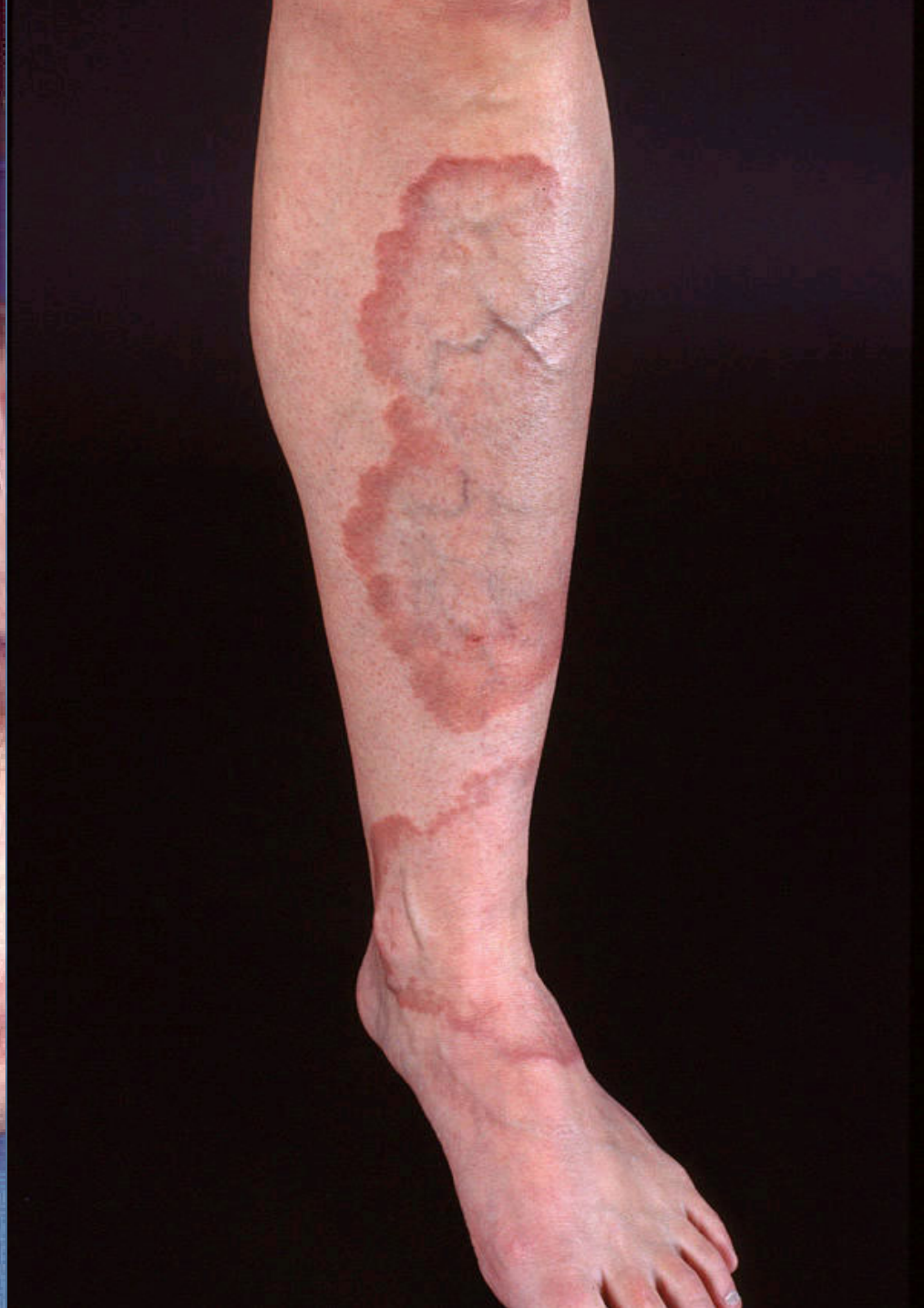
- Considered Secondary
  - Degos disease
  - Dermatomyositis
  - Granuloma annulare
  - Jessner's lymphocytic infiltrate
  - Lupus erythematosus

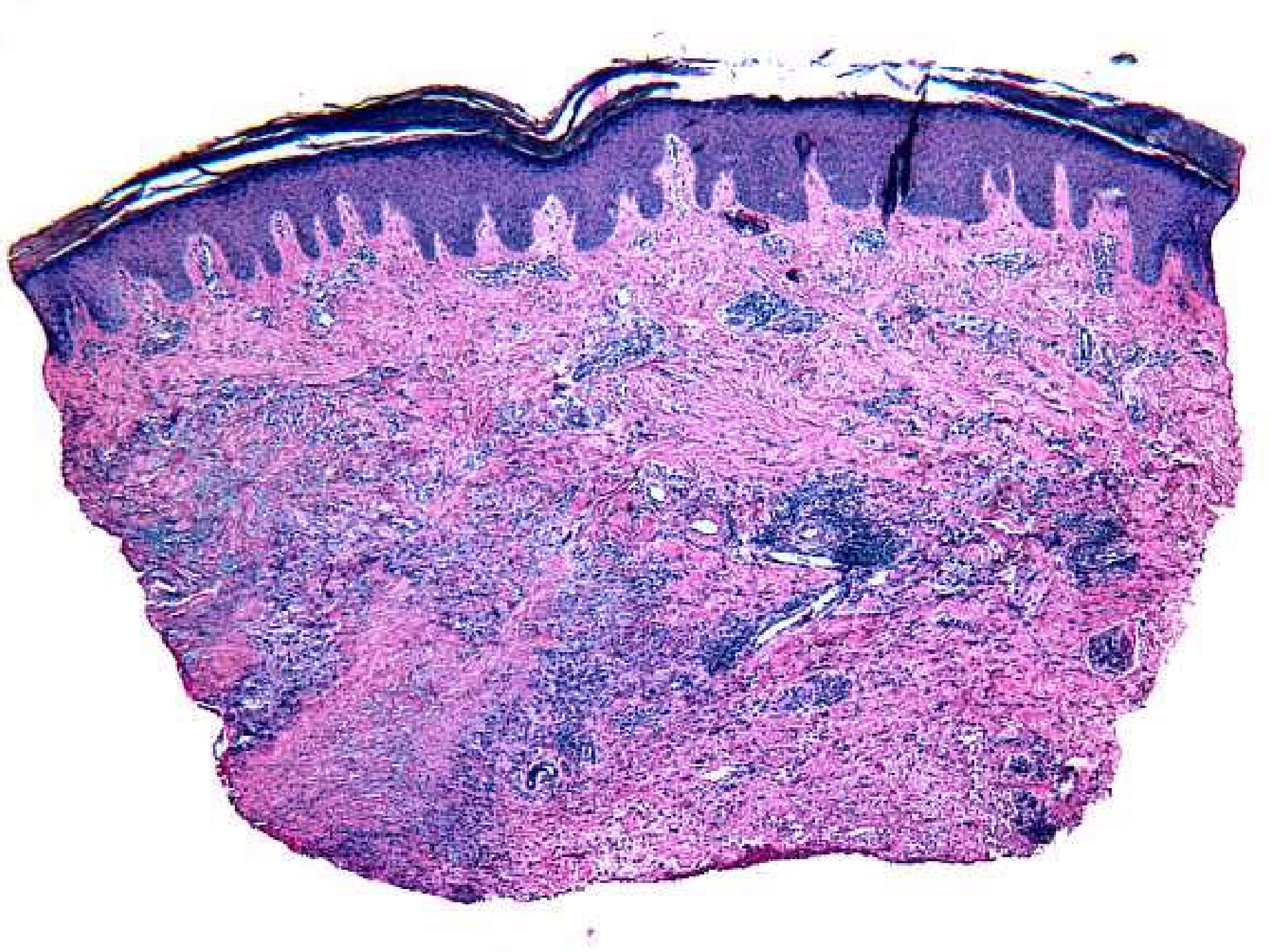
Stains

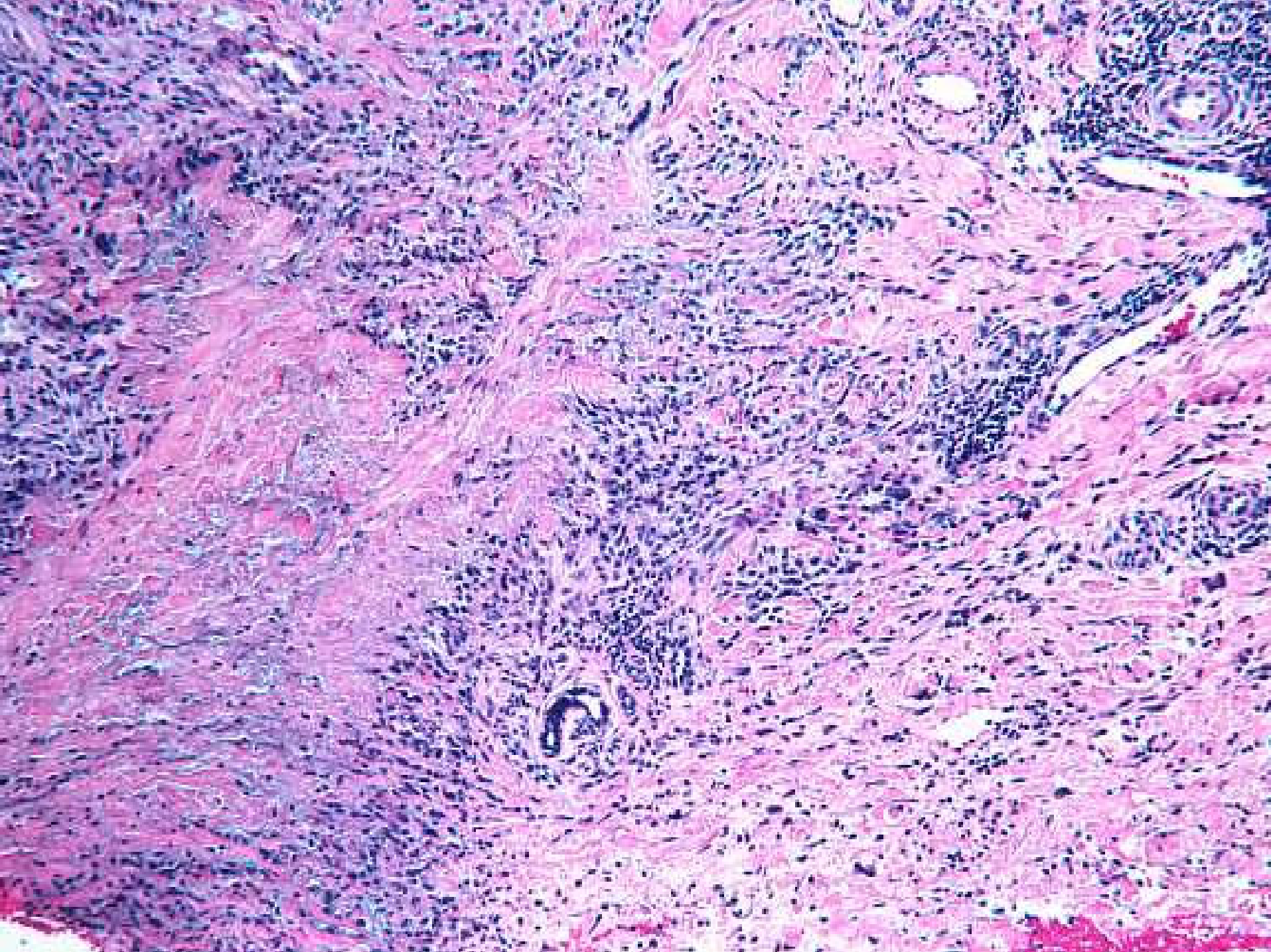
- Colloidal iron
- Alcian blue/PAS
- PAS
- Mucicarmine

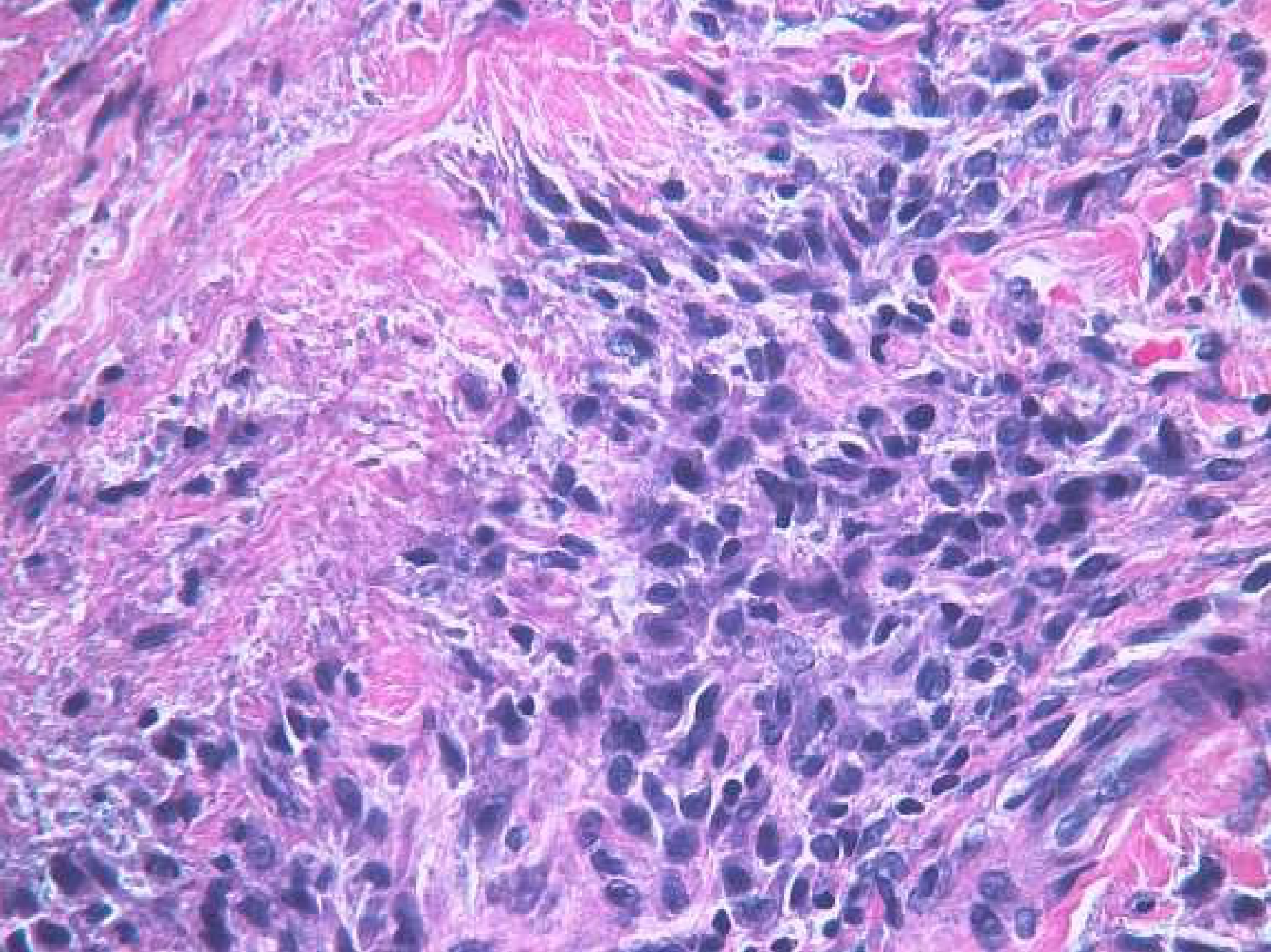
Mucopolysaccharide	Stain
Neutral (GI and prostate)	PAS
Acid (simple, or non-sulfated) (Epithelial cells with sialic acid)	PAS Alcian blue at pH 2.5 Colloidal iron Metachromatic dyes Hyaluronidase resistant
Acid (simple, mesenchymal) (Tissue stroma, sarcomas)	Alcian blue at pH 2.5 Colloidal iron Metachromatic dyes PAS negative Hyaluronidase sensitive
Acid (complex, or sulfated, epithelial) (Adenocarcinoma)	PAS Alcian blue at pH 1 Colloidal iron Mucicarmine Metachromatic stains Hyaluronidase resistant
Acid (complex, connective tissue) (Cartilage, bone, stroma)	Alcian blue at pH 0.5 PAS negative











Granuloma Annulare

- Variants
  - Localized GA
  - Generalized GA
  - Subcutaneous GA
  - Perforating GA
  - Arcuate dermal erythema

GA-Clinical Presentations

- Localized
  - Groups of 1-2 mm flesh-colored to erythematous papules, often in an annular arrangement, over distal extremities.
  - Grouped lesions may expand into arciform or annular plaques measuring 1-5 cm in diameter.
  - Centers of lesions may be slightly hyperpigmented and depressed relative to their borders
- Generalized
  - Few to thousands of 1-2 mm, flesh-colored to erythematous papules or nodules, symmetrically disposed over acral areas and the trunk
  - May coalesce into annular plaques, which measure 3-6 cm in diameter and may enlarge centrifugally over weeks to months.
- Subcutaneous
  - Firm, nontender, flesh-colored to pinkish nodule without overlying epidermal alteration.
  - Solitary but may occur in clusters.
  - Lower extremity (65% cases), often on pretibial surface
  - Deep dermal or subcutaneous nodules on the extremities are attached to fascia and thus are often mobile

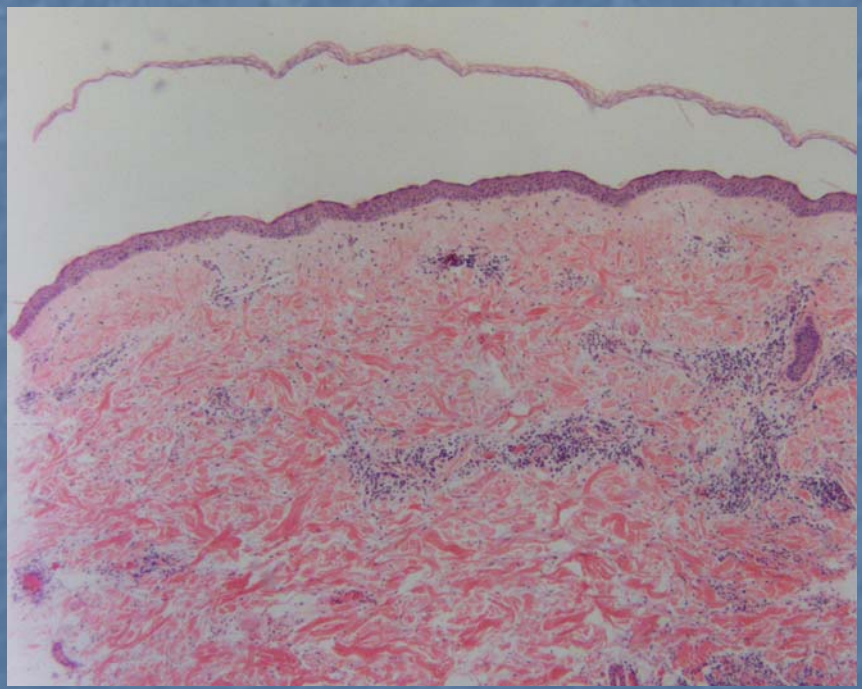
GA-Clinical Presentations

- Perforating
  - One to hundreds of grouped, flesh-colored to erythematous papules measuring 1-4 mm in diameter.
  - Papules often coalesce to form annular plaques.
  - May progress to yellowish pustular lesions
  - Extensor surfaces of extremities and dorsa of hands and fingers
- Arcuate dermal erythema
  - Uncommon form with infiltrated, erythematous patches, which may form large, hyperpigmented rings with central clearing
  - Papules are a less prominent feature in this variant
  - Patches that typically present over the trunk may spread centrifugally over weeks to months

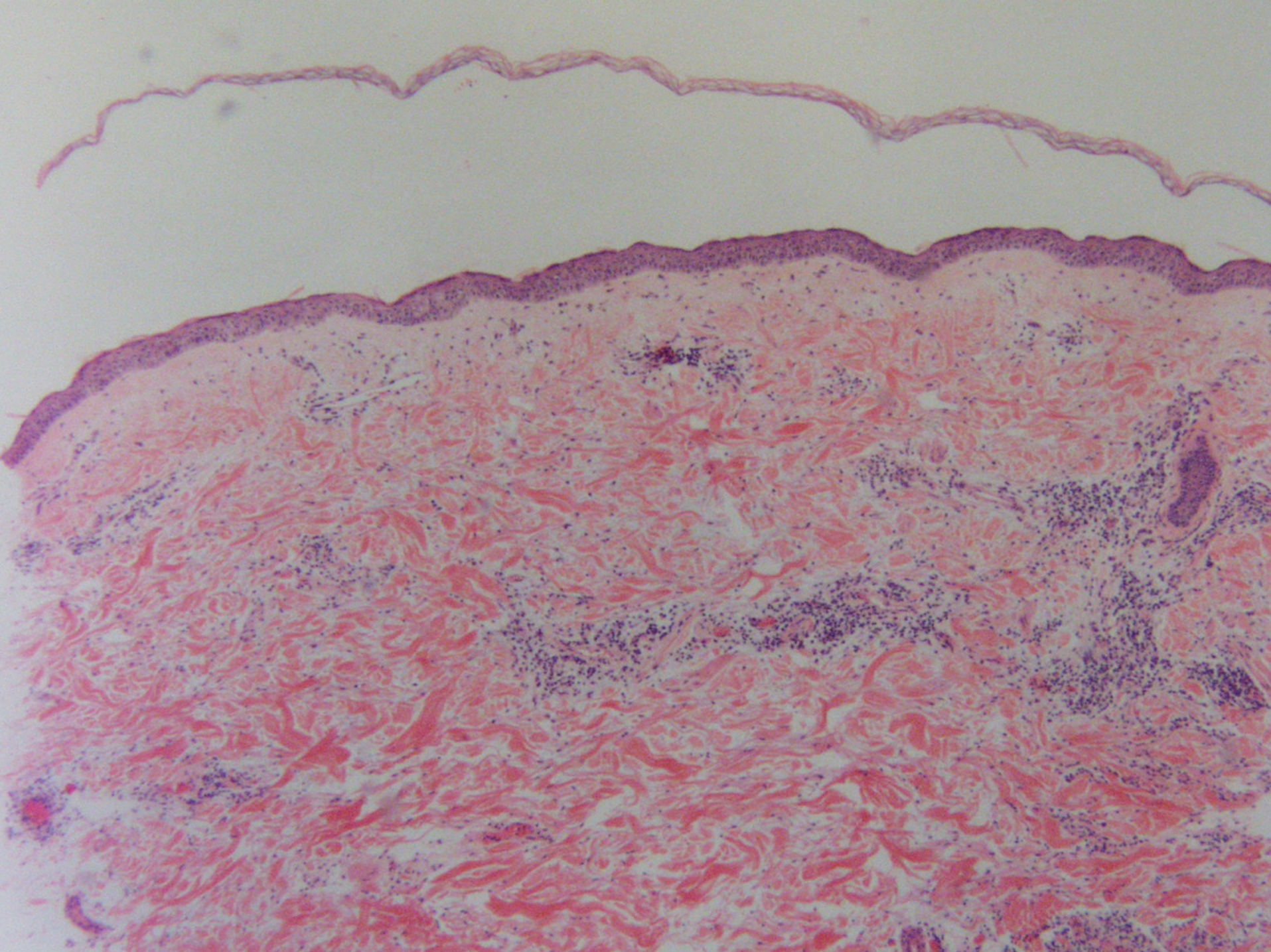
GA-Disease Associations

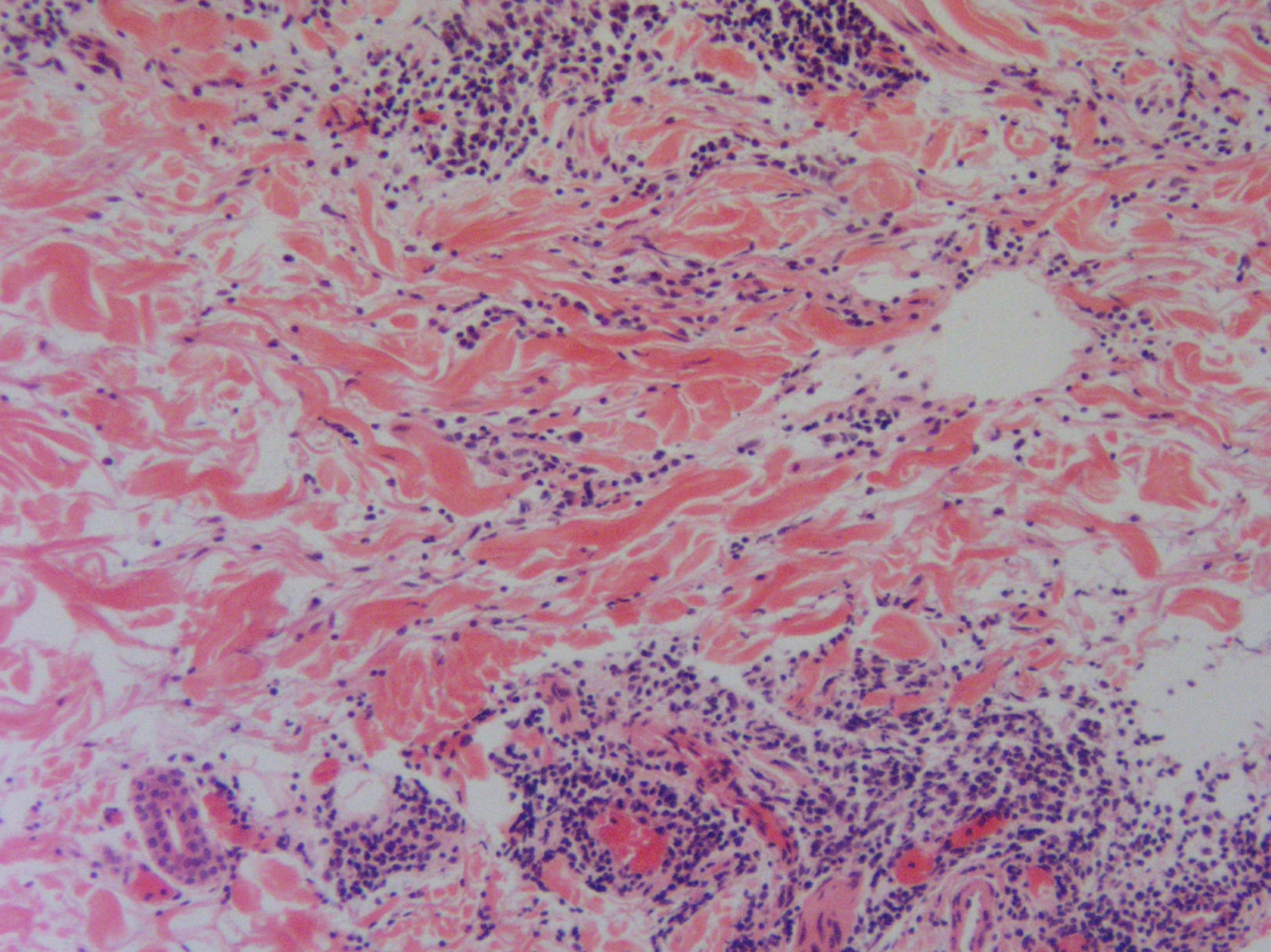
- Tuberculosis, insect bites, trauma, sun exposure, thyroiditis, and viral infections
- Familial cases of GA
  - HLA-B8 in localized
  - HLA-A29 and HLA-BW35 in generalized
- Relationship to systemic diseases
  - Diabetes mellitus
  - Thyroid disease
  - Malignancy
  - AIDS

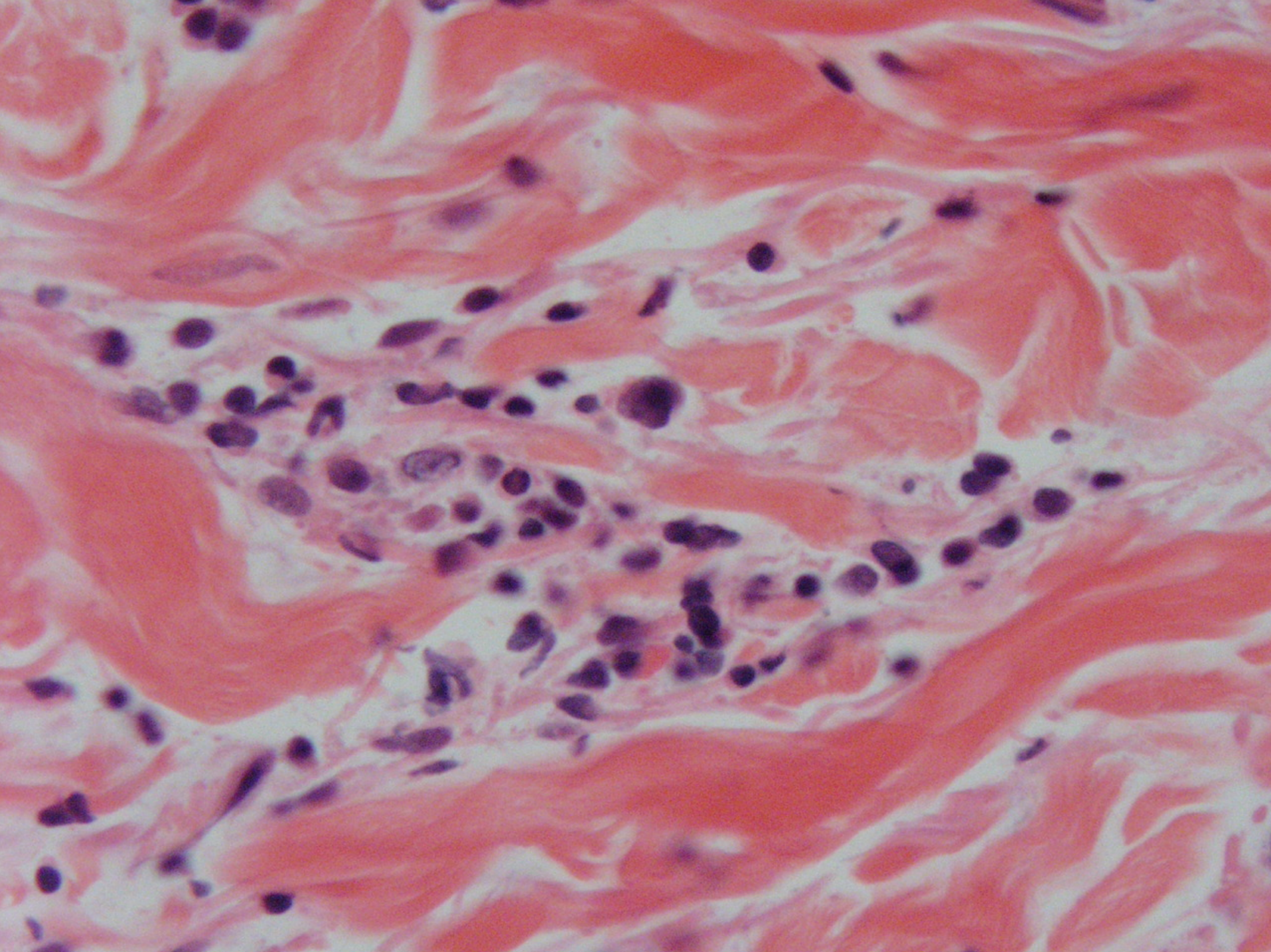
GA-Histopathology



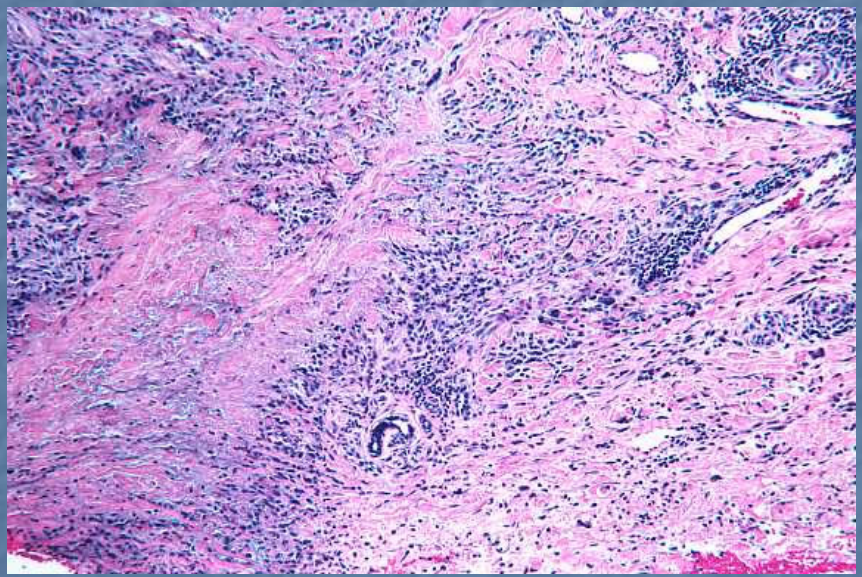
- Early "interstitial" or "incomplete“
  - Lymphocytes around vessels of the superficial and deep plexuses
  - Macrophages scattered between reticular dermal collagen bundles that are separated by mucin within which mast cells may be found
  - Mucin in GA is hyaluronic acid, confirmed by staining with colloidal iron or Alcian blue at pH 2.5
- Fully evolved lesions of GA and subcutaneous nodules of deep GA demonstrate palisaded granulomatous dermatitis
  - Septal and lobular panniculitis
  - Macrophages surround acellular, necrobiotic areas in which collagen bundles are thinned







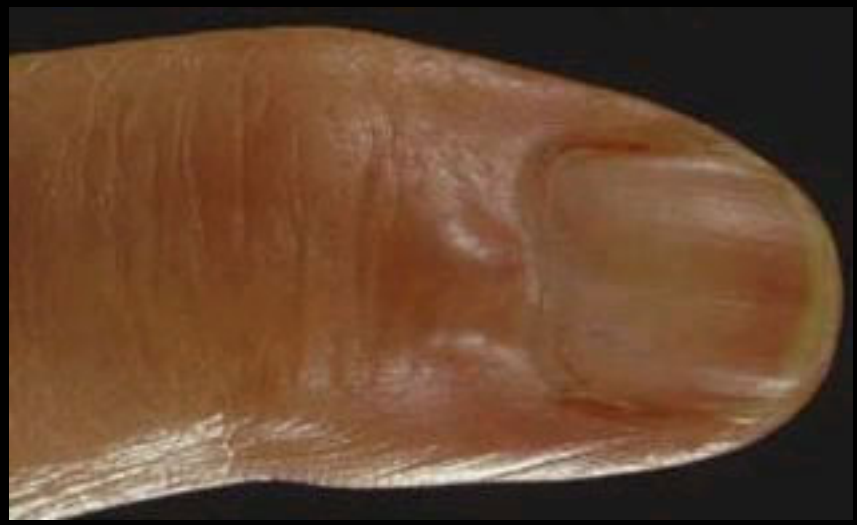
GA-Histopathology

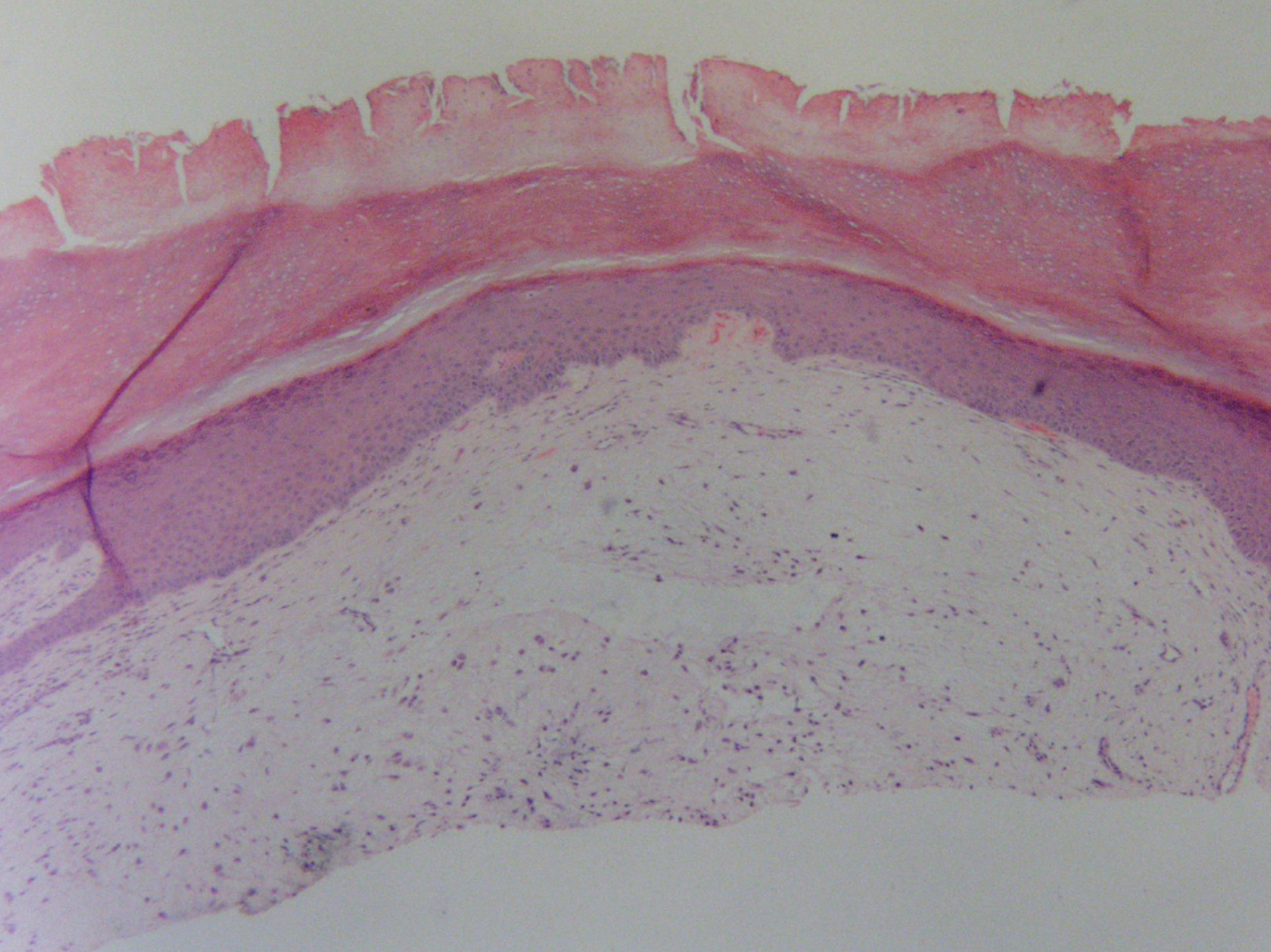


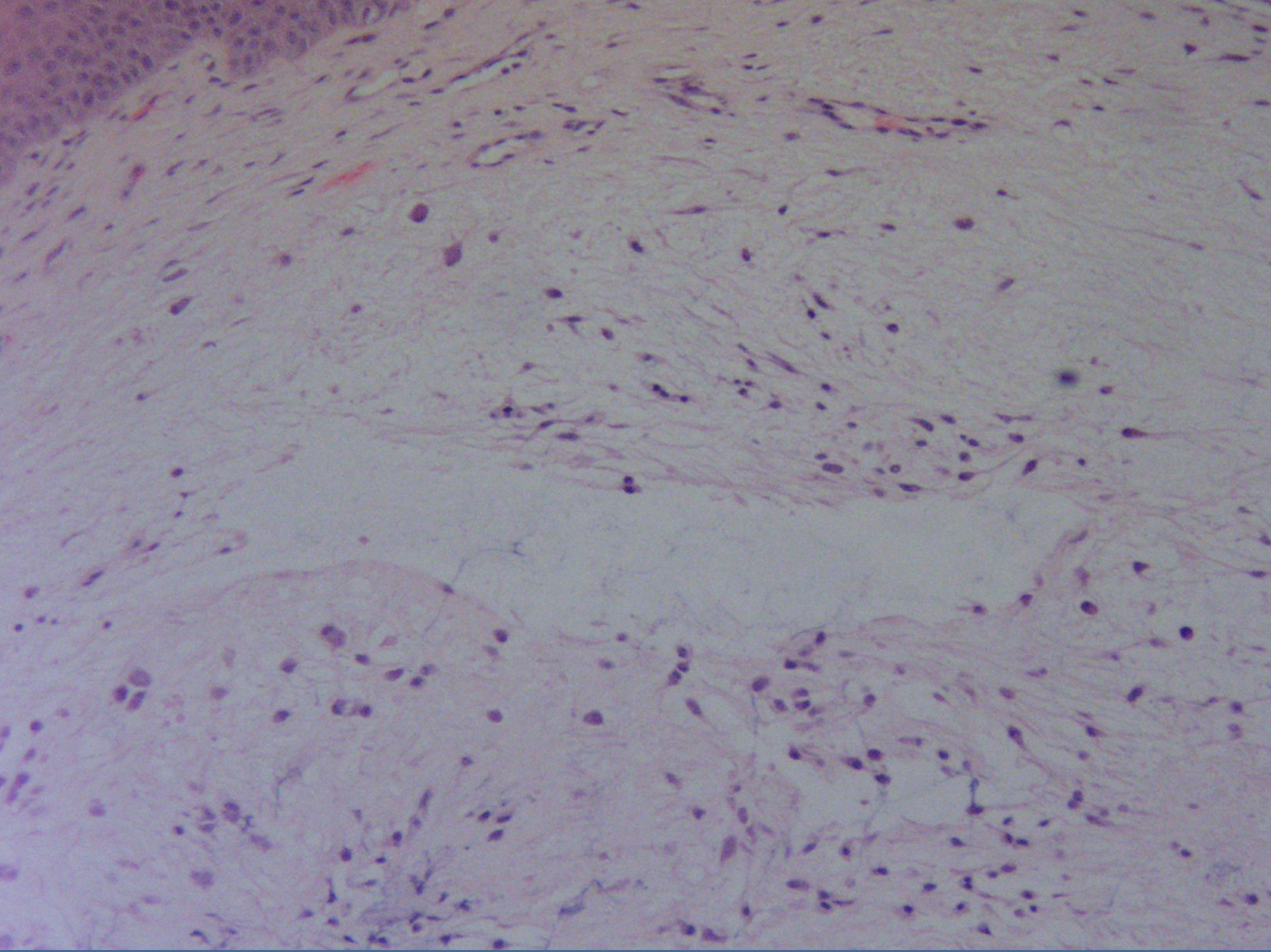
- Some centers of granulomas contain degenerated, homogeneous appearing collagen and are deeply eosinophilic
  - Necrotic, small vessels in the centers of palisaded foci are surrounded by nuclear dust
  - Presence of fibrinogen can be shown by direct immunofluorescence in the centers of palisaded granulomas
- Perforating lesions
  - Necrobiotic material is extruded through focal perforations
  - Epidermal hyperplasia at the edge of the perforation forms a pseudochannel communicating with an underlying necrobiotic granuloma.
- Rare cases of non-necrobiotic, sarcoidal or tuberculoid GA

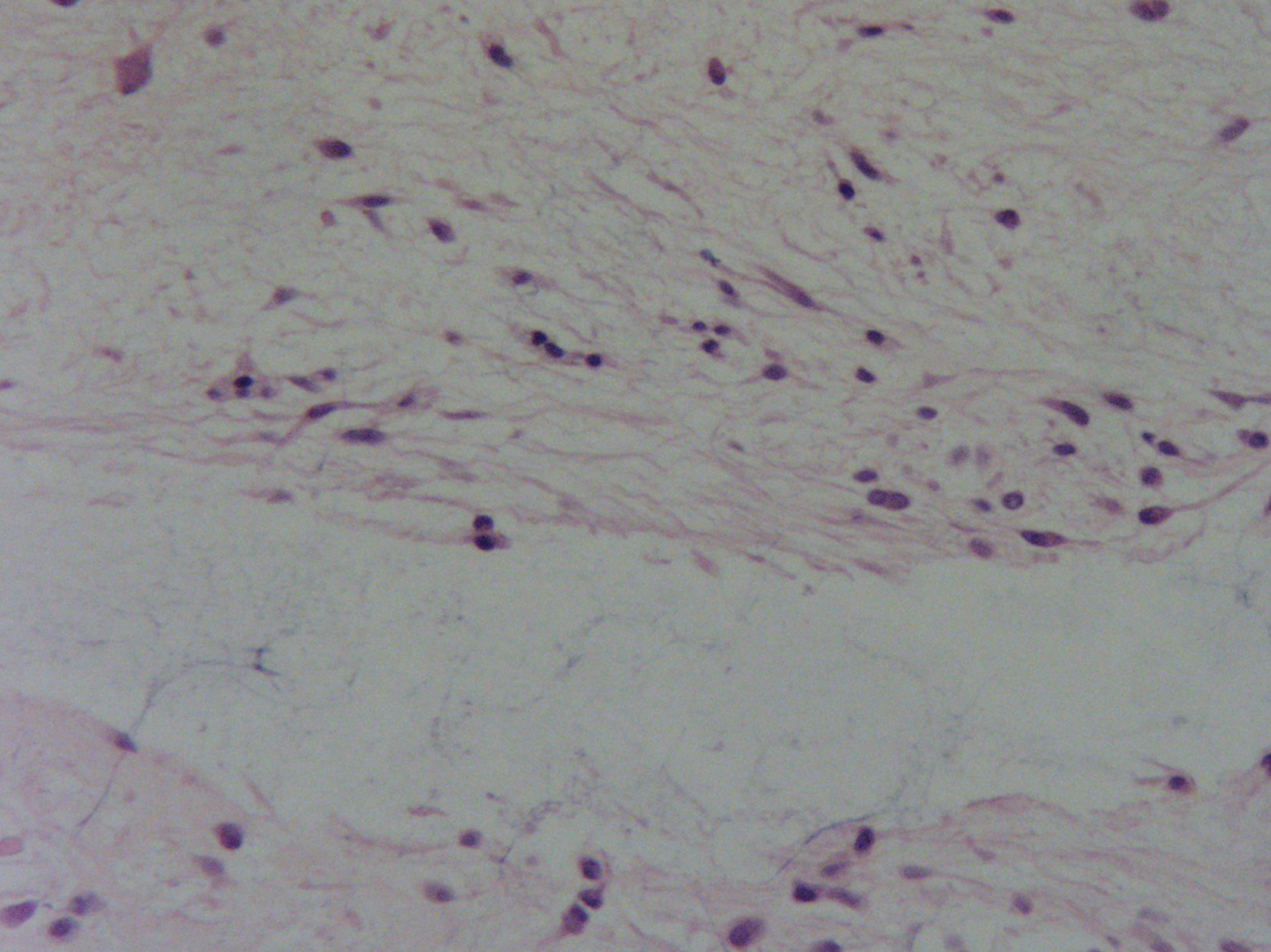
GA-Prognosis and Treatment

- Localized GA
  - Intralesional corticosteroids or potent topical corticosteroids used with or without occlusion
  - Cryotherapy may lead to hypo or hyperpigmentation, but effective
  - PUVA, systemic steroids, dapsone, pentoxifylline, hydroxychloroquine, isotretinoin, chlorambucil
  - Spontaneous resolution occurs within 2 years in 50% of cases
  - May last weeks to decades
  - Recurrence, often at the same site, is seen in 40%
- Generalized
  - Prolonged chronic course, with rare spontaneous resolution, poor response to treatment, and frequent relapses
- Subcutaneous
  - Often spontaneously regress
  - Local or distant recurrences have been reported in 20-75%







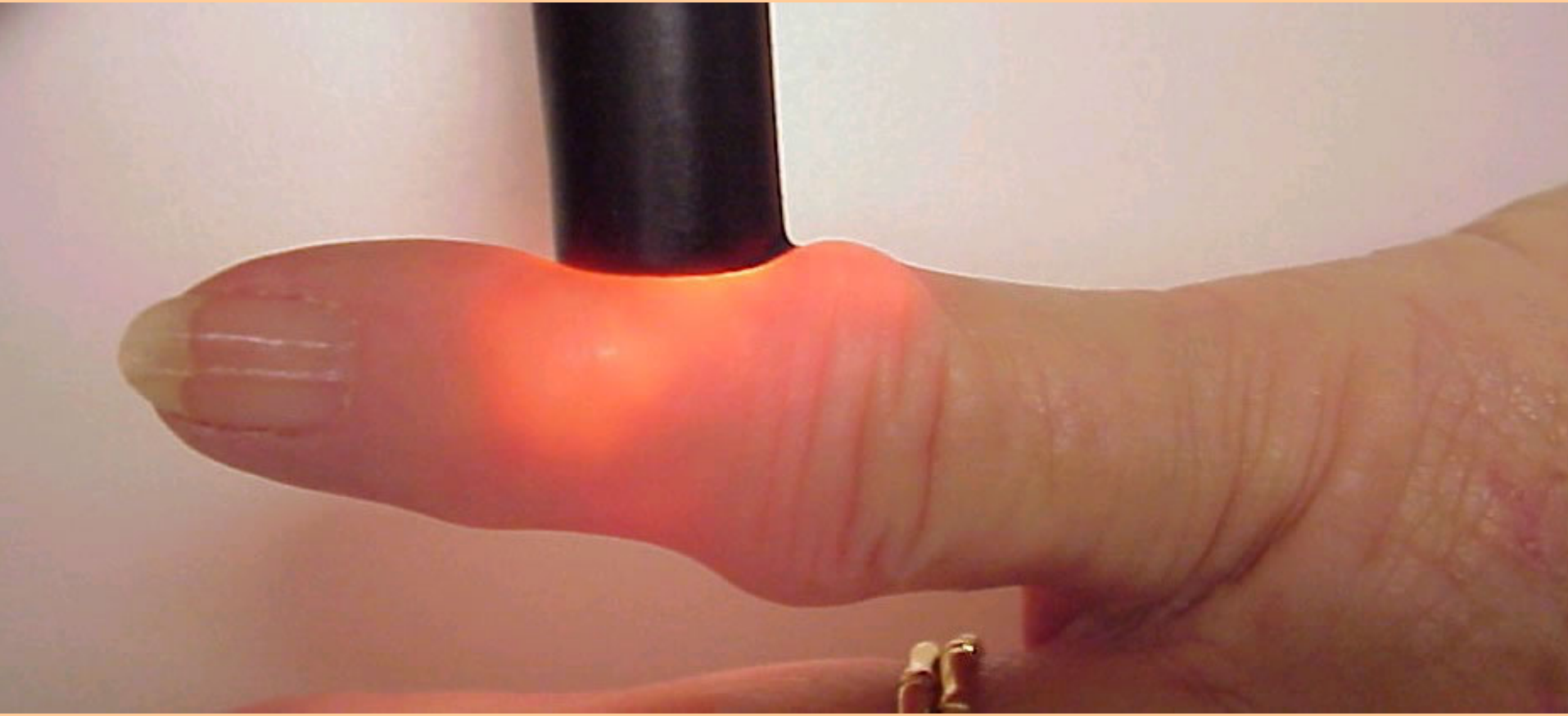


Digital Mucous Cyst

- Usually solitary, benign ganglion cysts of the digits, at DIP joints or in the proximal nail fold
- May appear suddenly or develop over a period of months. Grooving of the nail may precede the clinical manifestation of the cyst itself by up to 6 months
- Osteoarthritis of the small joints is noted at the site of cyst emergence
- Intermittent spontaneous discharge of cyst contents can occur, and, in a significant fraction of cases, cysts may disappear spontaneously.
- Antecedent trauma has been documented in a small minority of cases
- As cysts enlarge, pain is an increasingly common complaint

Digital Mucous Cyst

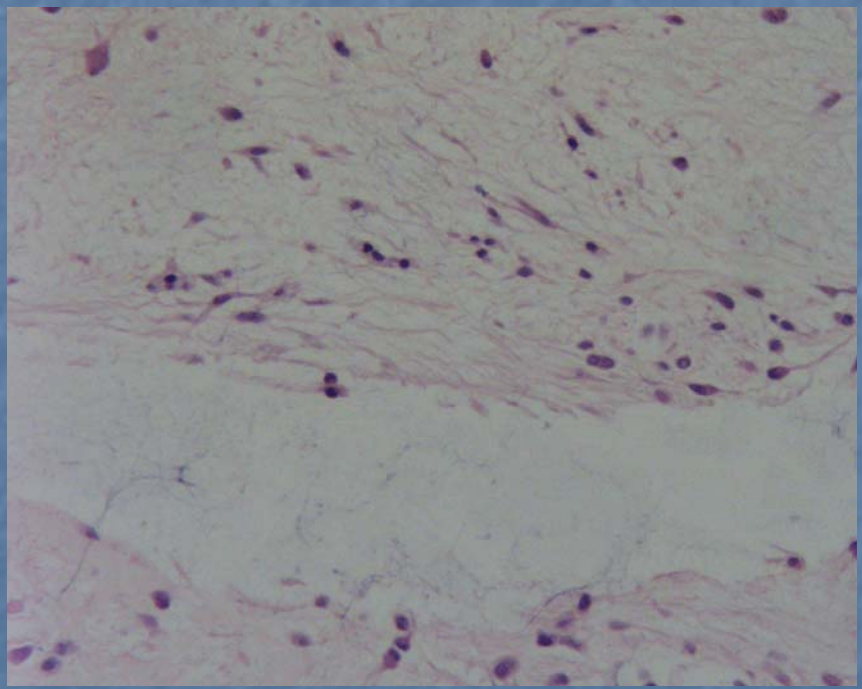
- Skin - Distribution
  - The cysts are located off the midline of the digits and, according to one series, are more common on the radial than ulnar aspect of the fingers.
  - They most often are found on the dorsolateral aspect of the fingers, intradermally, between the DIP and proximal nail fold. Less frequently, they occur between the proximal nail fold and the nail plate, beneath the nail matrix, or in the pulp of the digit.
  - Cysts most frequently are found on the middle or index finger of the dominant hand; toe involvement is less common.
- Skin - Color
  - DMCs are translucent to flesh-colored.
  - When they are under the nail matrix, a red lunula and a longitudinal brownish band may be seen.
- Nails
  - Longitudinal grooving or depression of the nail occurs when DMCs involve the posterior nail fold.
  - Grooving may be accompanied by transverse ridging and thinning of the nail overlying the cyst.
  - Gross disruption of the nail is less common.
  - DMCs are more likely to be above than below the nail matrix.



Digital Mucous Cyst

- Transillumination
  - Differentiating from giant-cell tendon sheath tumor
- Methylene blue infusion
  - Approximately 12 hours before surgery, the DIP may be injected with methylene blue and local anesthetic
  - Coloring of the entire cyst and pedicle at the time of surgery may facilitate removal of the entire cyst and minimize the risk of recurrence

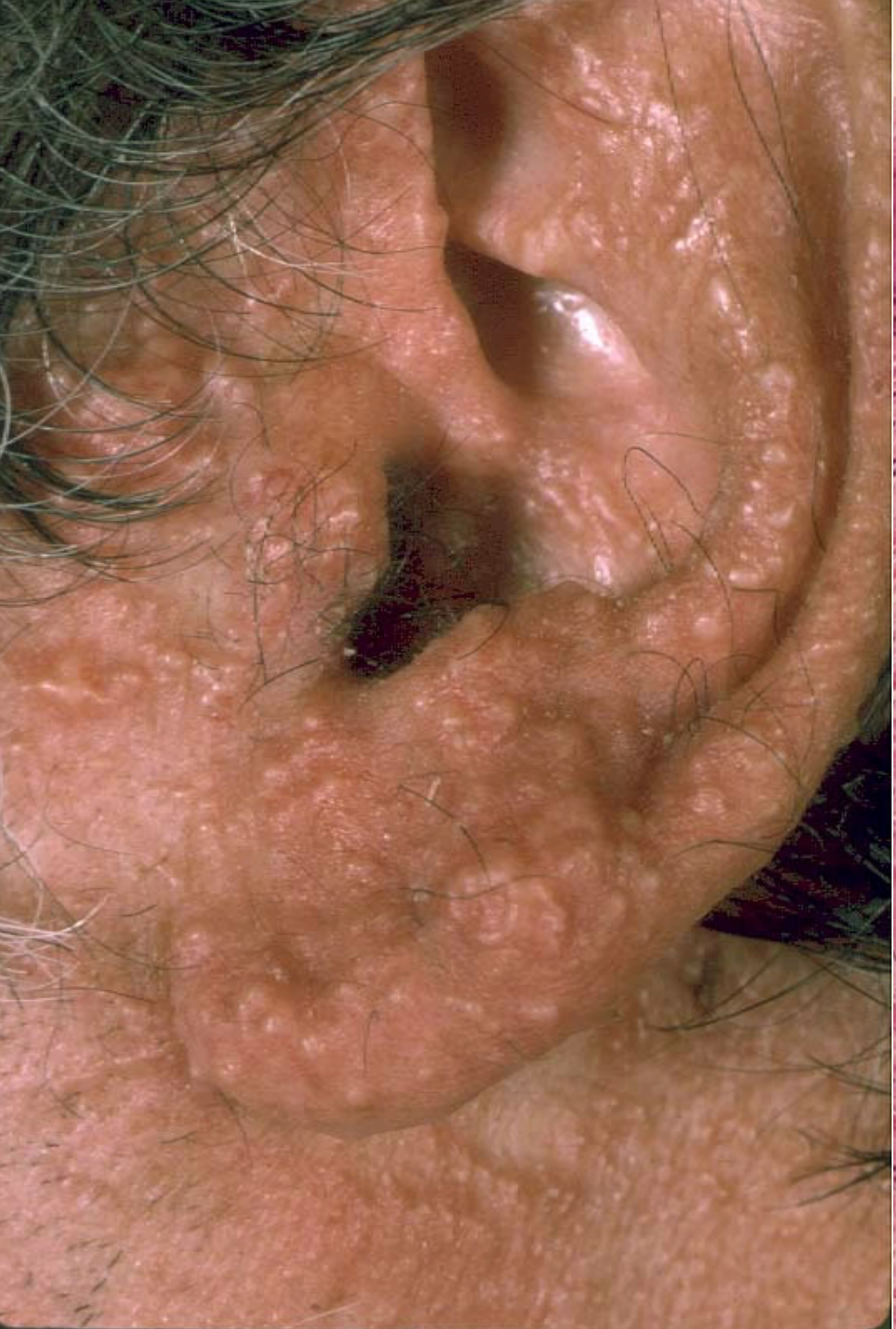
Digital Mucous Cyst

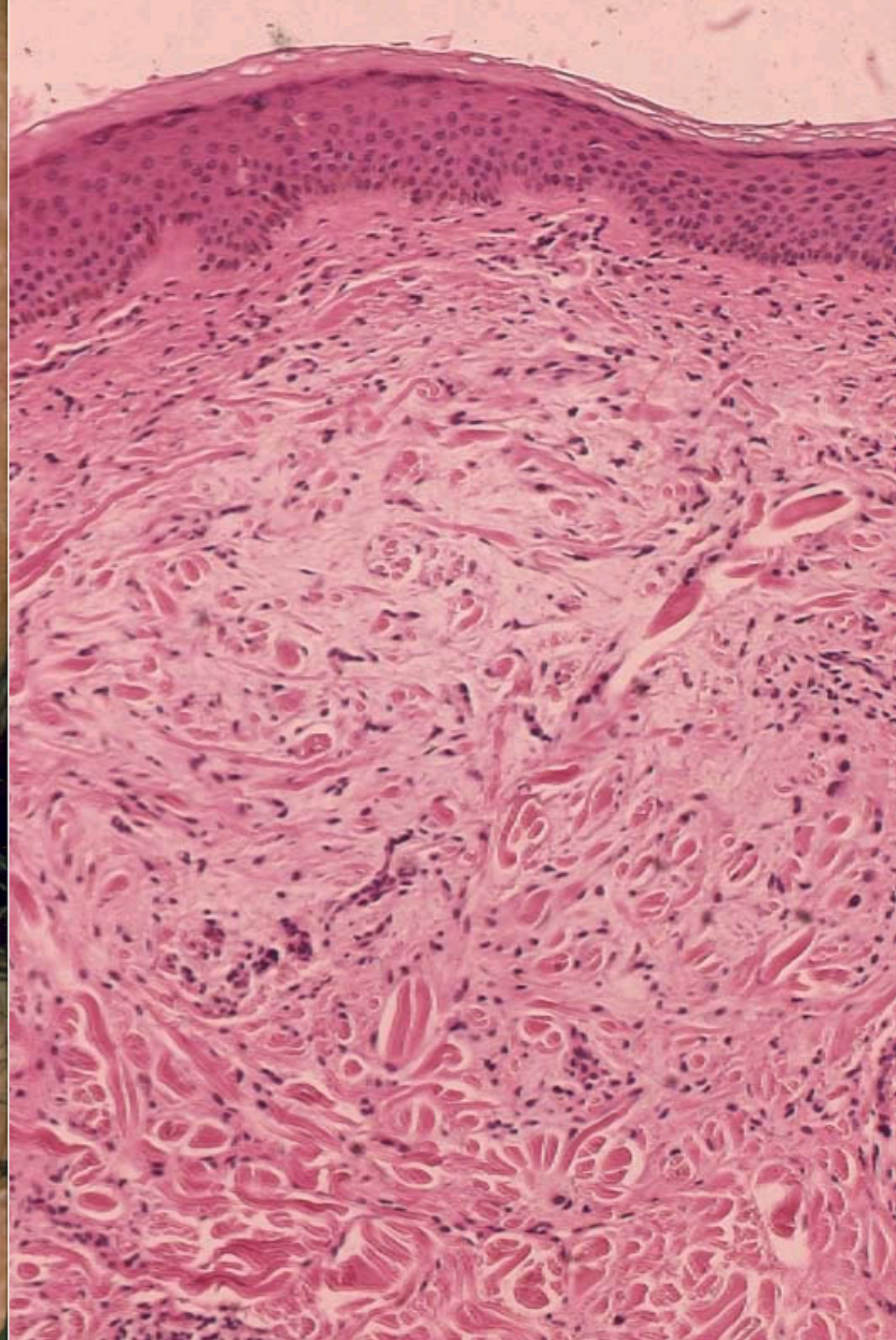


- Pseudocyst with a fibrous capsule and myxomatous stroma with scattered fibroblasts is seen
  - Partial mesothelial lining, but not a true cyst wall, may be found
- Overlying surface epithelium with compact hyperkeratosis and collarette of hyperplastic epidermis
- Mucinous contents stain basophilic with H and E
- Colloidal iron or Alcian blue-stained for acid mucopolysaccharides

Digital Mucous Cysts

- Dermatologists
  - Conservative treatments such as multiple needling or aspiration followed by steroid injection; they have reported high success rates and relatively low risks of recurrence.
- Hand surgeons
  - Success and rare recurrence with osteophyte excision and debridement, but their patient population is comprised of those who fail other treatments
- Conservative treatments offer the prospect of low cost, low morbidity, and the elimination of disability and time loss related to recovery from surgery.
- Reasonable treatment plan for symptomatic DMCs may entail initial needling or aspiration and injection
  - If these modalities fail repeatedly, patients may be referred to a hand surgeon for more radical surgery but must be forewarned of the increased risk of complications





Papular Mucinosis/Scleromyxedema

- Papular mucinosis/Lichen Myxedematosus
  - Localized, less severe cases
- Scleromyxedema
  - Generalized, confluent papular forms with sclerosis
- Papular mucinosis is frequently used as a synonym for all three forms

Papular Mucinosis/Scleromyxedema

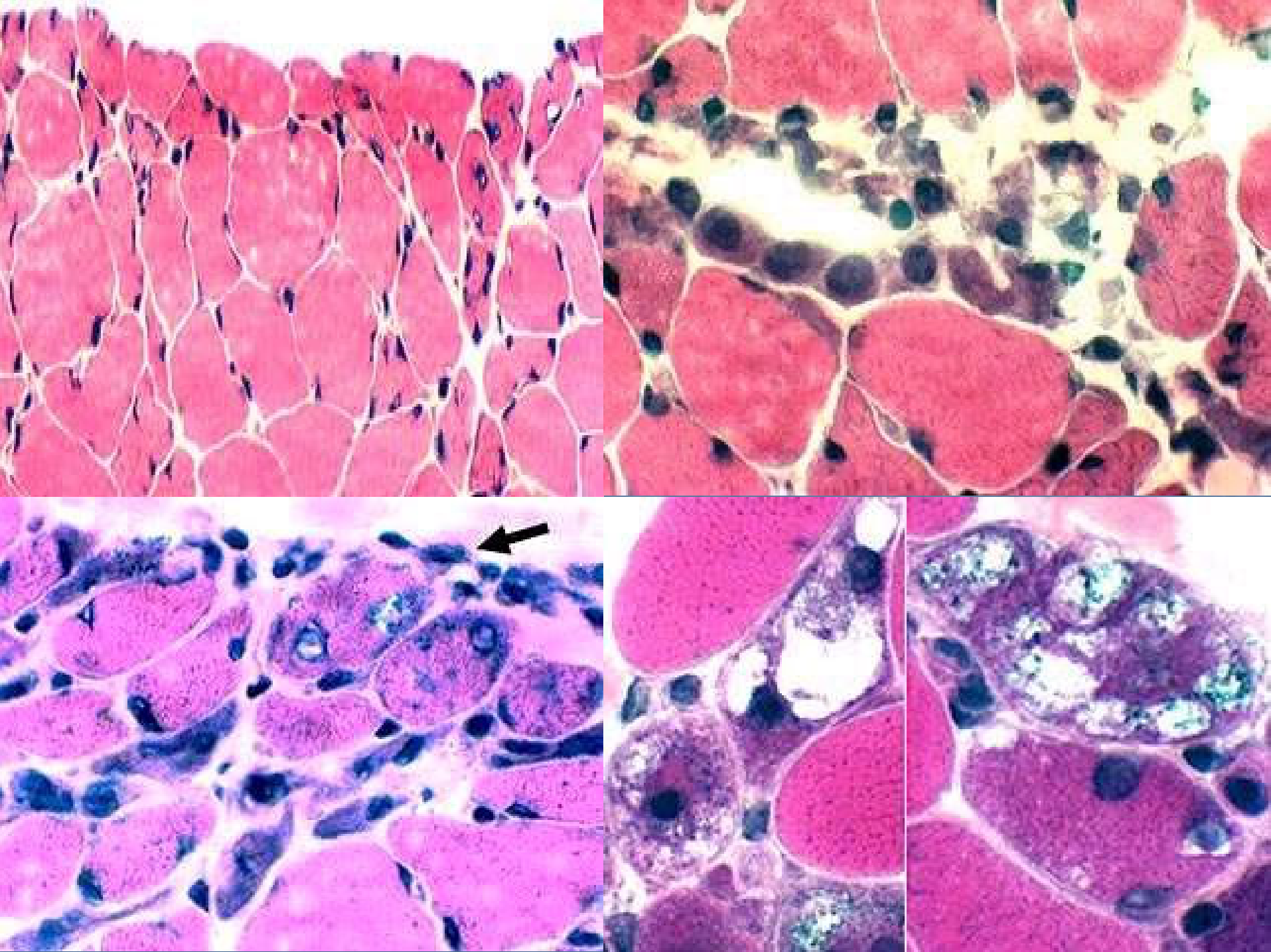
- Lichen myxedematosus or papular mucinosis
  - Patients report a slow onset of asymptomatic or mildly pruritic papules, which may be localized or generalized.
  - Patients are otherwise healthy and do not have systemic symptoms.
- Scleromyxedema
  - Patients with this form present with more widespread progressive induration and decreased mobility of the face, fingers, and extremities.
  - Patients are also noted to have cysts and urticarial lesions.
  - Patients may report systemic symptoms, such as dysphagia or weakness, and symptoms that resemble those of organic brain disease

Scleromyxedema

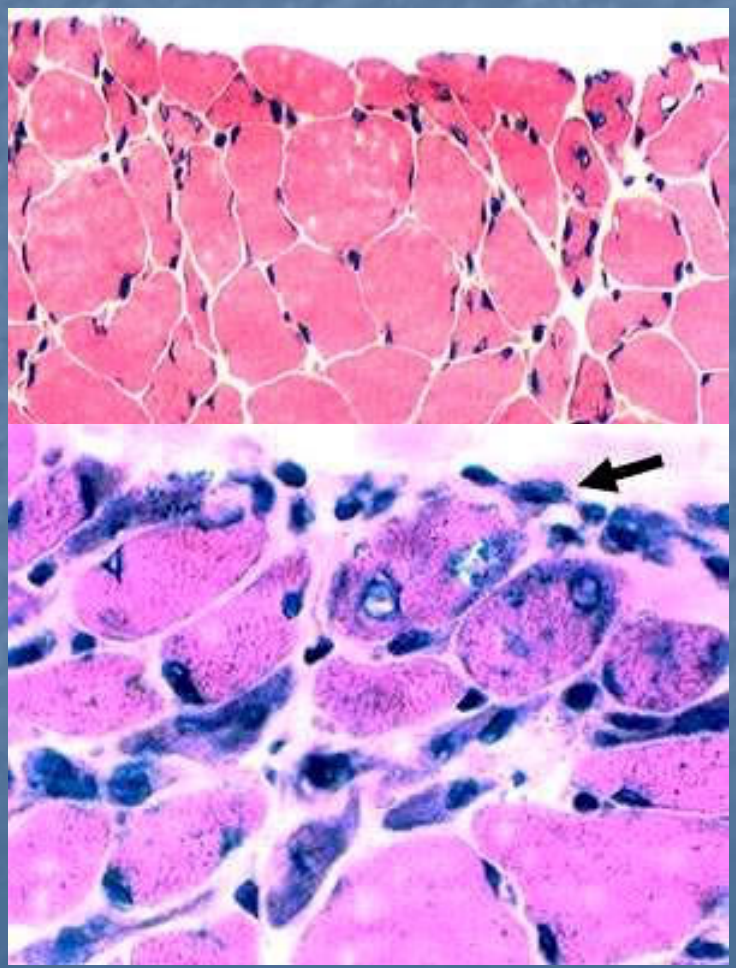
- Rare
- Adults of both sexes equally (30 and 80 yrs)
- Chronic and progressive
- Primary lesions are waxy, 2-to-4-mm, dome-shaped or flat-topped papules and may coalesce into plaques or appear in a linear array
  - Less frequently, urticarial, nodular, or sometimes annular lesions may be appreciated
- Dorsal aspect of the hands, face, elbows, and extensor portions of the extremities
- Leonine facies with coalescence of papules on the face, particularly of the glabella, results in longitudinal folding
- Mucosal lesions are absent

Scleromyxedema

- May involve large parts of the body
- Skin shows erythematous, scleroderma-like induration accompanied by reduced mobility of the lips, hands, arms, and legs
- Systemic manifestations
  - Proximal myopathy, inflammatory polyarthritis, central nervous system symptoms, esophageal aperistalsis, and hoarseness
- Visceral involvement of scleromyxedema may be fatal

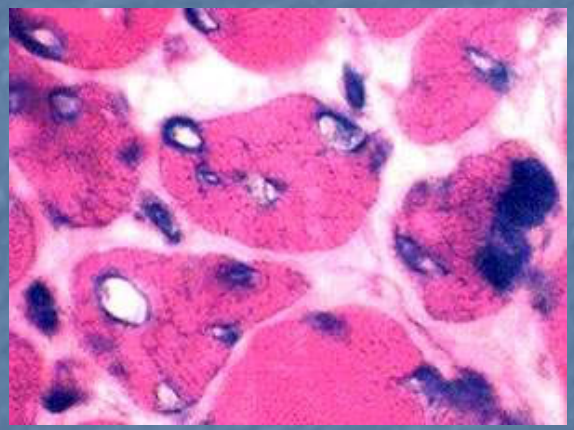


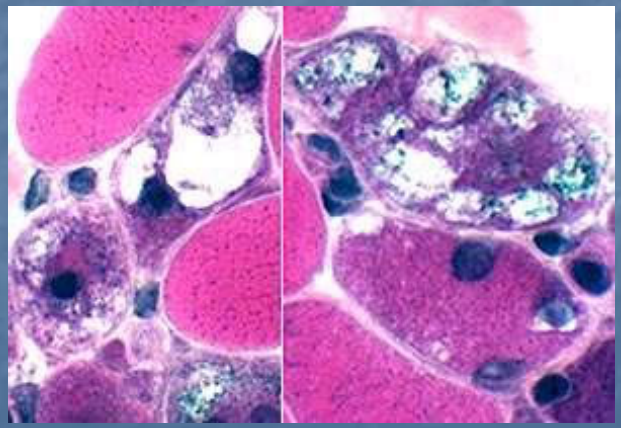
Scleromyxedema Skeletal Muscle



- Atrophic muscle fibers
  - Especially common in perifascicular regions
  - May be near perimysial cellularity

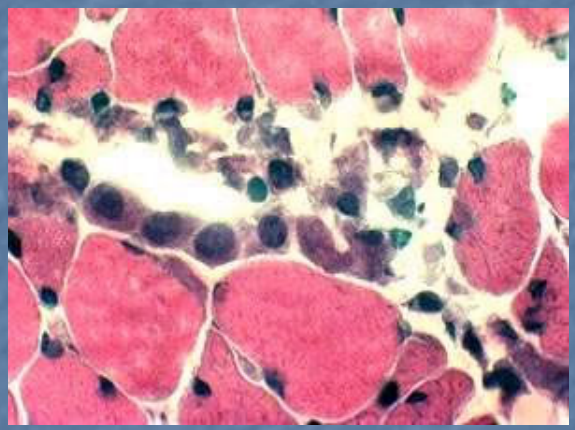
Scleromyxedema Skeletal Muscle

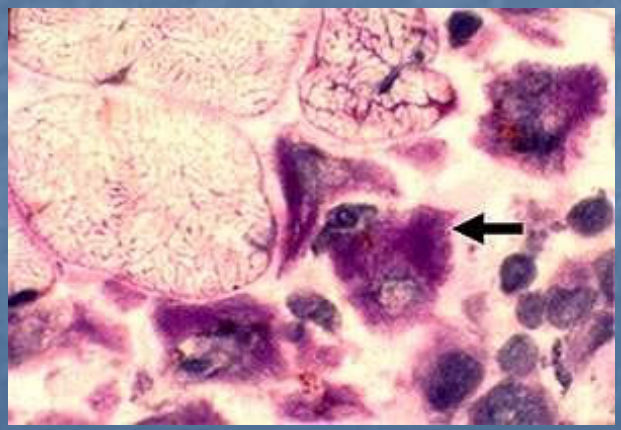




- Atrophic skeletal muscle
  - May contain rimmed vacuoles

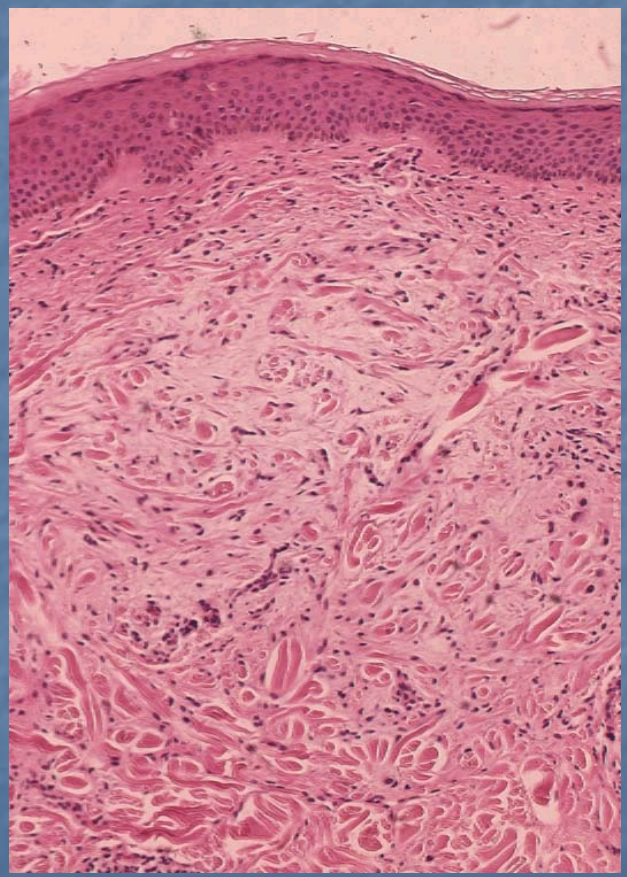
Scleromyxedema-Skeletal Muscle





- Skeletal muscle atrophy
  - Cells in perimysium
  - Large PAS positive

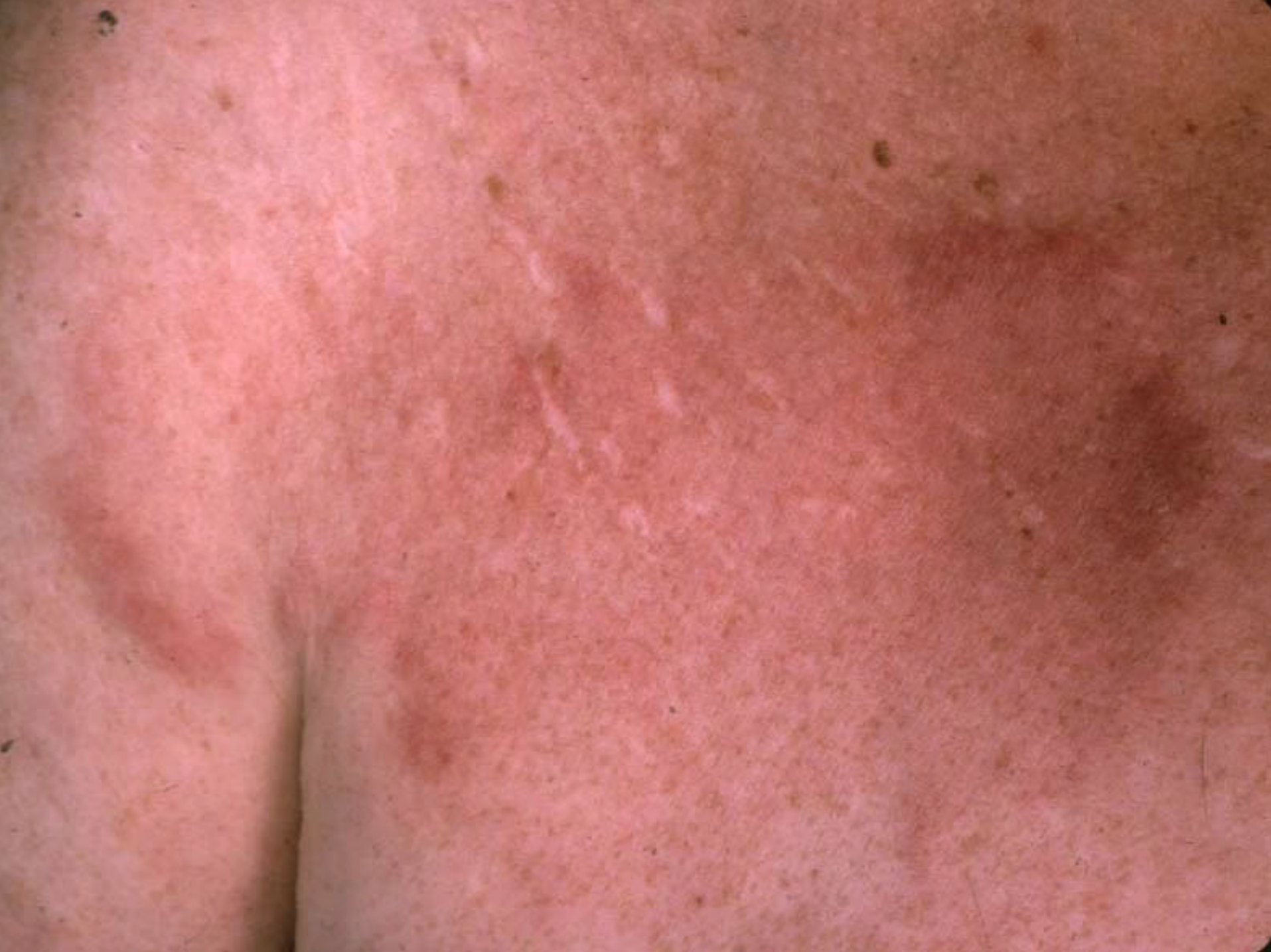
Papular Mucinosis

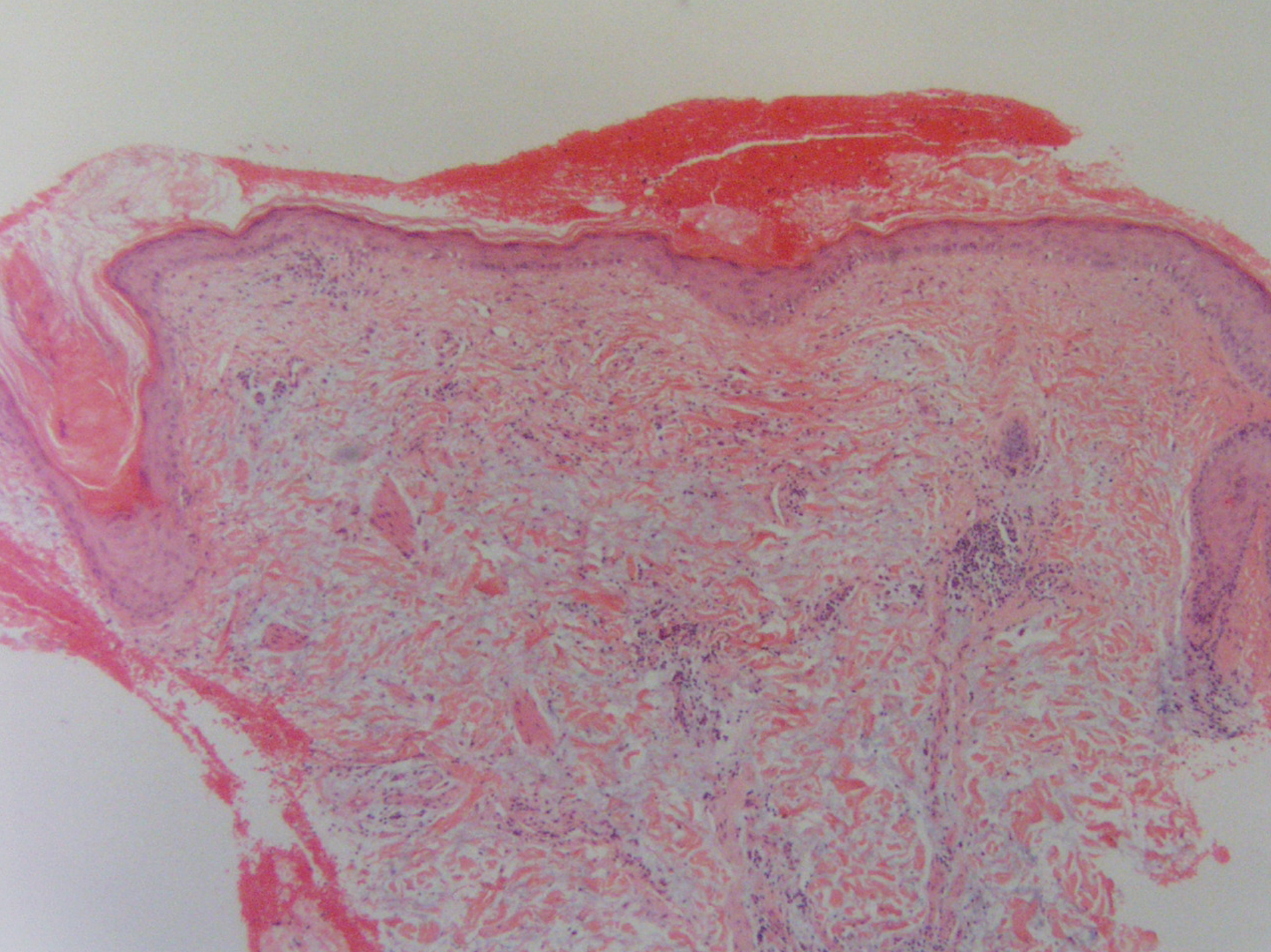


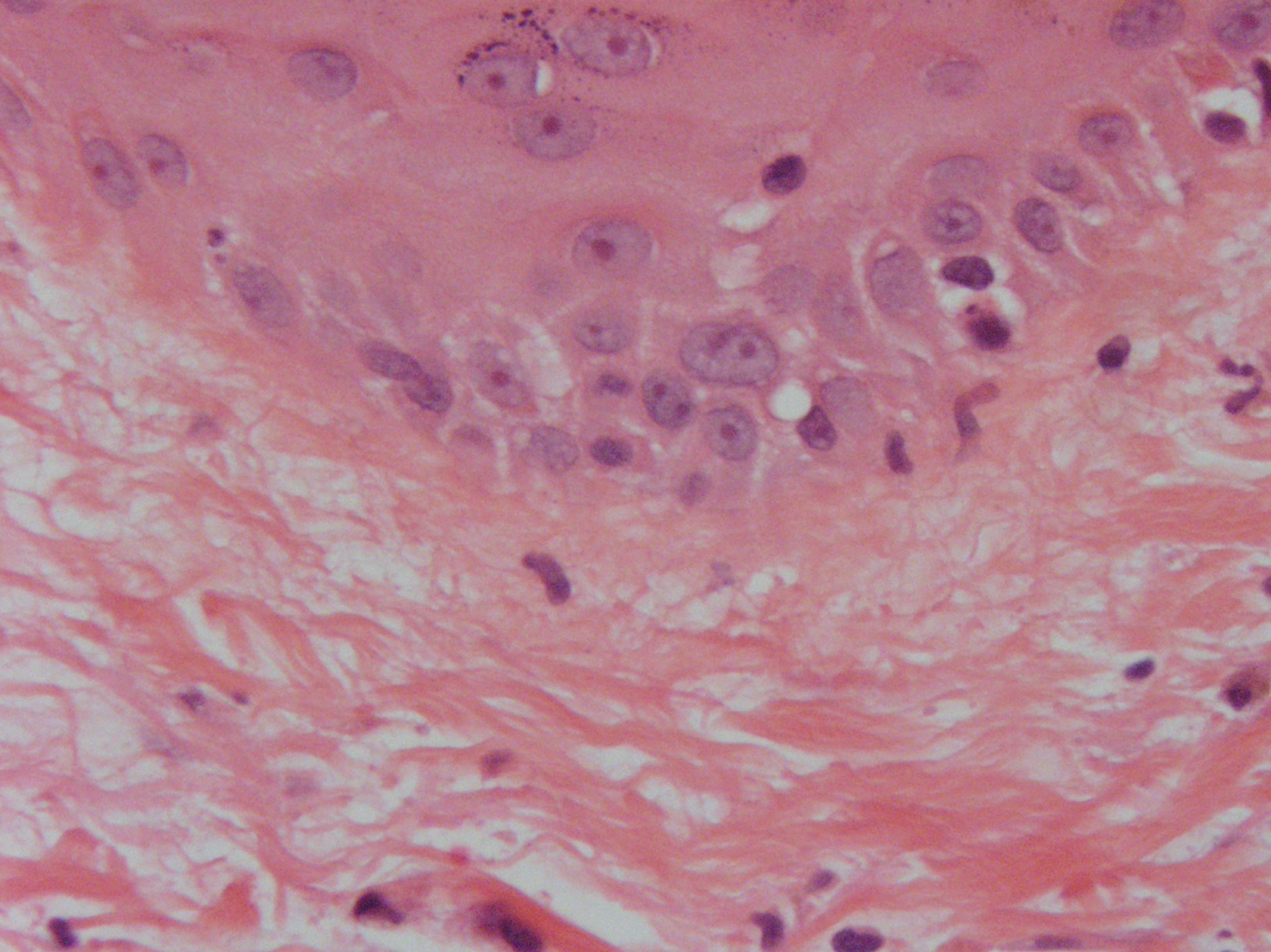
- Abnormal paraprotein in 90% of cases, usually of the IgG type
- Plasma-cell dyscrasia of ten present
- Skin biopsy shows a horizontal band of mucinous material between collagen bundles in the upper dermis
- Increase in fibroblasts and dermal fibrosis
- Glycosaminoglycan positive for alcian blue at pH 2.5
  - Hyaluronidase sensitive

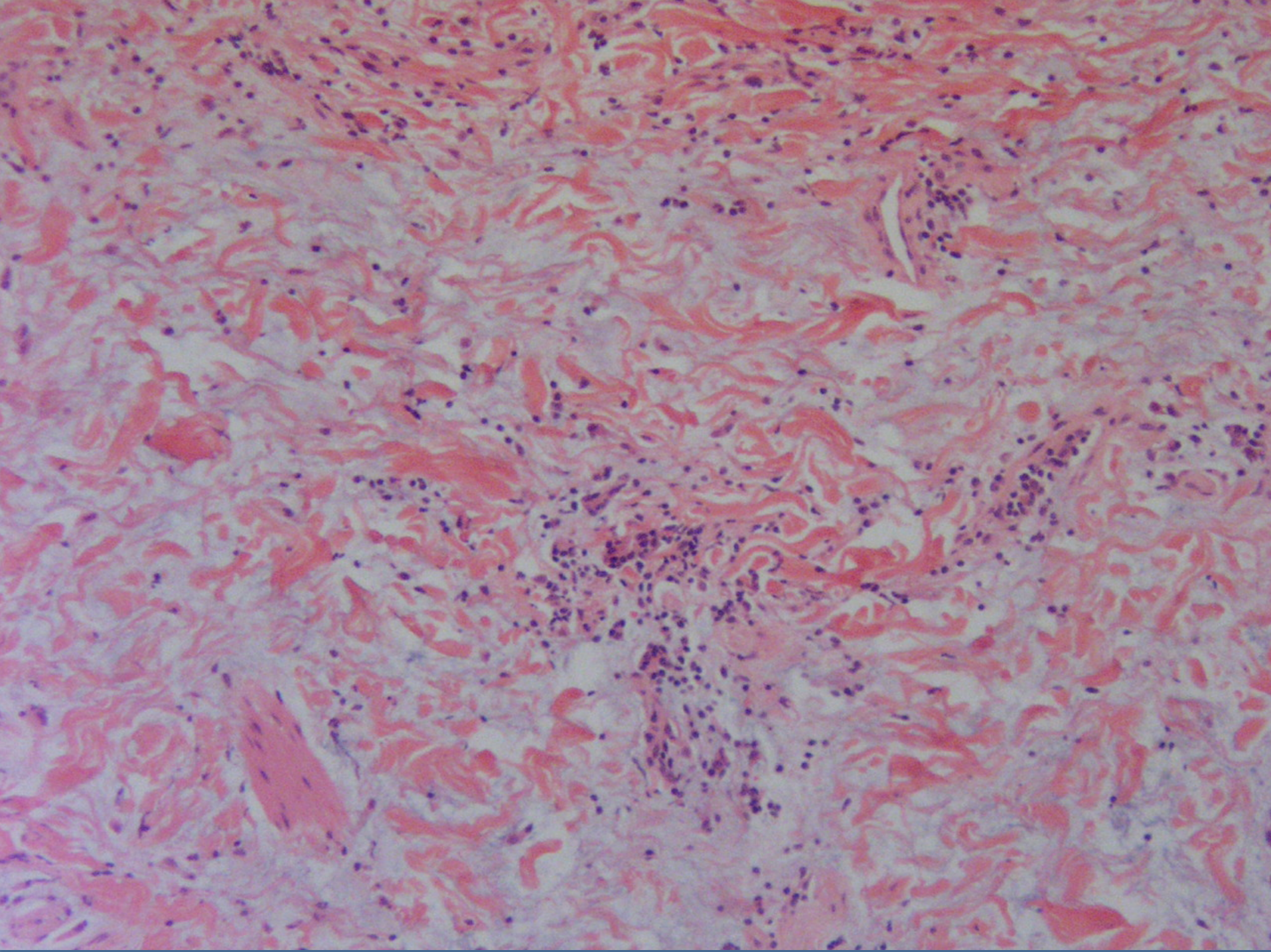
Papular Mucinosis

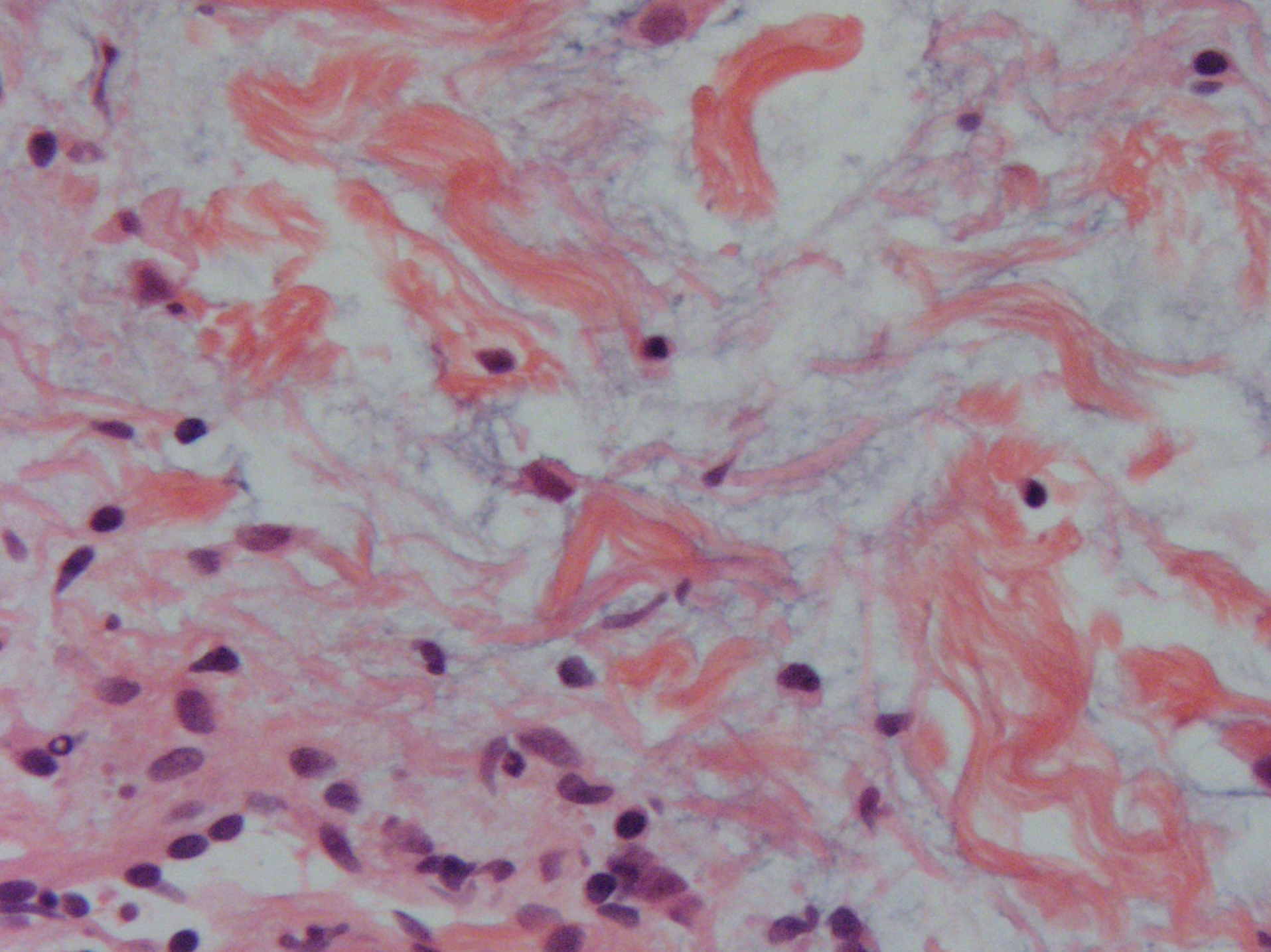
- Chemotherapy
  - Melphalan and cyclophosphamide alone or in combination with prednisone
  - Isotretinoin and etretinate
  - Interferon-alpha
  - Cyclosporine
  - PUVA photochemotherapy
  - Electron-beam therapy
  - IVIg
  - Dermabrasion
- Overall prognosis for extensive disease is poor







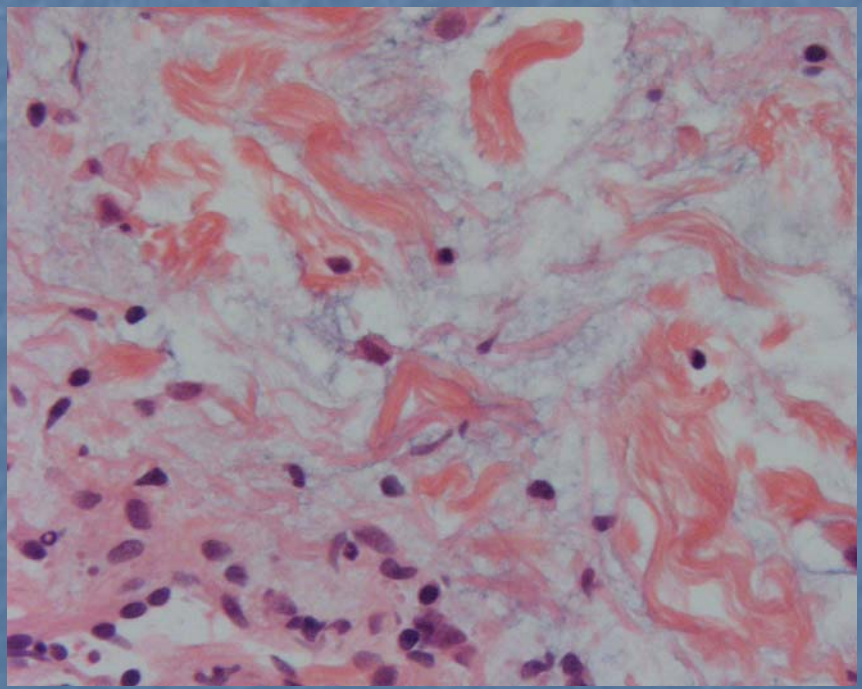




Tumid Lupus

- Smooth, indurated, pink-to-violaceous papules, plaques, or nodules
- Sun-exposed sites
- Mean duration of 2.5 years (range two weeks to nine years)

Tumid Lupus



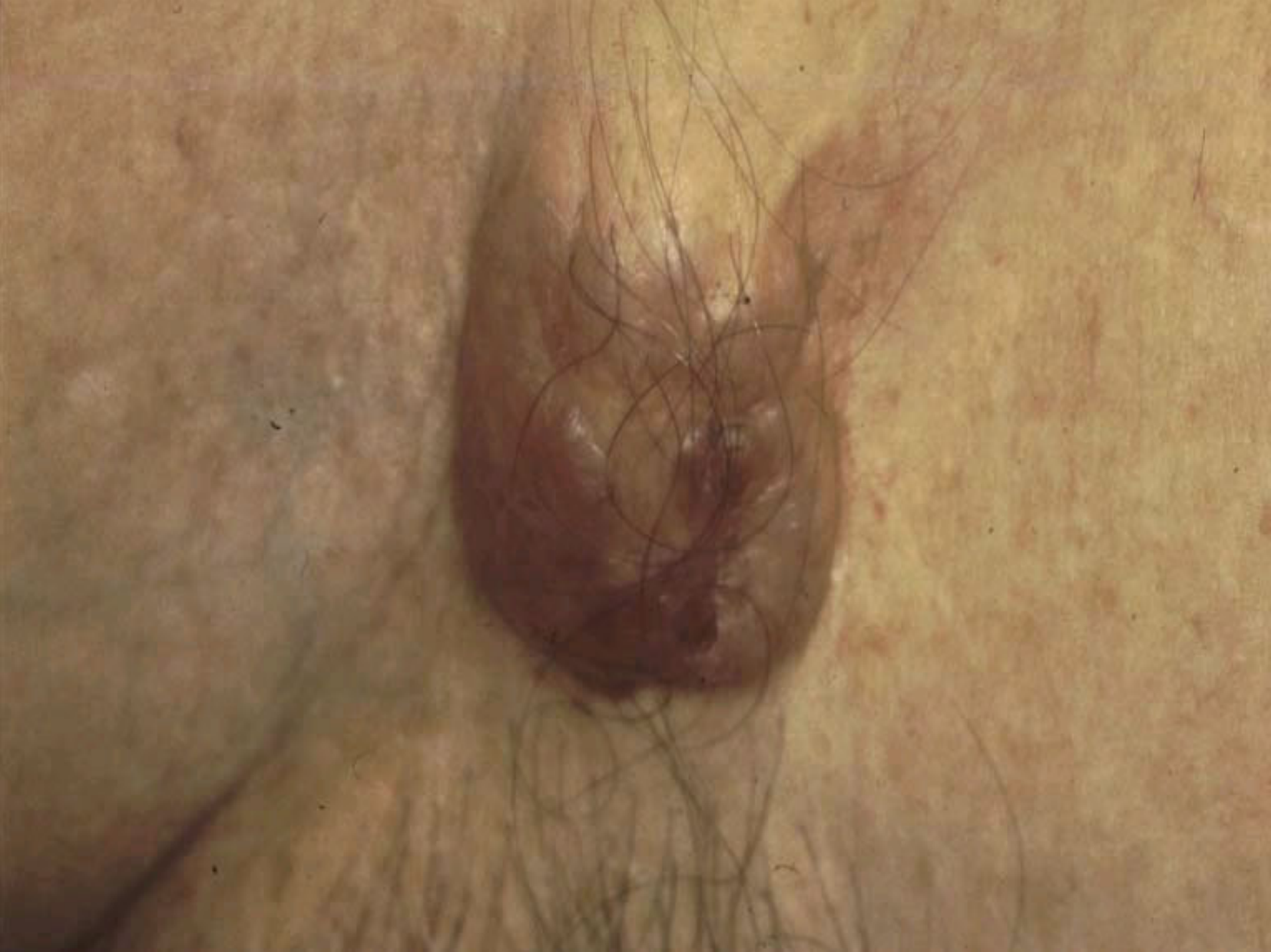
- Moderately dense, superficial and deep, perivascular, and occasionally periadnexal infiltrate of lymphocytes
- Absence or focal junctional involvement
- Mucin diffuse in dermis
- IPOX:
  Infiltrate predominantly CD3-positive and CD4-positive lymphocytes whereas a minority were CD8-positive
  - Ratio of CD4 to CD8 cells was roughly 3:1

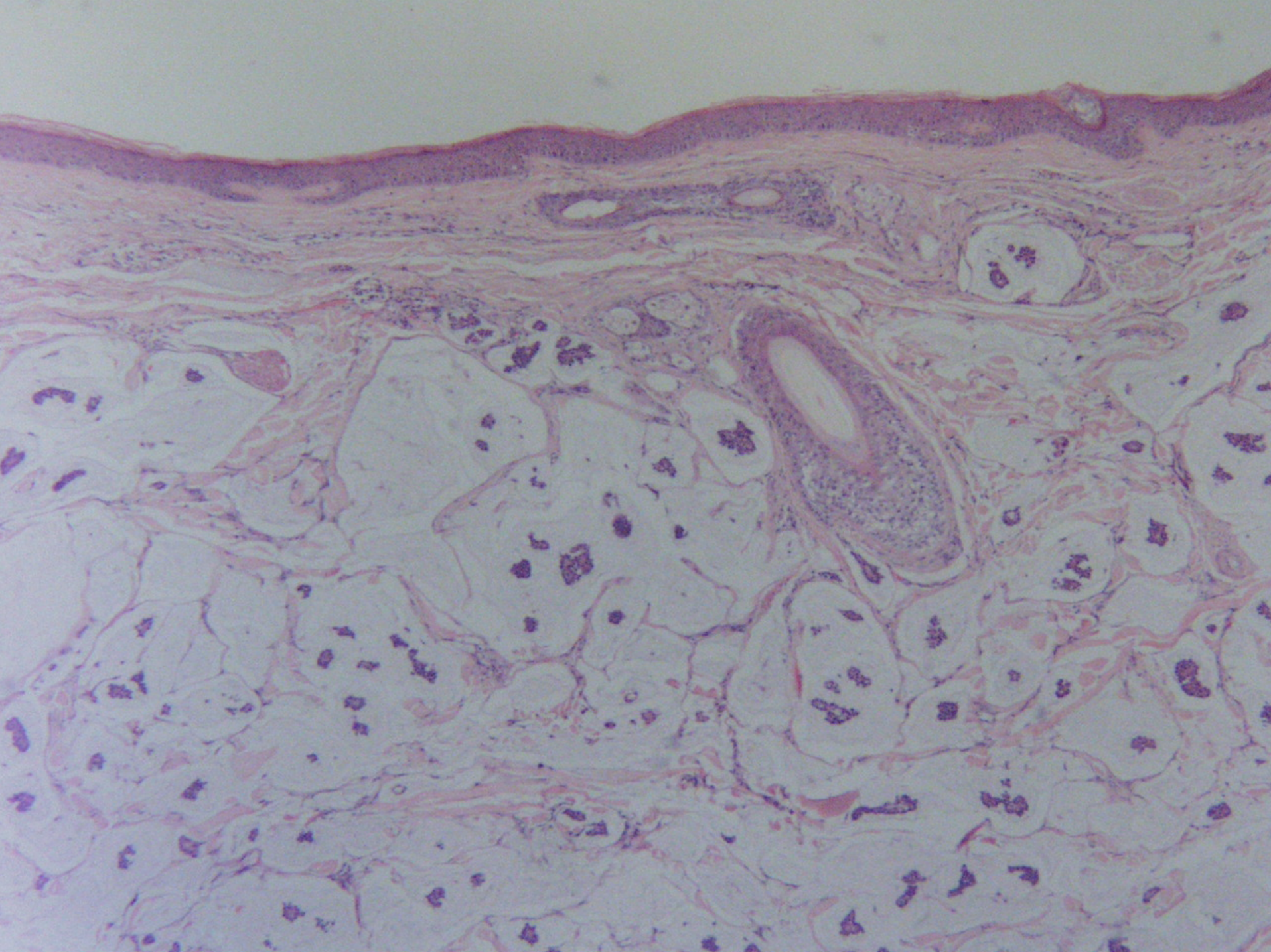
Tumid Lupus DDX

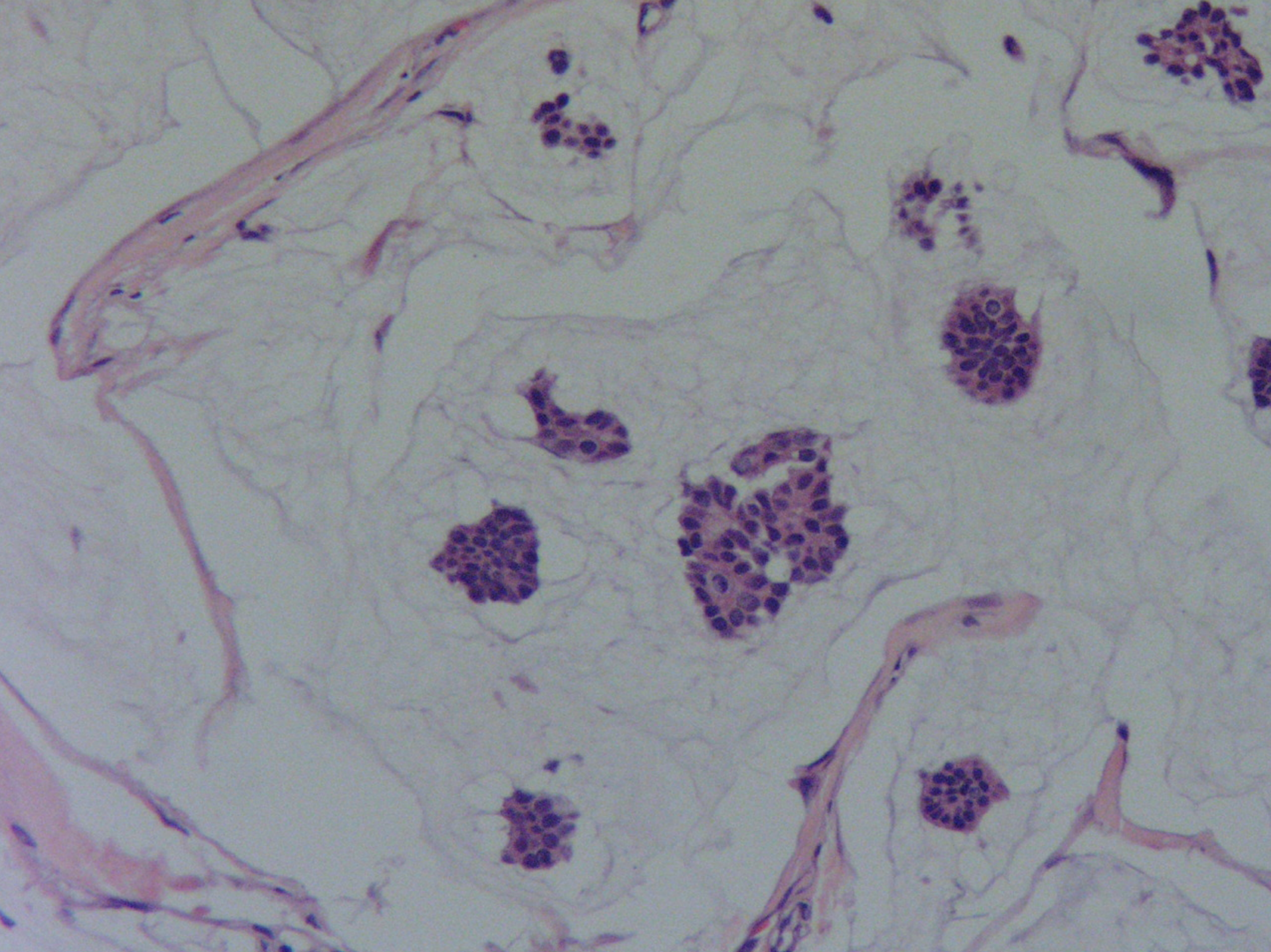
- Polymorphous light eruption
  - CD8-predominant infiltrates
- Jessner's lymphocytic infiltrate

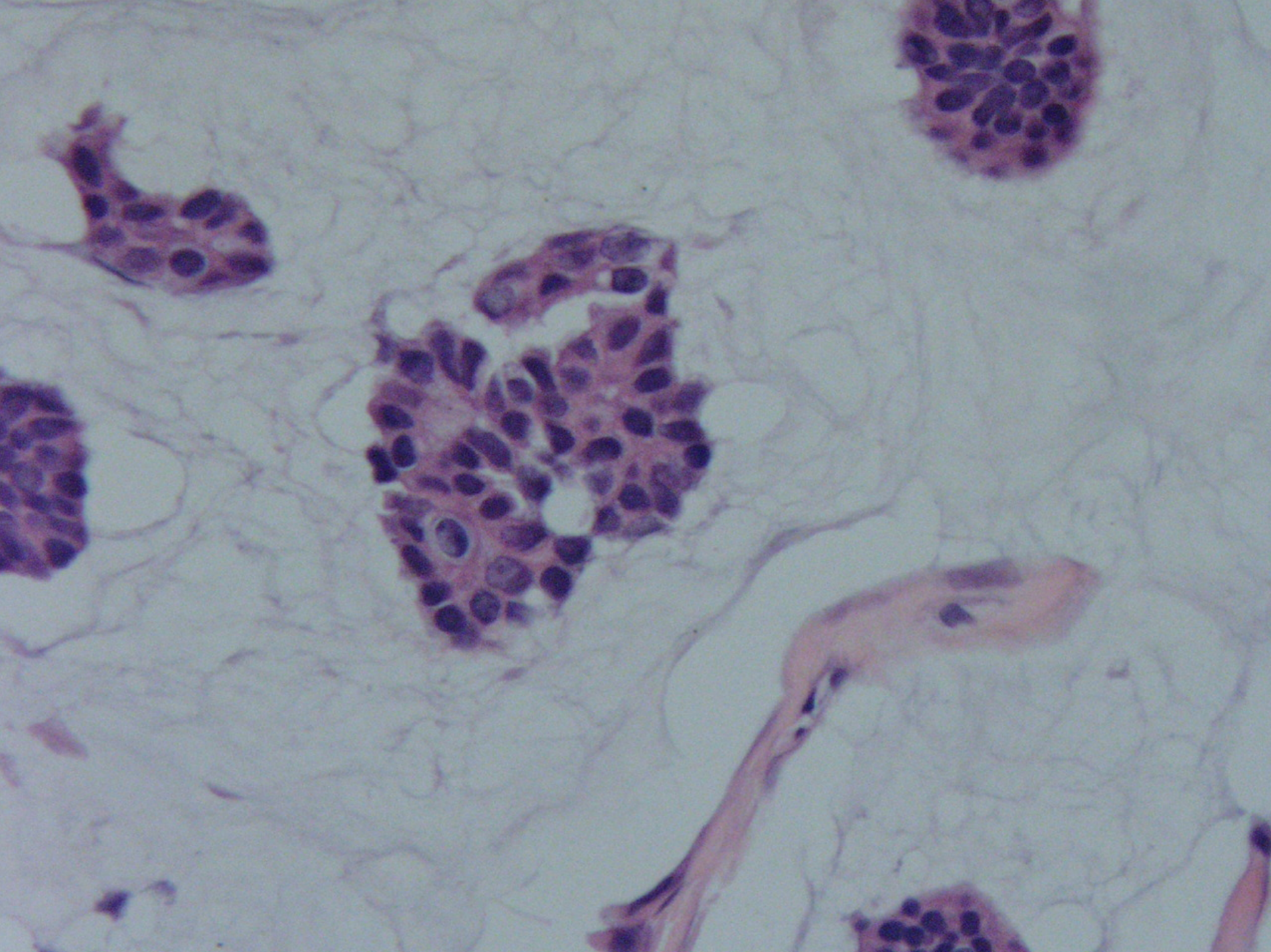
Tumid Lupus Pgx and Tx

- Rarely may progress to SLE although some feel it is a variant of SLE
- Treat underlying lupus









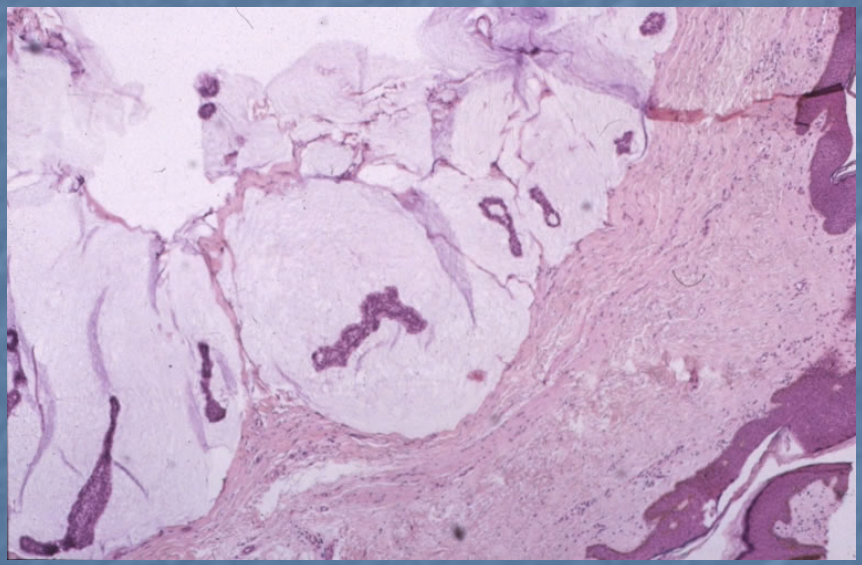
Mucinous Carcinoma of the Skin

- Most commonly located on the head
- Slowly growing dome shaped with a translucent hue or subcutaneous mass
- Must rule out metastatic visceral mucinous carcinoma (breast, colon, stomach, lung, ovary or pancreas)
  - No evidence of primary tumor at these sites

Pathogenesis

- Apocrine origin
  - Decapitation secretion present in luminal cells
  - Histologically indistinguishable from breast colloid carcinoma
  - Cells similar to neoplastic cells of pale-cell hidradenoma, a neoplasm of apocrine origin
  - Plasmacytoid cells float in the lakes of mucin, an alleged apocrine feature
  - Positive staining for lactalbumin and gross cystic disease fluid protein-15
- Eccrine origin
  - Admixture of dark and light cells, like the secretory portion of the ecrine coil
  - Enzyme histochemistry similar to that found in eccrine secretory epithelium: positive reactions with succinate dehydrogenase and phosphorylase
  - Immunohistochemical reaction against anti-CEA as other eccrine tumors
    Co-expression of cytokeratin and vimentin as fetal secretory cells of the ecrine sweat glands
  - Secretion similar to that of the dark, mucinous, cell of the ecrine coil by electron microscopy
    The findings of extracellular mucin and accumulation of it to form intercellular canaliculi have also been considered to favor ecrine origin

Mucinous Carcinoma-Histopathology



- Dermal pools of pale-staining sialomucin separated by thin fibrous septa. Small cellular islands "float in the pools".
- Round or cuboidal cells, with a high nuclear:cytoplasmatic ratio. Some of them have vacuolated cytoplasm forming ductal lumina.
- Inflamation or atypia nearly absent.
- Recurs locally: metastases infrequent
- Treatment of choice: surgery. Moh's surgery

Questions

- Public speaking is very easy.

Dan Quayle (1947 -), to reporters in 10/88