Cutaneous Deposition Diseases

Cutaneous Deposition Disorders

- Group of unrelated conditions characterized by the presence of endogenous or exogenous substances within the dermis or subcutis
- Our focus: endogenous depositions

Endogenous Cutaneous Deposition Disorders

- **Amyloidosis**
- **Lipoid Proteinosis**
- Colloid Milium
- Porphyrias

Learning Objectives

- Amyloidosis and Lipoid Proteinosis
  - Pathogenesis
  - Clinical presentation
  - Diagnosis
  - Histopathology
  - Treatment

THE HUMAN AMYLOIDOSES

	FIBRIL PROTEIN	MAIN CLINICAL SETTINGS
Systemic	Immunoglobulin L-chains	Plasma-cell disorders
	Transthyretin (TTR)	Familial amyloid, SCA
	AA	Inflammation-associated, FMF
	β_2 microglobulin	Dialysis-associated amyloidosis
	Immunoglobulin H-chains	Systemic amyloidosis
Hereditary renal	Fibrinogen $^{\alpha}$ chain	Familial systemic amyloid
	Apolipoprotein AI	Familial systemic amyloid
	Lysozyme	Familial systemic amyloid
CNS	ß protein precursor	Alzheimer, Down, HCHWA-Dutch
	Prion protein	CJD, GSSD, FFI
	Cystatin C	HCHWA-Icelandic type
Ocular	Gelsolin	Familial amyloidosis-Finnish
	Lactoferrin	Familial corneal amyloidosis
	Kerato-epithelin	Familial corneal dystrophies
Localized	Calcitonin	Medullary thyroid carcinoma
	Amylin (IAPP)	Insulinoma, type II diabetes
	Atrial natriuretic factor	Isolated atrial amyloidosis
	Prolactin	Pituitary amyloid
	Keratin	Cutaneous amyloidosis
	Medin	Aortic amyloidosis in elderly

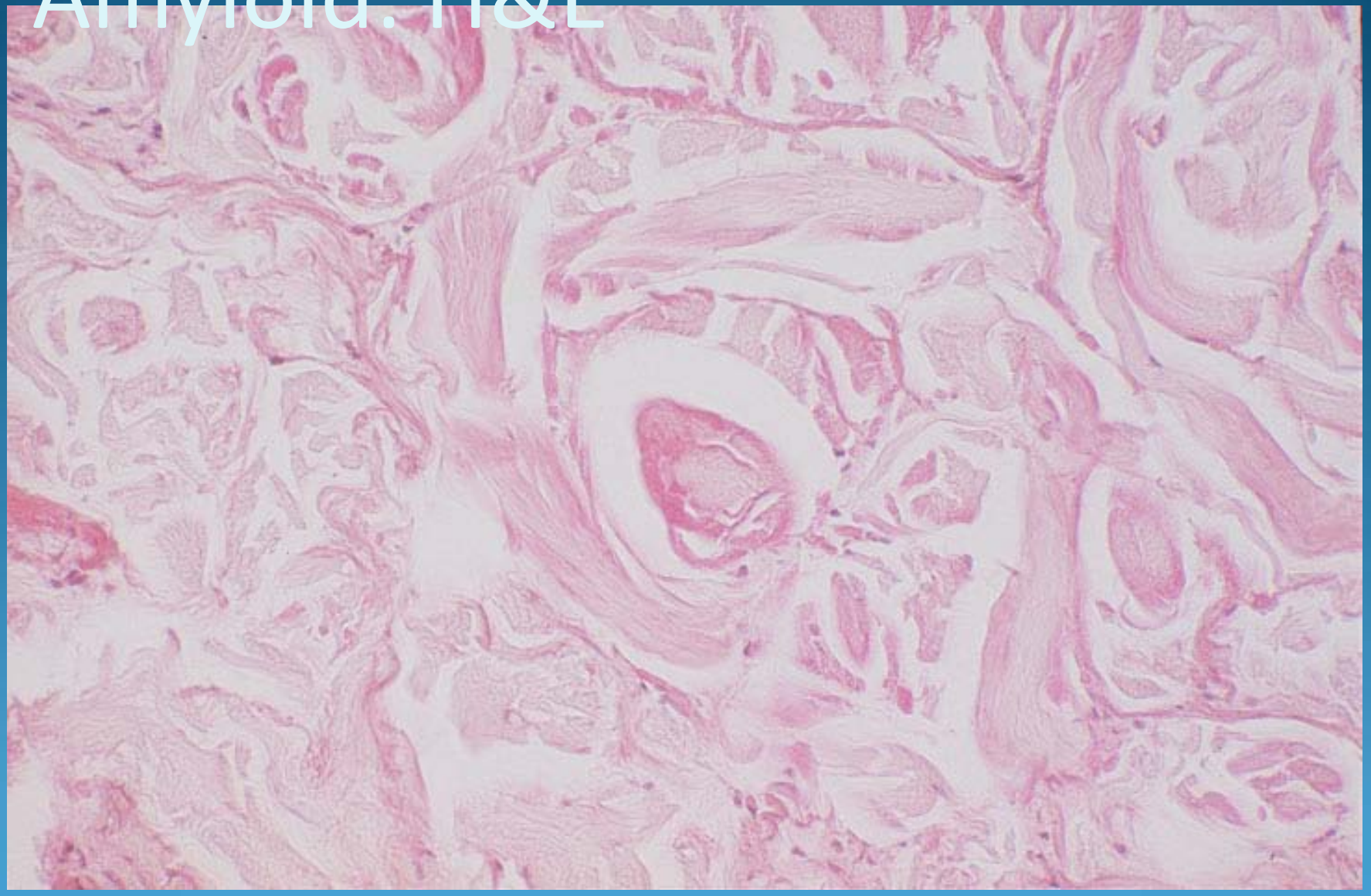
Amyloidosis

- Term coined by a German botanist to describe the cellulose-like substance of plants
- Extracellular deposition of *any of a group of unrelated proteins*
- Distorts tissue architecture and function

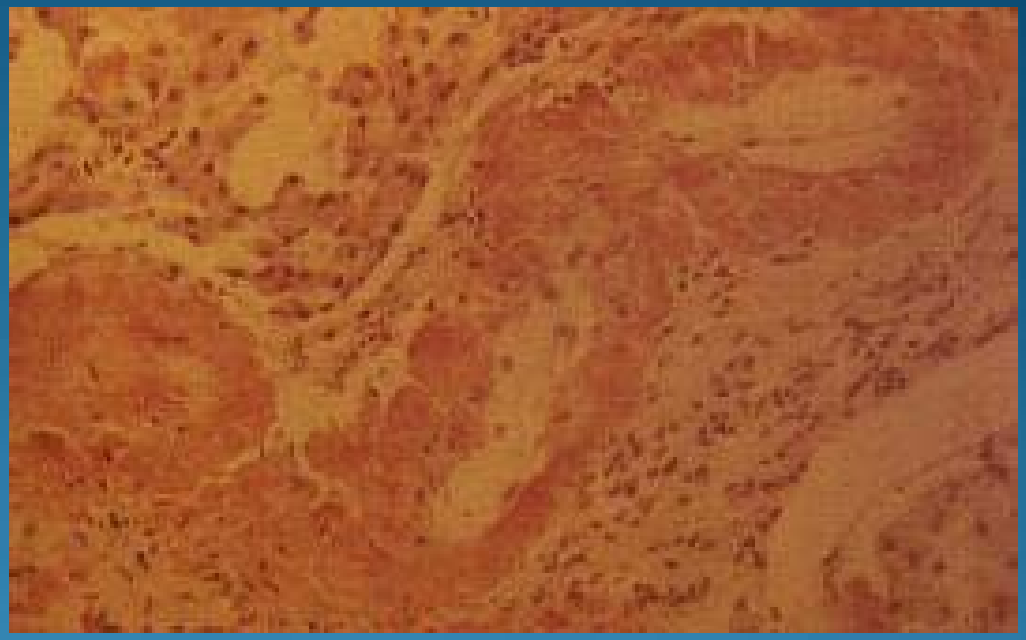
Amyloid Ultrastructure

- Light Microscopy
  - eosinophilic, amorphous substance
  - **Congo Red stain with polarized light: apple-green birefringence**
- Electron Microscopy
  - 7.5-10nm wide linear, nonbranching tubular fibrils loosely arranged in a meshwork
  - fibrils are composed of several filaments arranged in a **β-pleated sheet** configuration

Amyloid: H&E

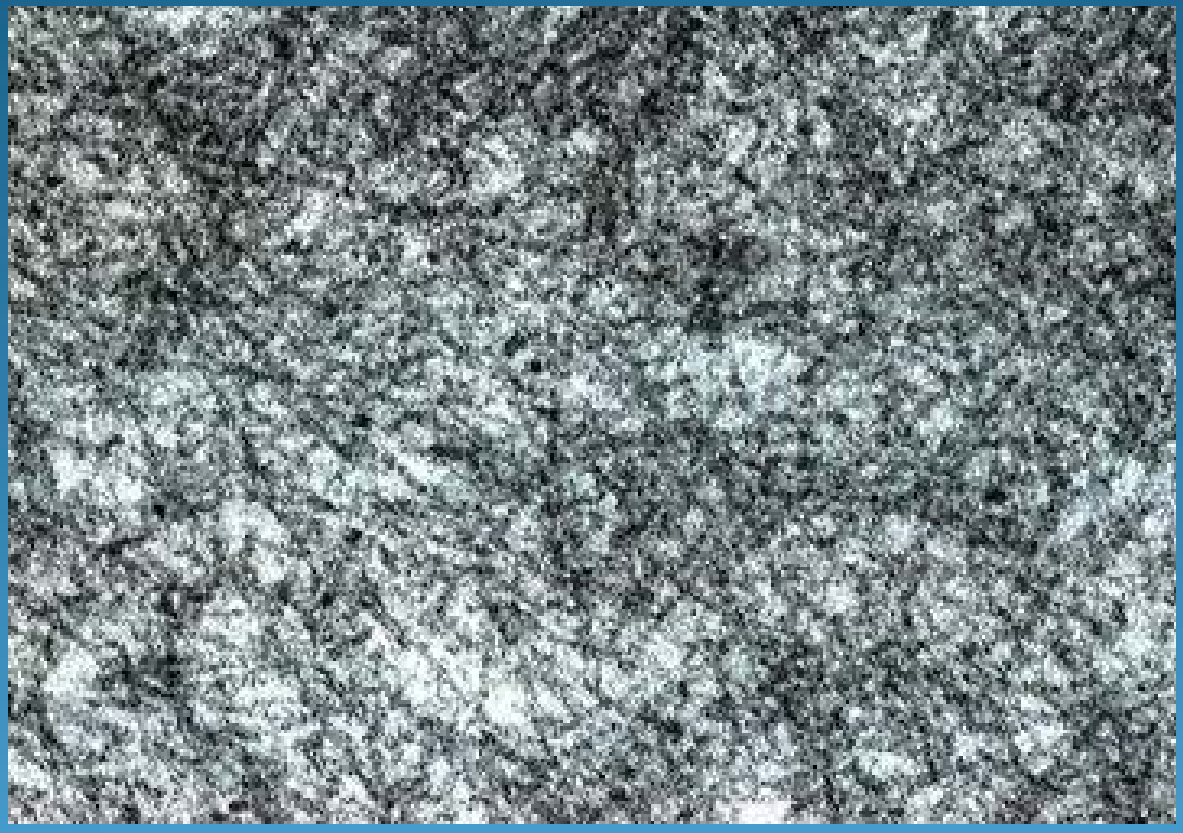


Congo Red H&E

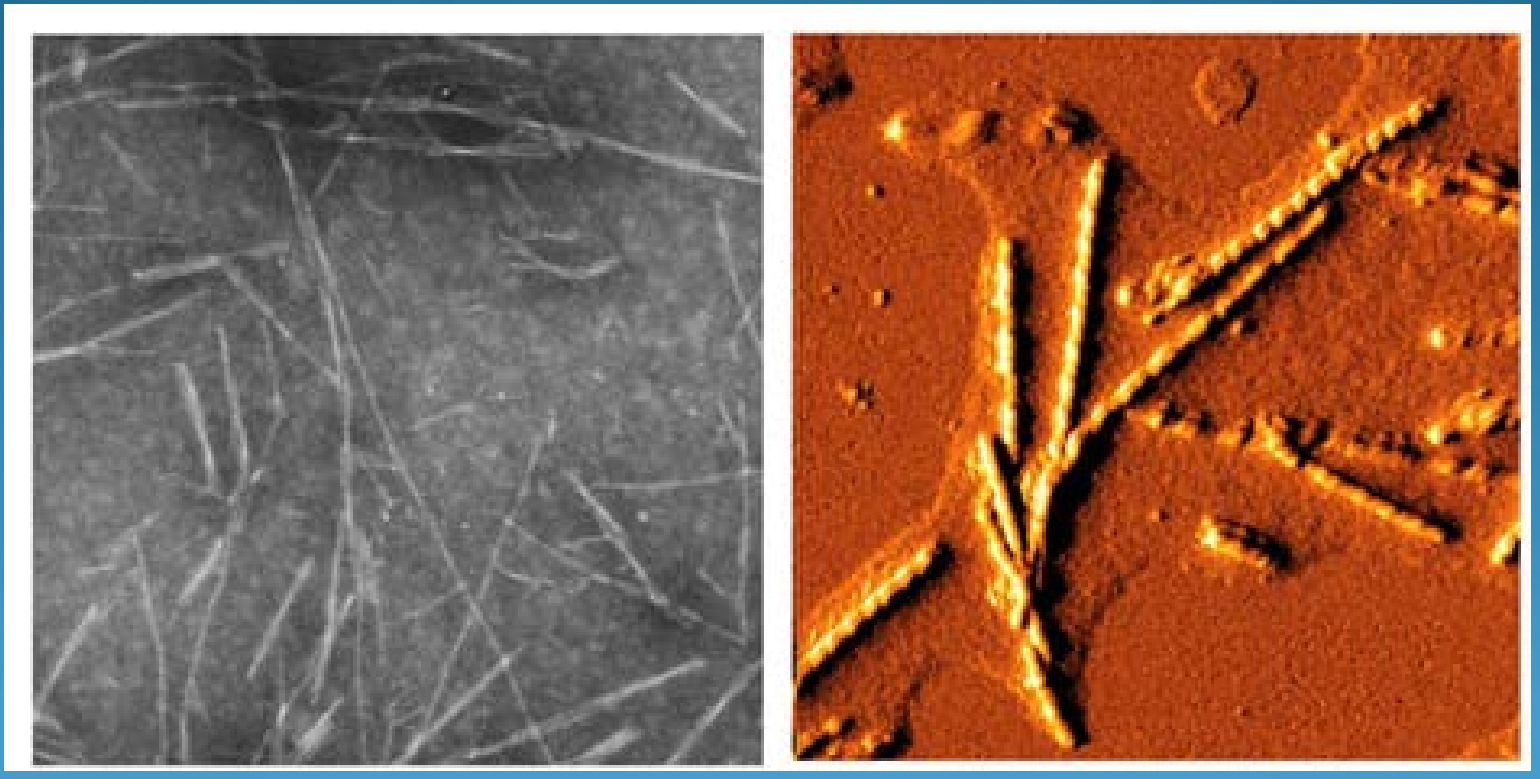


Congo Red under Polarized Light

Amyloid: EM



Amyloid EM
(Beta-2 Microglobulin)



Amyloidosis Classification

- The **clinical type** of amyloidosis depends on the **amyloid fibril protein** and the **pathogenic mechanism of deposition**

- Amyloidosis can present with either **systemic or localized** deposits

Amyloidosis Classification

- **Systemic**
  - *Primary*
  - *Myeloma-Associated*
  - Secondary/Reactive
  - Heredofamilial
  - Hemodialysis-Related
- **Local Cutaneous**
  - Primary
    - Nodular
    - Macular
    - Lichenoid
  - Secondary
    - Incidental

Pathogenesis (what *is* amyloid??)

- **Amyloid deposits contain a nonfibrillar protein called *Amyloid-P***
- Amyloid-P is identical to Serum Amyloid P (SAP), a normal circulating plasma globulin
- SAP is an integral constituent of the microfibrillar sheath of normal elastic fibers
- SAP is related to C-Reactive Protein and is an elastase inhibitor

Pathogenesis

- **SAP** and the **beta-pleated sheet** configuration protect amyloid deposits from degradation and phagocytosis

- Thus, the progressive and irreversible course of amyloidosis

Pathogenesis: Systemic Amyloidosis

Primary and Myeloma-Associated Amyloidosis

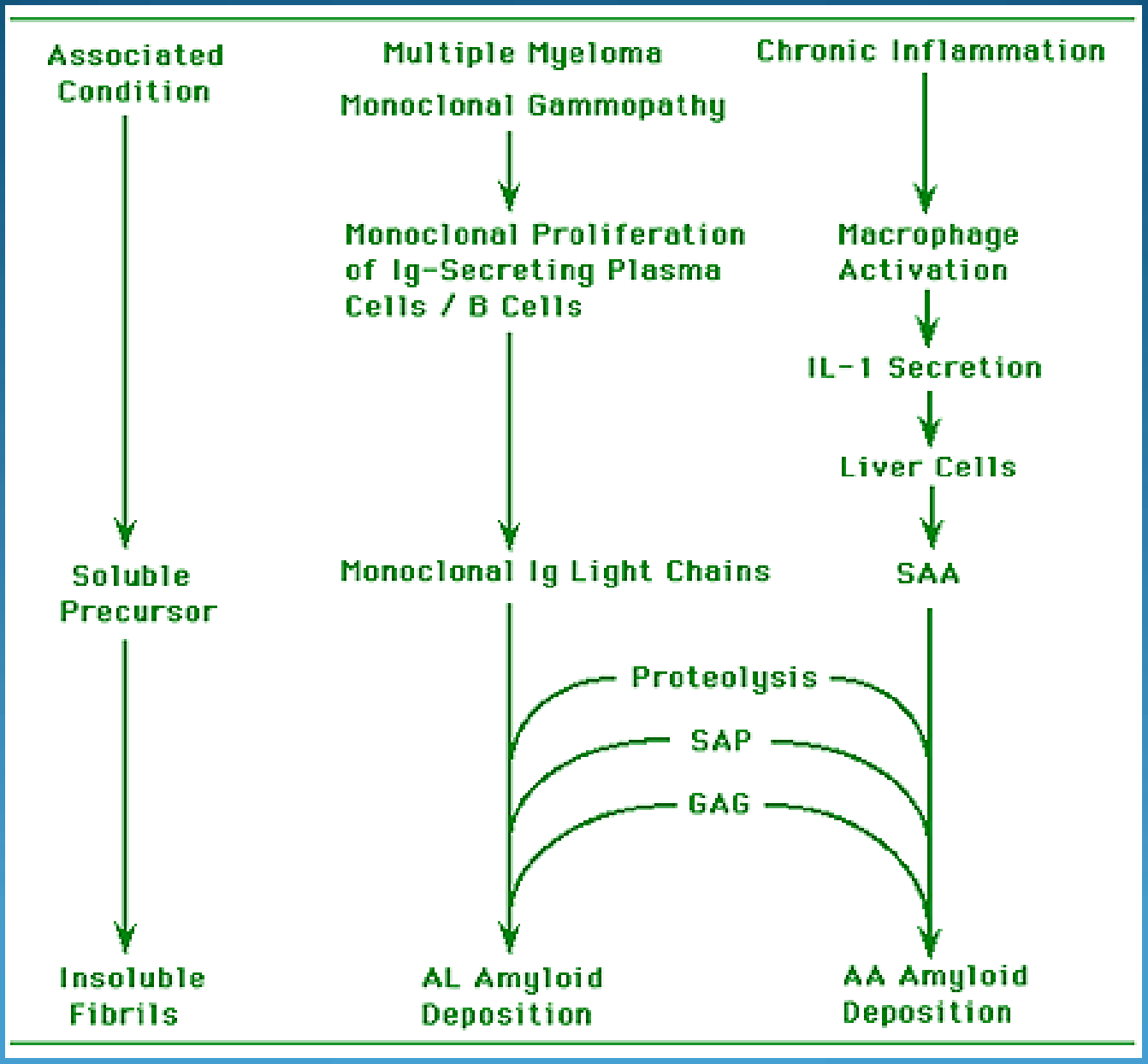
- Immunoglobulin light chains (lambda) are the precursors to the amyloid fibril protein, designated as **Amyloid L (AL)**
- The light chains are derived from serum immunoglobulins originating from a **clonal plasma cell dyscrasia**
- The plasma cell dyscrasia is occult in the primary form or overt in myeloma

Secondary Systemic Amyloidosis

- Serum Amyloid A (SAA) is the precursor to the amyloid fibril protein, designated **Amyloid A (AA)**
- SAA is a high density lipoprotein and an acute-phase reactant in healthy patients
- Elevated SAA in amyloidosis is linked to chronic inflammation with persistent activation of the acute phase response

Diseases Associated with Secondary Amyloidosis

- Infectious
- Autoimmune
- Malignant
- Miscellaneous
- Chronic Cutaneous Diseases


Associated Condition
Multiple Myeloma
Monoclonal Gammopathy
Chronic Inflammation
Monoclonal Proliferation of Ig-Secreting Plasma Cells / B Cells
Macrophage Activation
IL-1 Secretion
Liver Cells
Soluble Precursor
Monoclonal Ig Light Chains
SAA
Proteolysis
SAP
GAG
Insoluble Fibrils
AL Amyloid Deposition
AA Amyloid Deposition

Pathogenesis: Heredofamilial Forms

- Familial Mediterranean Fever: AA Amyloid
  - Recurrent polyserositis and fever; MEFV gene
- Muckle-Wells Syndrome: AA Amyloid
  -Urticaria/Deafness/Amyloid
- Familial Nephropathic, Polyneuropathy, and Cardiac: Prealbumin (transthyretin)

Pathogenesis: Hemodialysis-Related Amyloidosis

- High levels of *β2-microglobulin*
  - protein not cleared by certain HD membranes
- Limited deposition in articular structures
- Presents with Carpal Tunnel Syndrome
- Skin manifestations rare
  - finger "wrinkling"; truncal lichenoid lesions

Pathogenesis: Localized Cutaneous Amyloidosis

Pathogenesis: Nodular Amyloidosis

- **AL Amyloid**
- **Cutaneous plasmacytoma** locally produces Ig light chains as precursors to AL fibrils
- Local neoplastic (monoclonal) vs. reactive (polyclonal) deposition

Pathogenesis: Macular and Lichenoid Forms

- Degenerated or altered **keratin**
- *Fibrillar Body Theory*
  - Necrotic epidermal cells are transformed into amyloid by dermal macrophages and fibroblasts
- *Secretion Theory*
  - Amyloid precursors are secreted by disrupted basal cells and assembled at the DEJ

Bottom Line

The exact characterization and pathogenesis of all forms of amyloidosis is not quite clear

Summary: Classification/Fibrils

I. **Systemic**

1. Primary — AL
2. Myeloma-Associated — AL
3. Secondary — AA
4. Heredofamilial
   a. Familial Med. Fever — AA
   b. Muckle-Wells — AA
   c. Nephropathic, neuro, cardio. — Transthyretin
5. Hemodialysis Associated — β2- MG

Summary: Classification/Fibrils

II. Localized

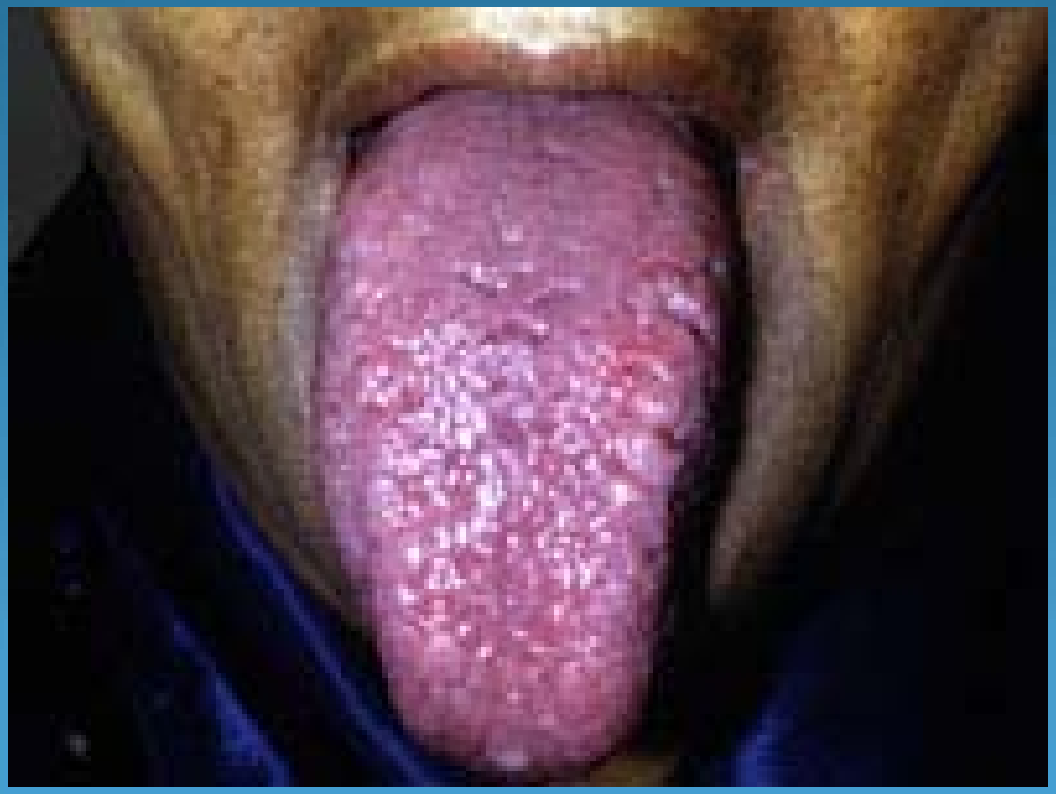
1. Primary Cutaneous
    - a. Nodular — AL
    - b. Macular — Keratin
    - c. Lichenoid — Keratin
2. Secondary Cutaneous
    - a. Tumors and PUVA — Keratin

Amyloidosis: Clinical Features

Primary Systemic Amyloidosis

- Non-Cutaneous
  - Constitutional symptoms
    - Fatigue, weight loss, edema, dyspnea, syncope, paresthesias
  - Macroglossia

Systemic Amyloid: Macroglossia



Primary Systemic Amyloidosis

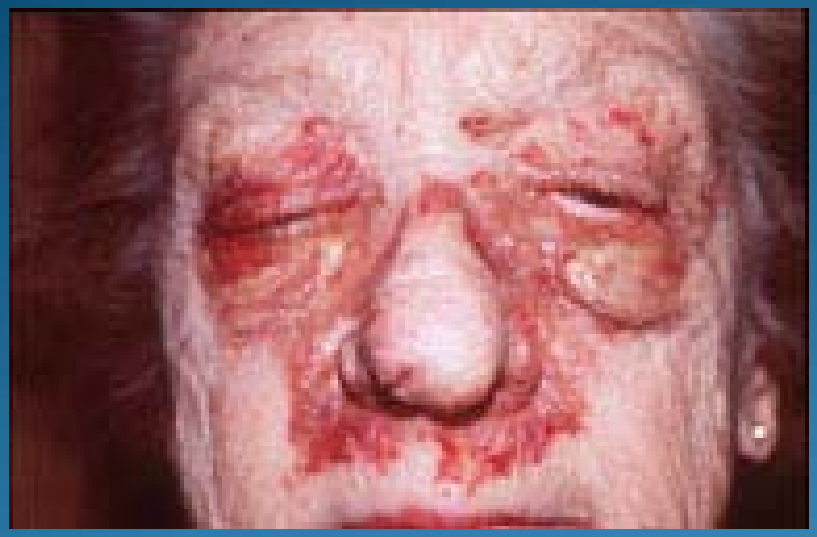
- Carpal Tunnel
- Sicca Syndrome
- Shoulder Pad Sign
- RA-like deposition in small joints
- GI bleed, peripheral neuropathy, cardiac sx

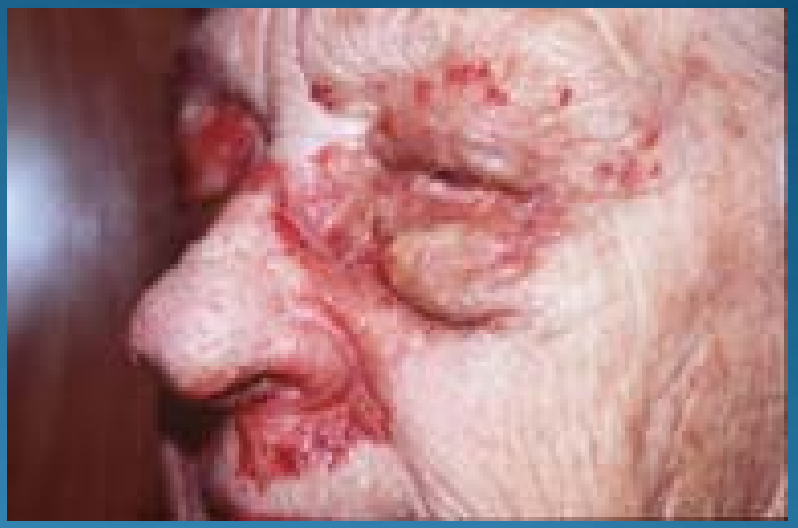
Primary Systemic Amyloidosis

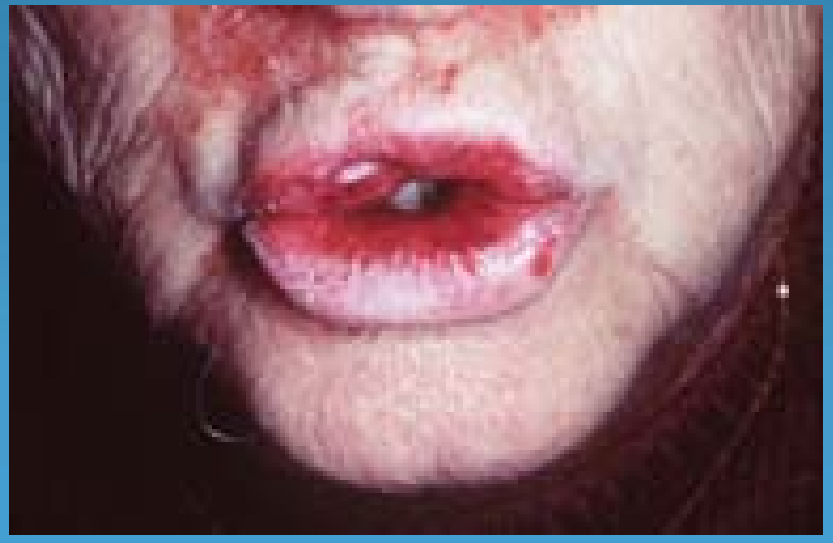
- CHF and arrhythmia cause death in 40% of patients with systemic amyloidosis

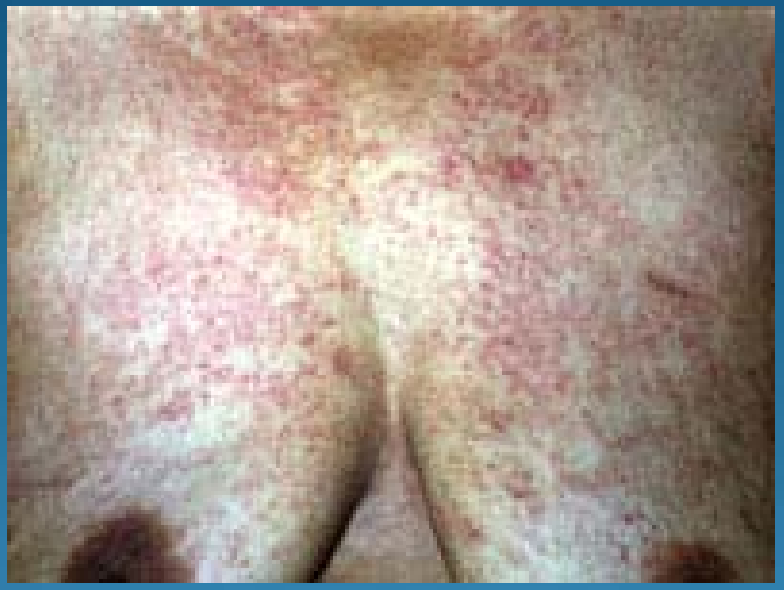
Primary and Myeloma-Associated Amyloidosis

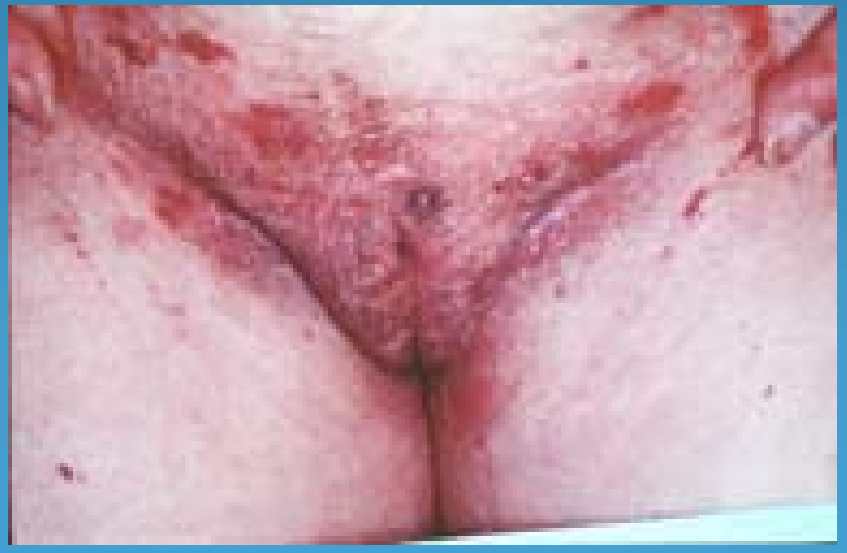
- **Skin or mucous membrane lesions are seen in ~ 40% or less**
- **Purpura** is most common
  - Amyloid deposition in vessel walls +/- coagulopathy from infiltration of liver
  - after minor trauma (**pinch purpura**)
  - Eyelids, axilla, umbilicus, anogenital
  - Facial purpura after Valsalva or proctoscopy





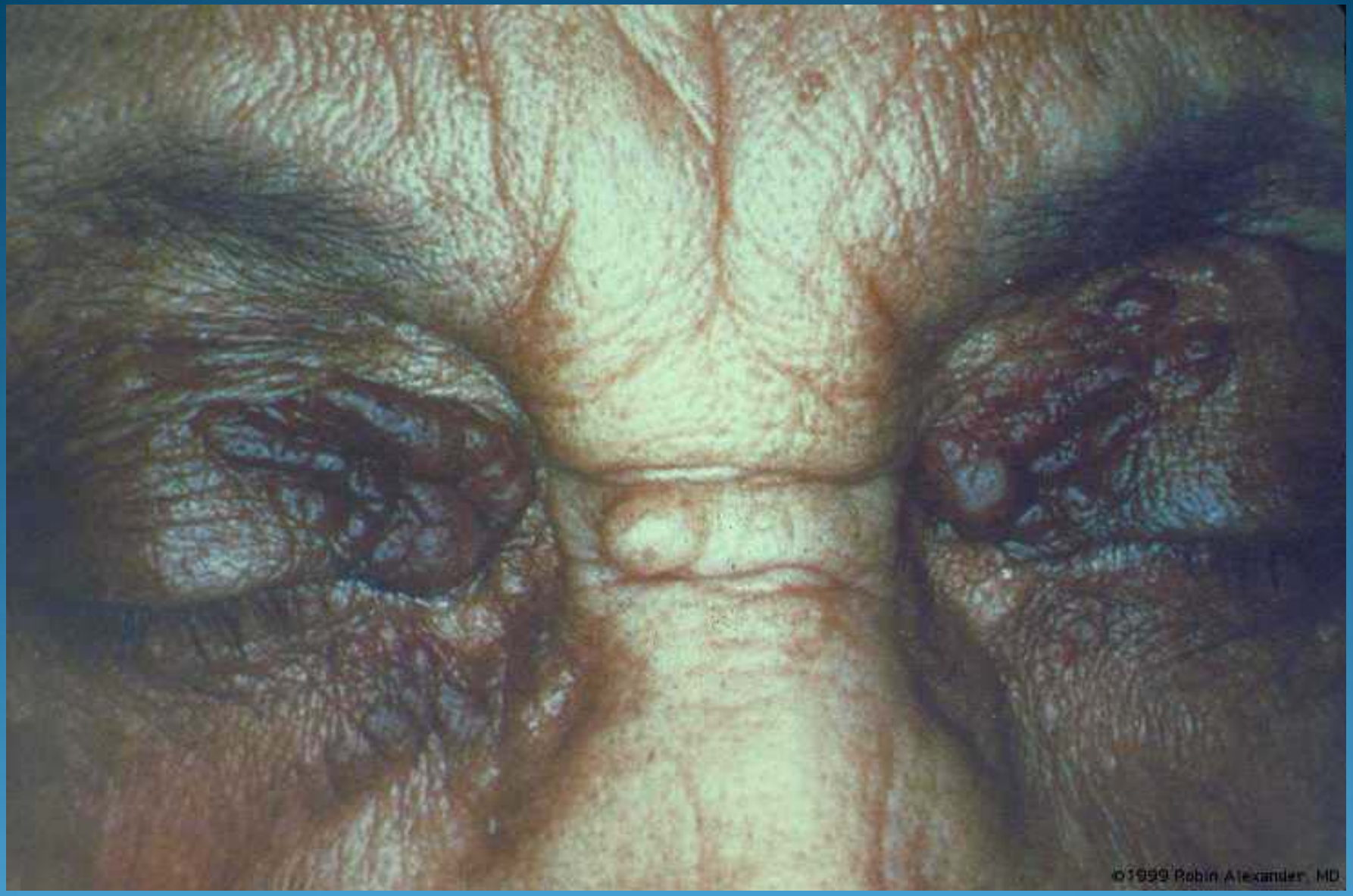




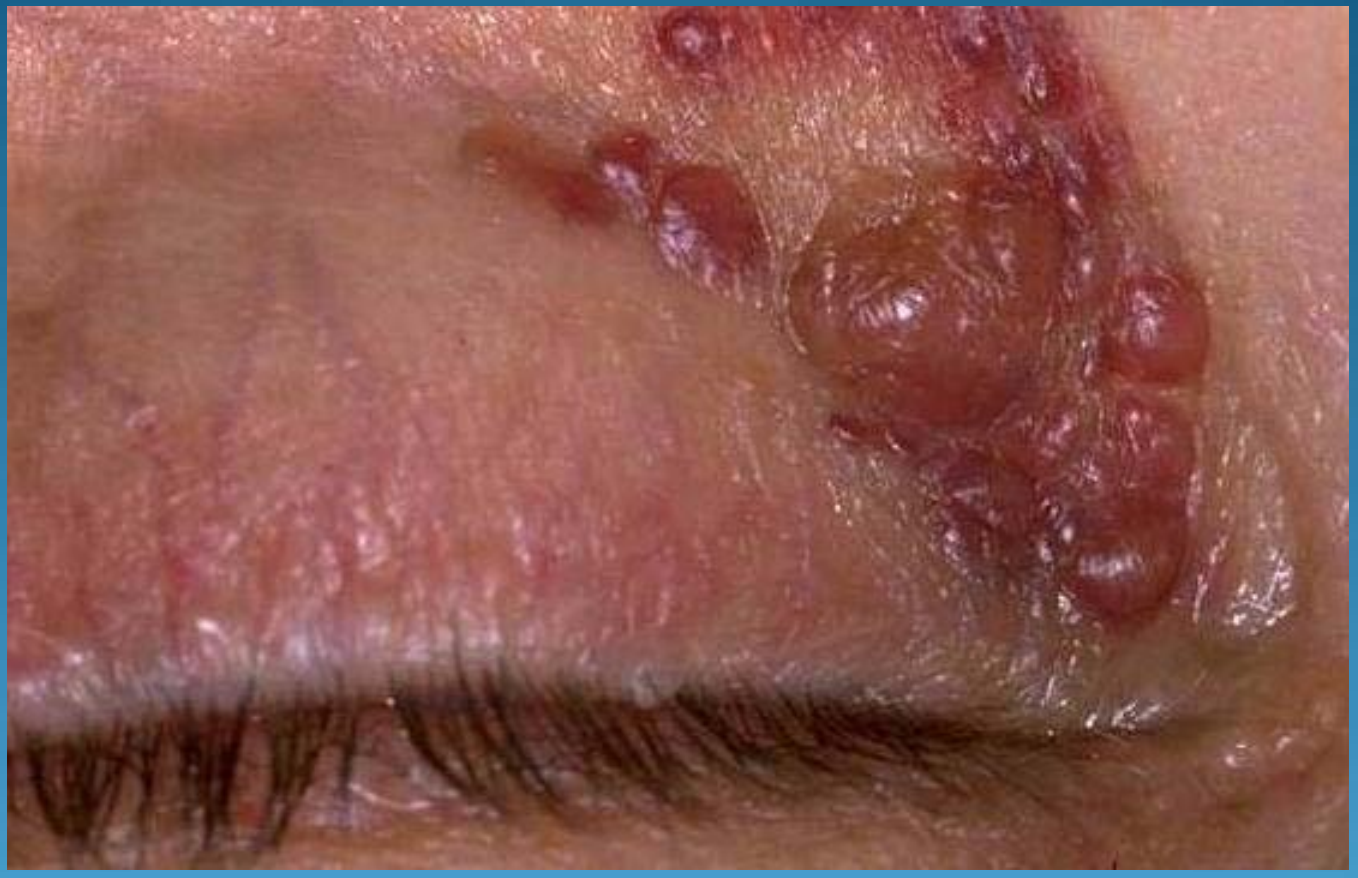


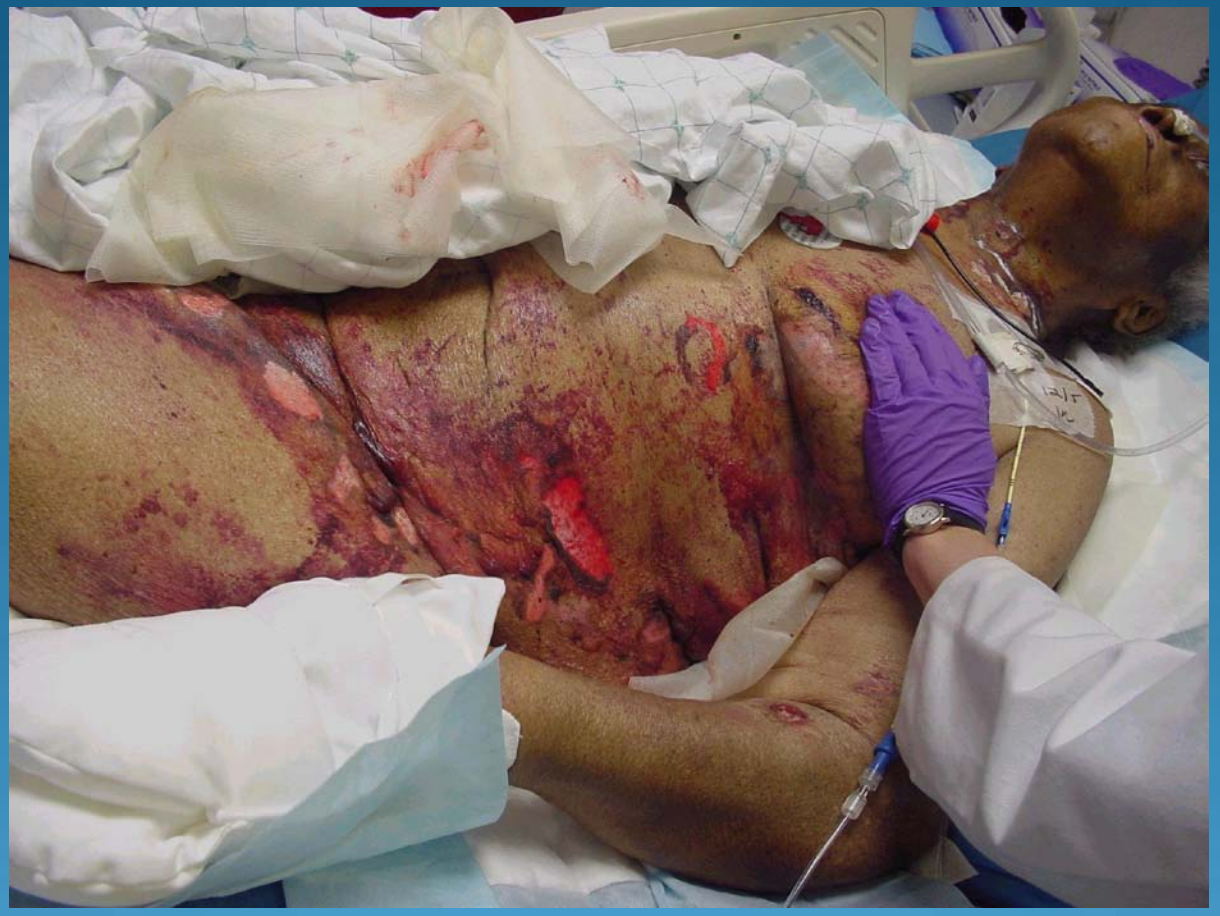
Primary and Myeloma-Associated Amyloidosis

- **Less common cutaneous manifestations**:
- Asymptomatic *waxy, hemorrhagic papules*, plaques and nodules in *flexures*, central face, retroauricular folds, and tongue
- Sclerodermatous infiltration
- Bullae
- Alopecia
- Cutis Laxa



Waxy, hemorrhagic periorbital papules of systemic amyloidosis





Bullous Amyloidosis

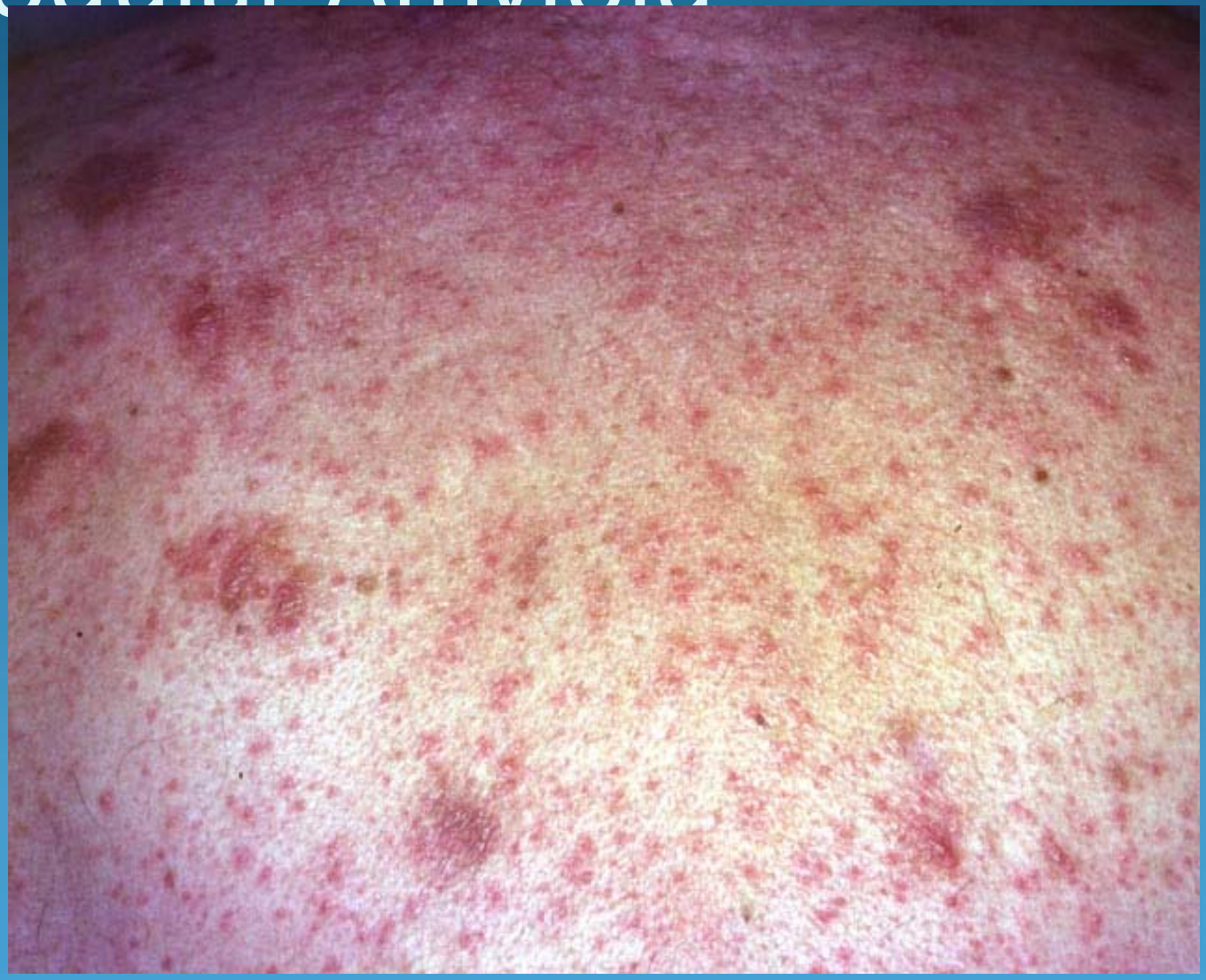
Clinical: Nodular Amyloidosis

- **Rarest form of cutaneous amyloidosis**
- Firm, waxy subcutaneous nodules on the face, extremities, trunk or genitalia
- May be atrophic, anetodermic, or bullous
- Female:male = 2:1
- Presents in the 6th or 7th decade
- Rare association with **Sjogren's Syndrome**

Nodular Amyloid

- Think of Jodi's patient

Nodular Amyloid



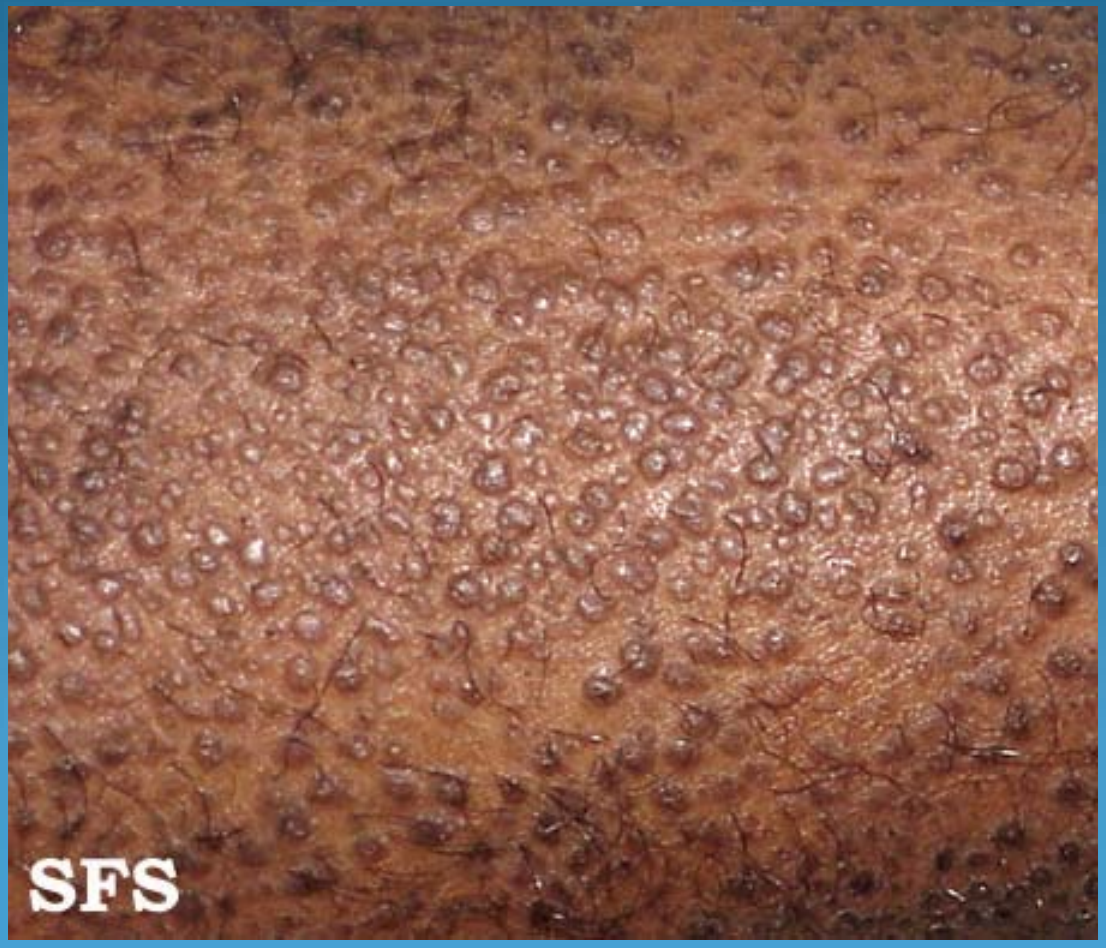
Clinical: Nodular Amyloidosis

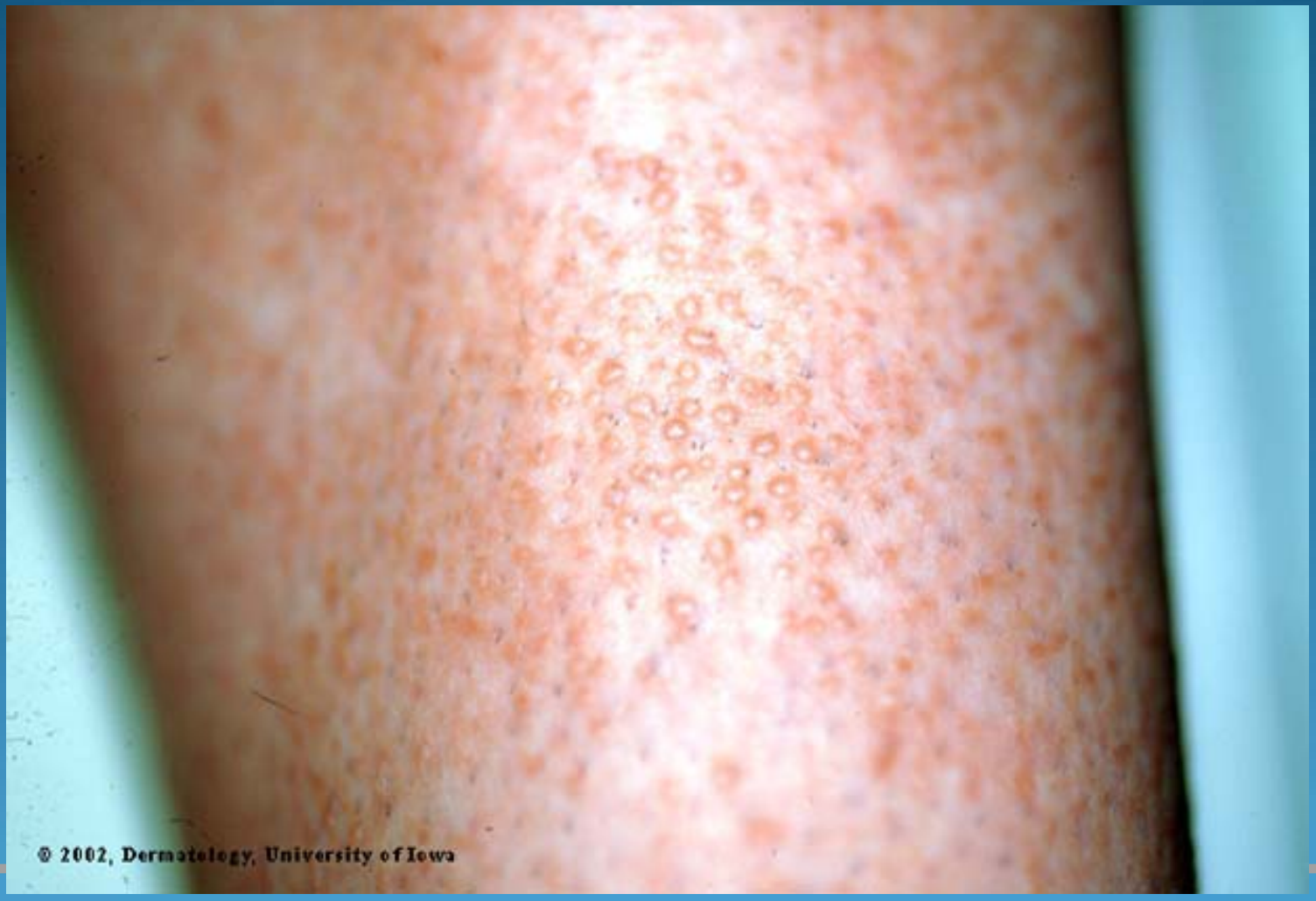
- Less than 15% of localized nodular lesions will progress to systemic amyloidosis
- If this occurs, investigate for a latent paraproteinemia and systemic disease

Clinical: Lichen Amyloidosis

- Red-brown, pruritic, hyperkeratotic papules on the shins with spread to the dorsal feet and thighs
- Chinese ancestry most commonly affected

Lichen Amyloidosis

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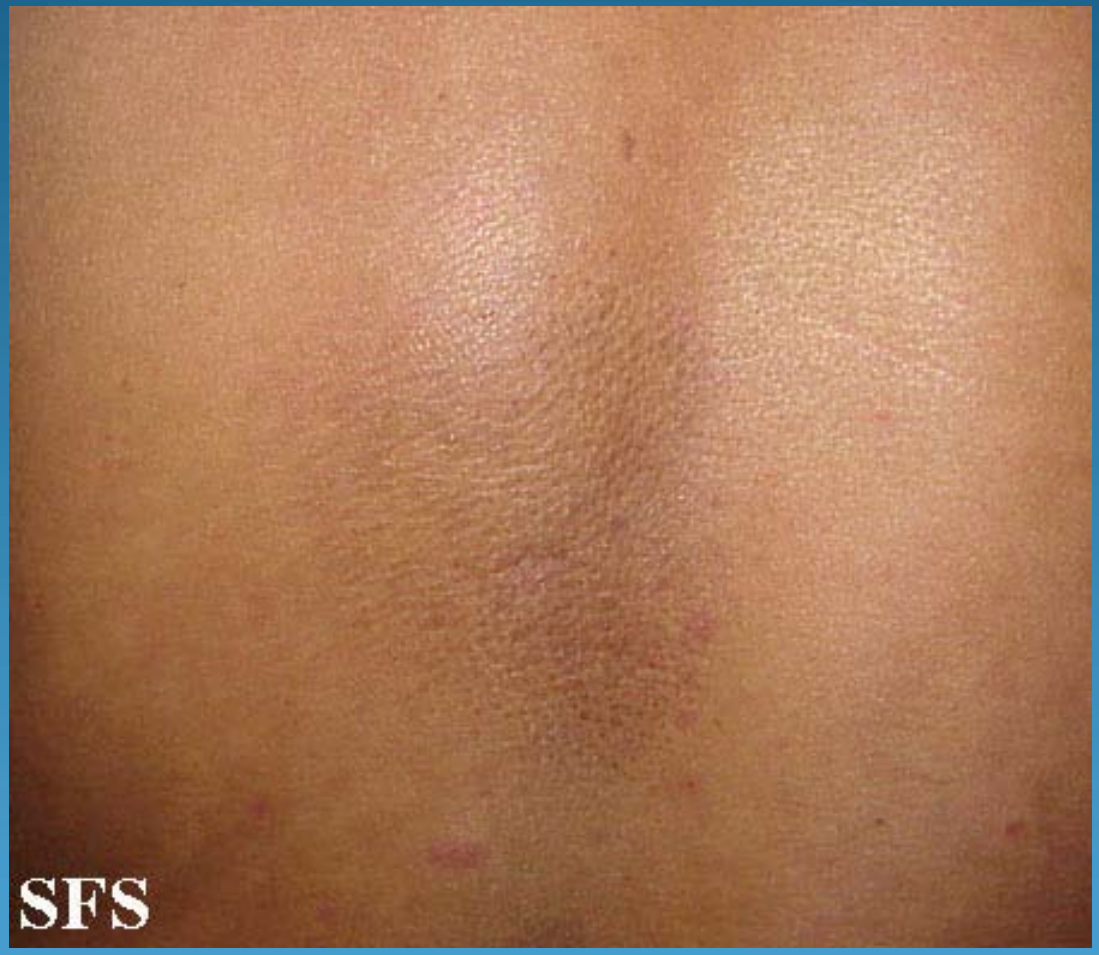
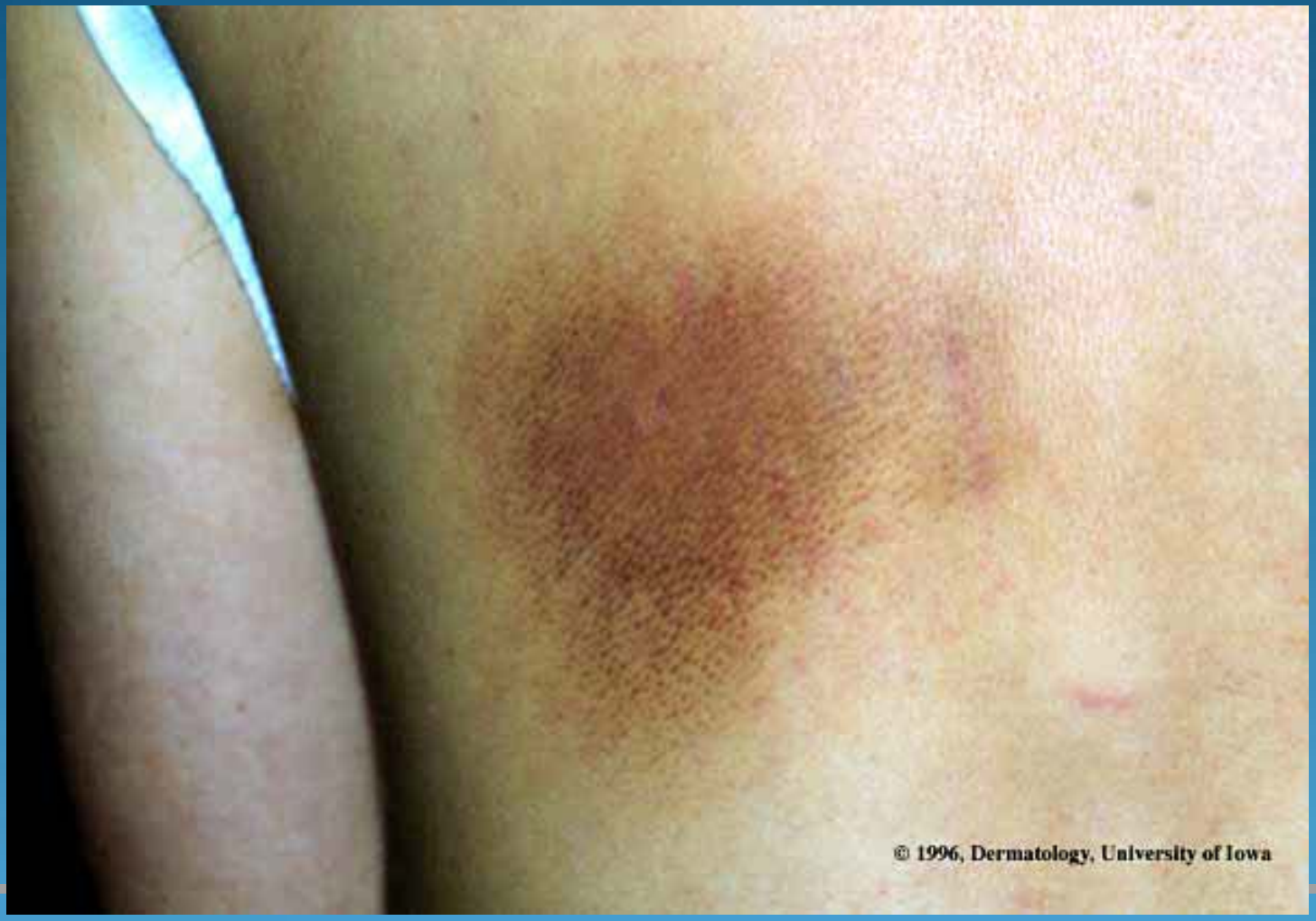
Clinical: Macular Amyloidosis

- Gray-brown pruritic papules/patches
  - upper back, trunk, or extremities
  - Notalgia Paresthetica commonly associated
- Central and South American, Asian, and Middle Eastern patients most common
- *Lichen and macular amyloid have not been reported to progress to systemic disease*

Macular Amyloid


SFS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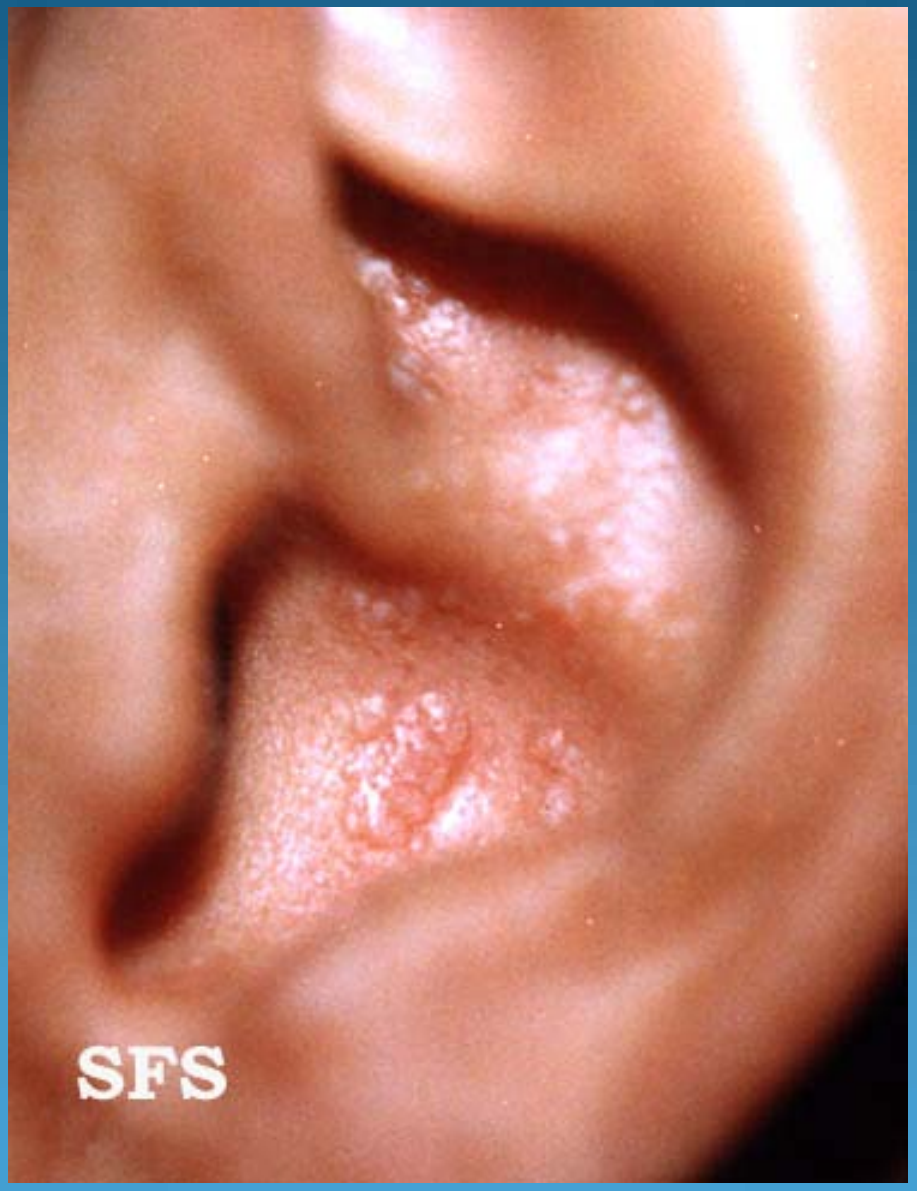
Variants of Primary Localized Amyloidosis

- Periorbital hyperpigmentation
- Auricular Papules
- Whorled biphasic form in Blaschko's Lines
  - Macular and lichenoid lesions in the same patient


SFS

Rare Variants of Primary Localized Amyloidosis

- Poikilodermatous Cutaneous Amyloid: PCA
  - focal or generalized
  - PCA Syndrome: AD disease with poikiloderma, lichenoid papules, photosensitivity, blistering, and short stature
- Familial- pruritic, swirled pigmentation on trunk or extremities beginning in childhood

Secondary Localized Amyloidosis

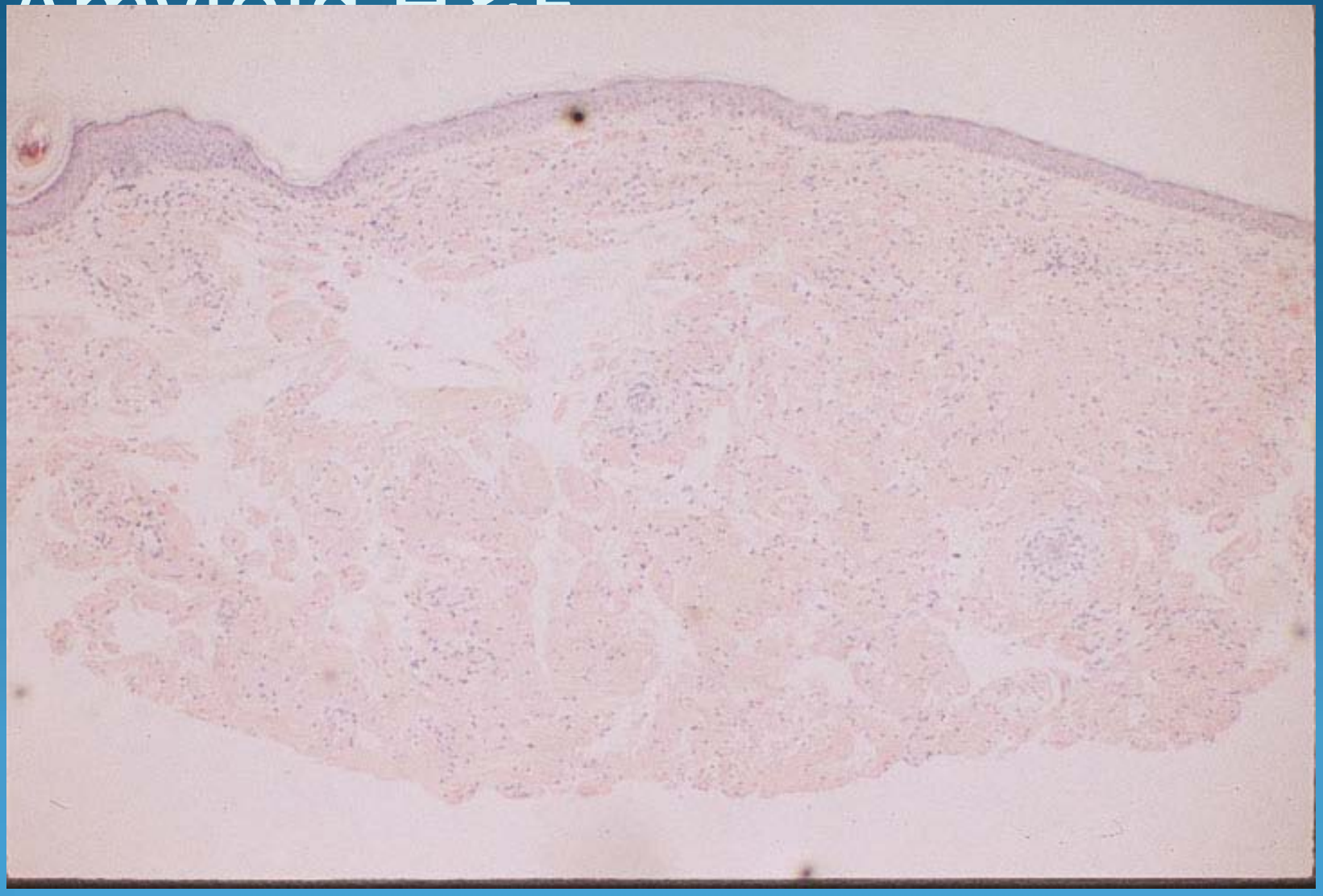
- Clinically insignificant microscopic deposits of amyloid as a secondary phenomenon associated with skin tumors
  - BCC, SCC, Seb K, DSAP
  - PUVA
- Mechanism analogous to lichen and macular forms (keratinocyte destruction)

Amyloidosis: Histology

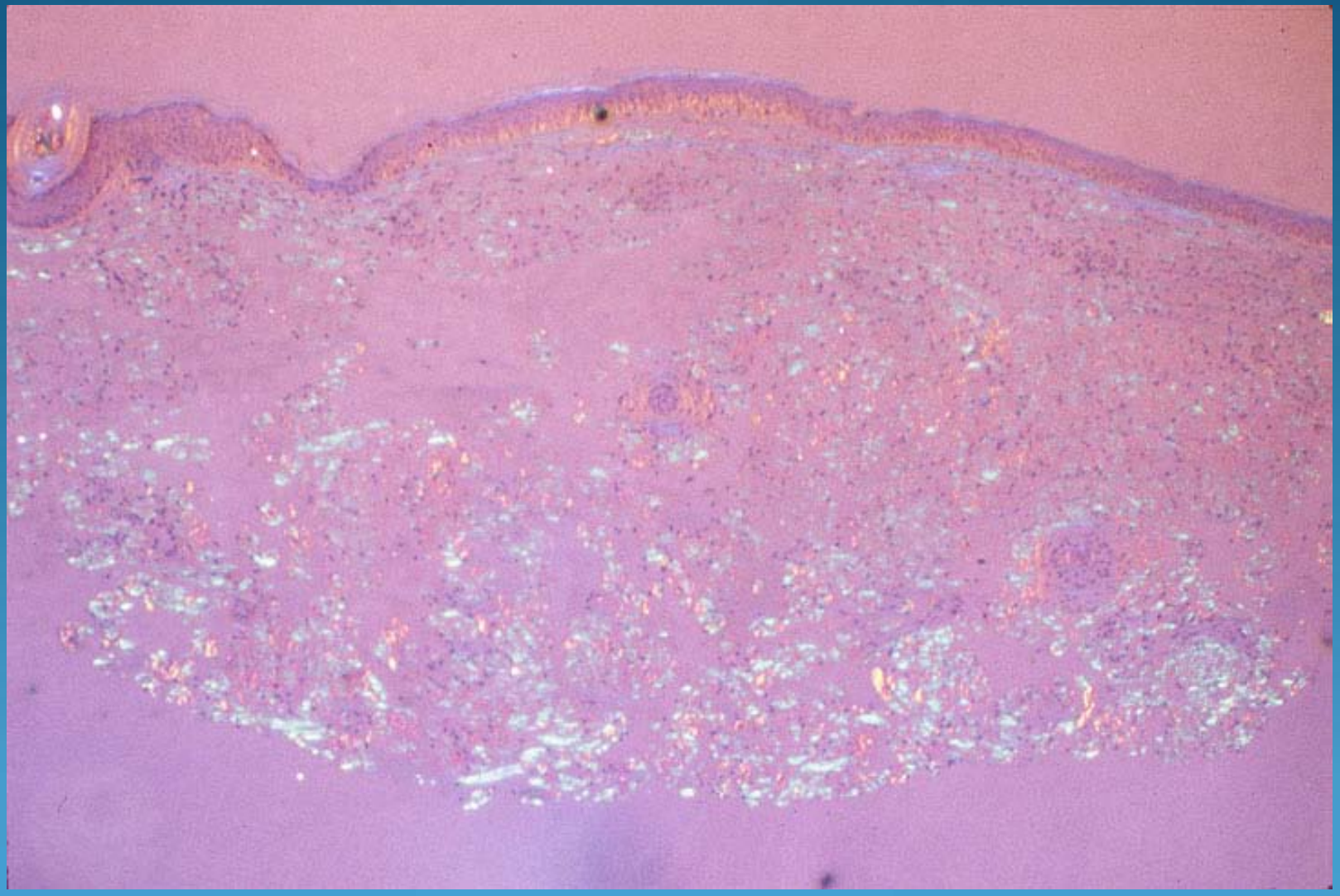
Amyloid Stains

- **Congo Red**
  - apple-green birefringence under polarized light
- **Potassium Permanganate + Congo Red**
  - Secondary amyloid (AA) loses its staining with Congo Red after pretreatment with PP
  - Primary systemic, myeloma-associated, and localized amyloid deposits are resistant to PP

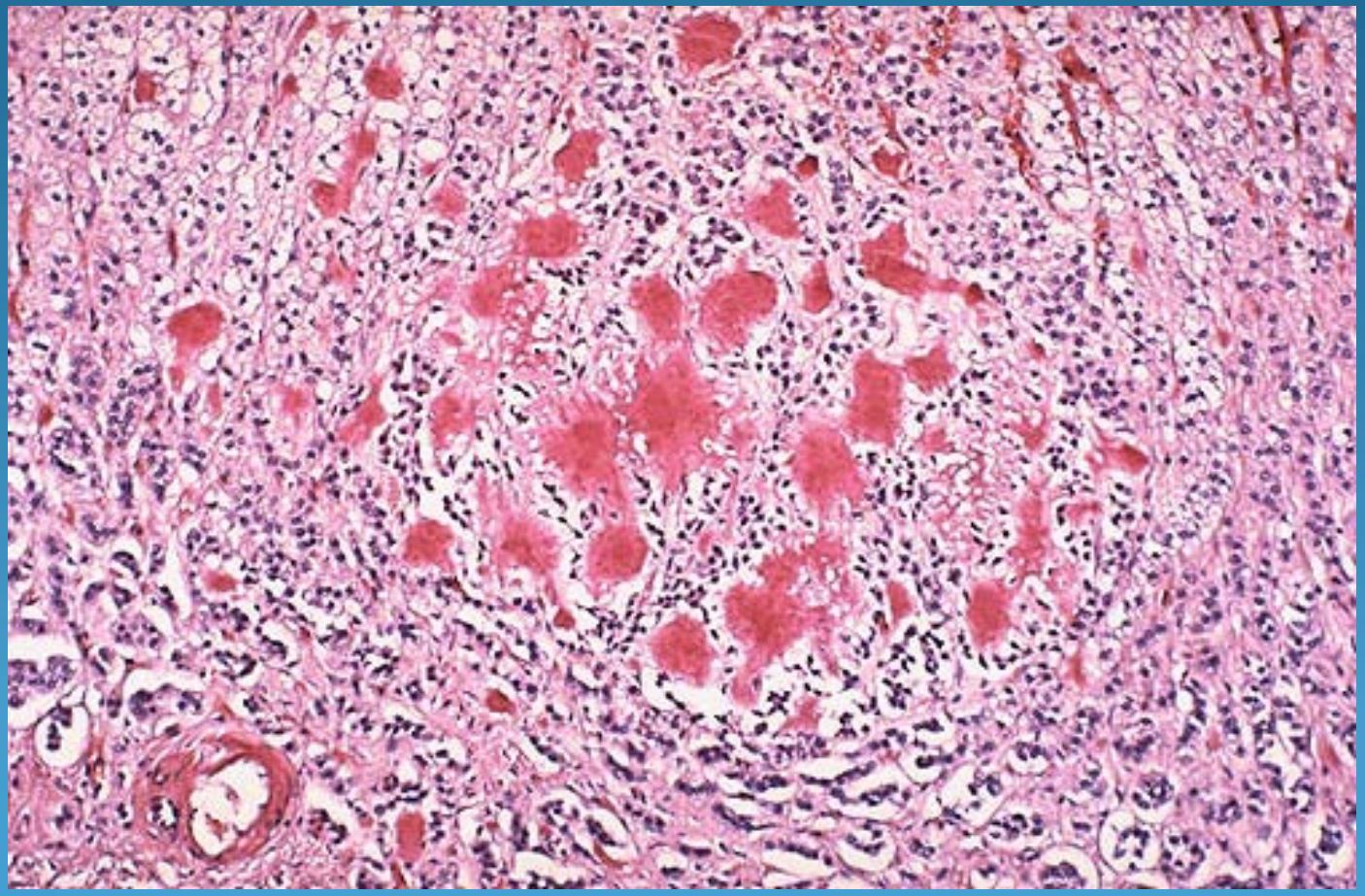
Amyloid H&E



Amyloid: Congo Red



Congo Red: H&E

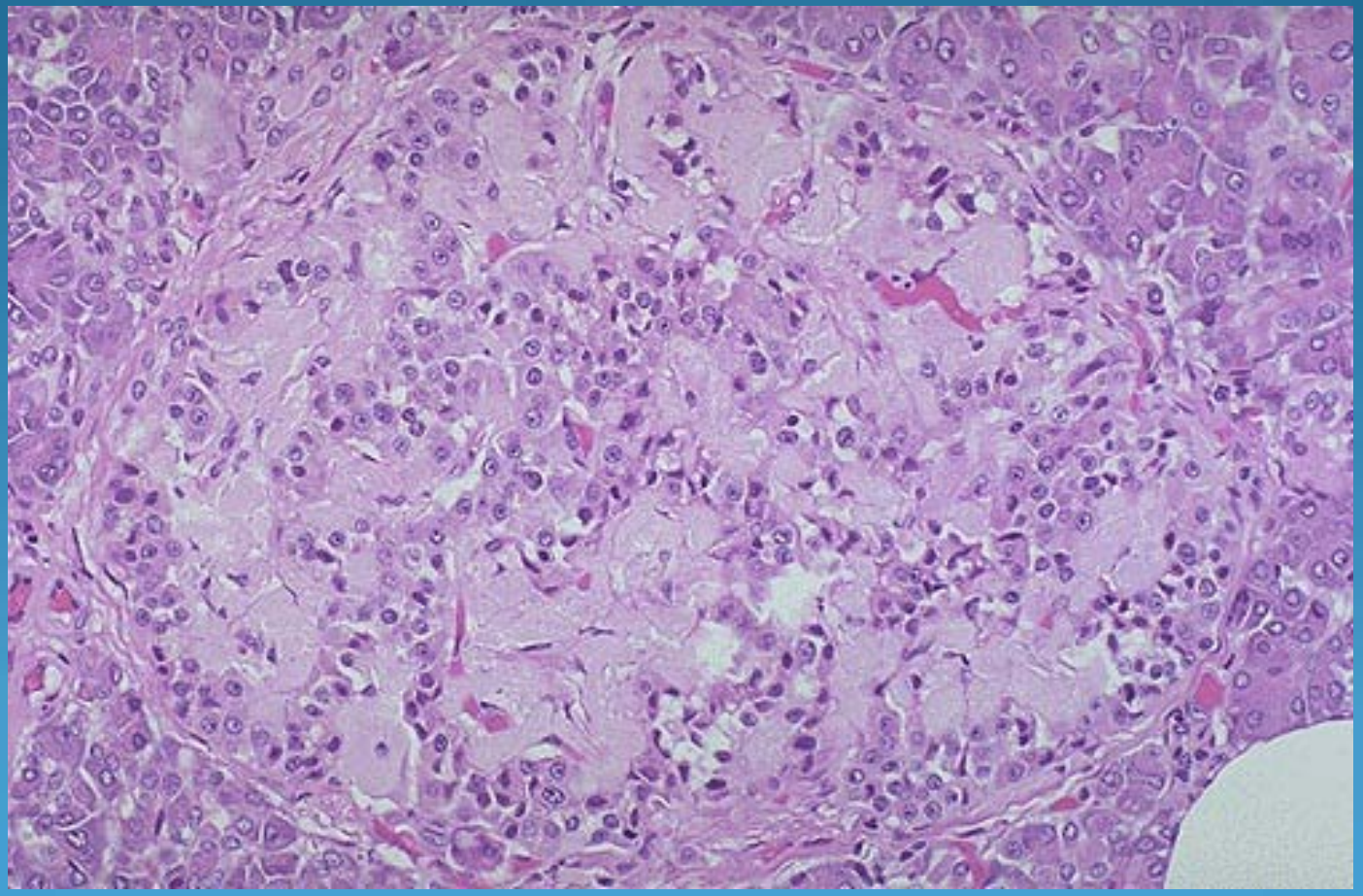


Congo Red: Polarized Light

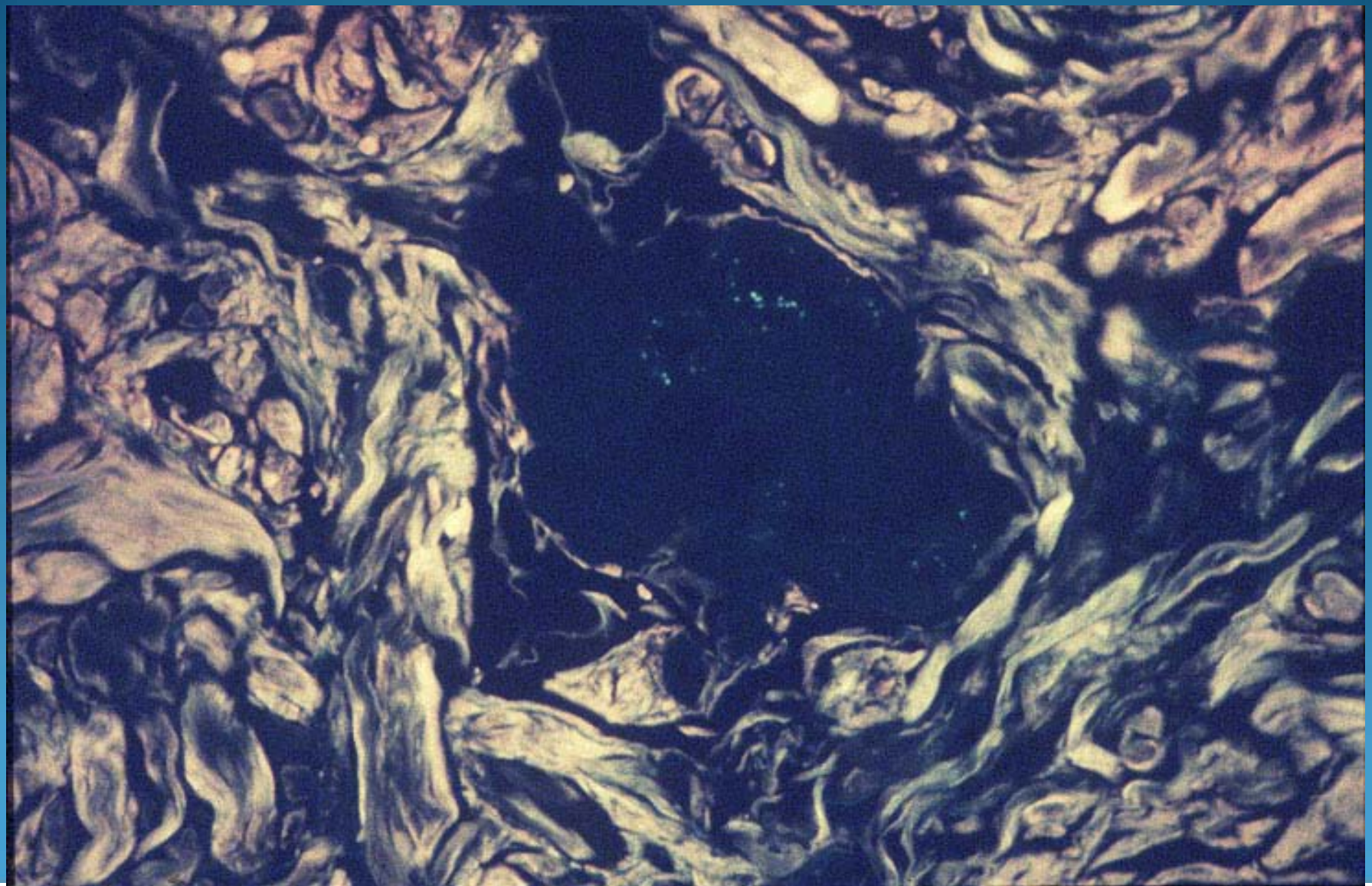
Amyloid Stains

- Periodic acid- Schiff (PAS)
- Methyl violet
- Crystal violet
- Cotton dyes: sirius red, pagoda red, dylon
- Fluorescent dyes: thioflavin-T, phorwhite BBU
- Antisera to fibril proteins is most sensitive

Amyloid H&E (kidney)

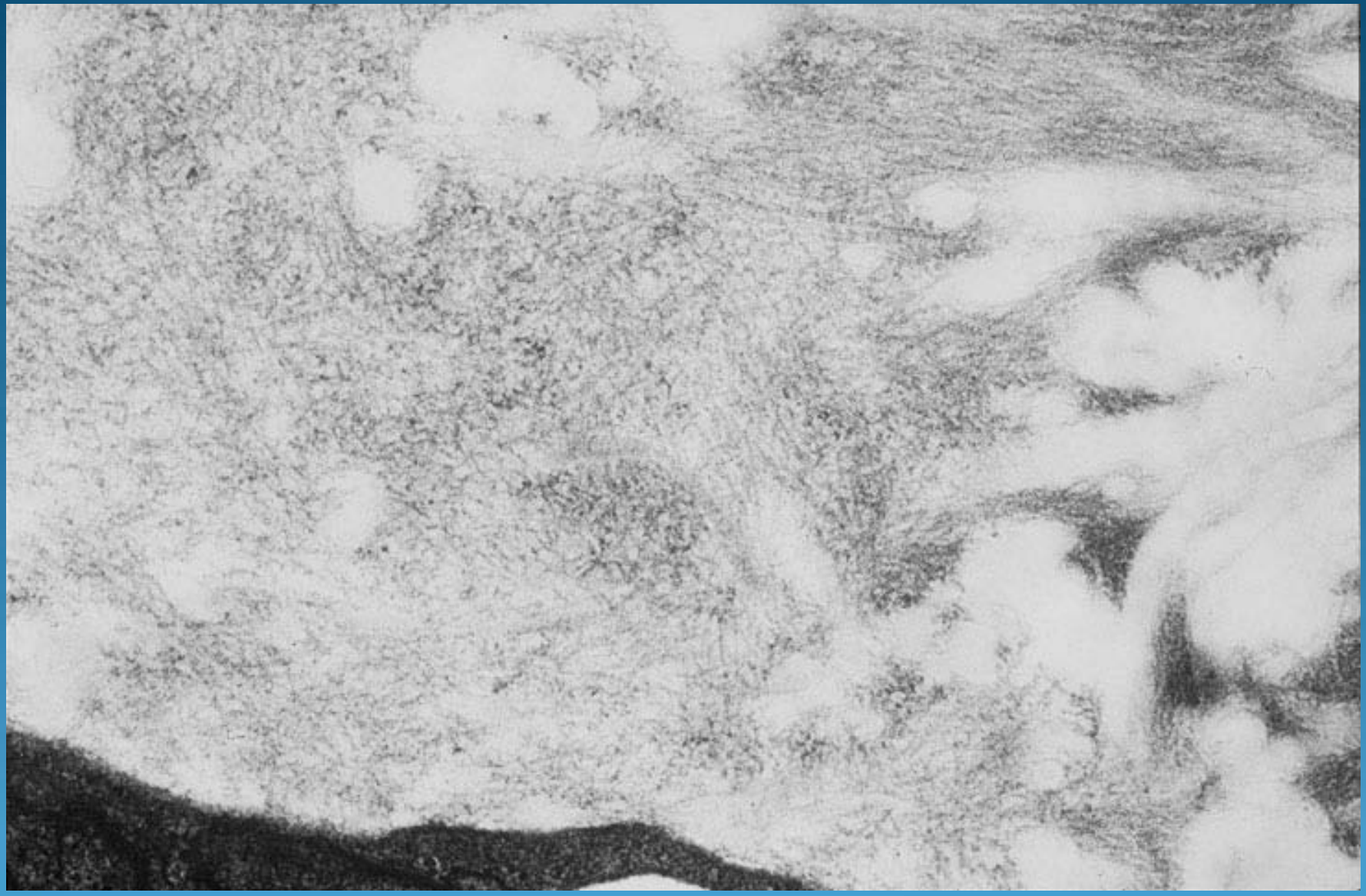


Amyloid: Thioflavin-T



Amyloid Electron Microscopy

- Formalin fixed tissue can be used for EM
- Amyloid deposits contain 6-10nm wide, straight, non-branching, non-anastomosing filaments arranged in a loose meshwork

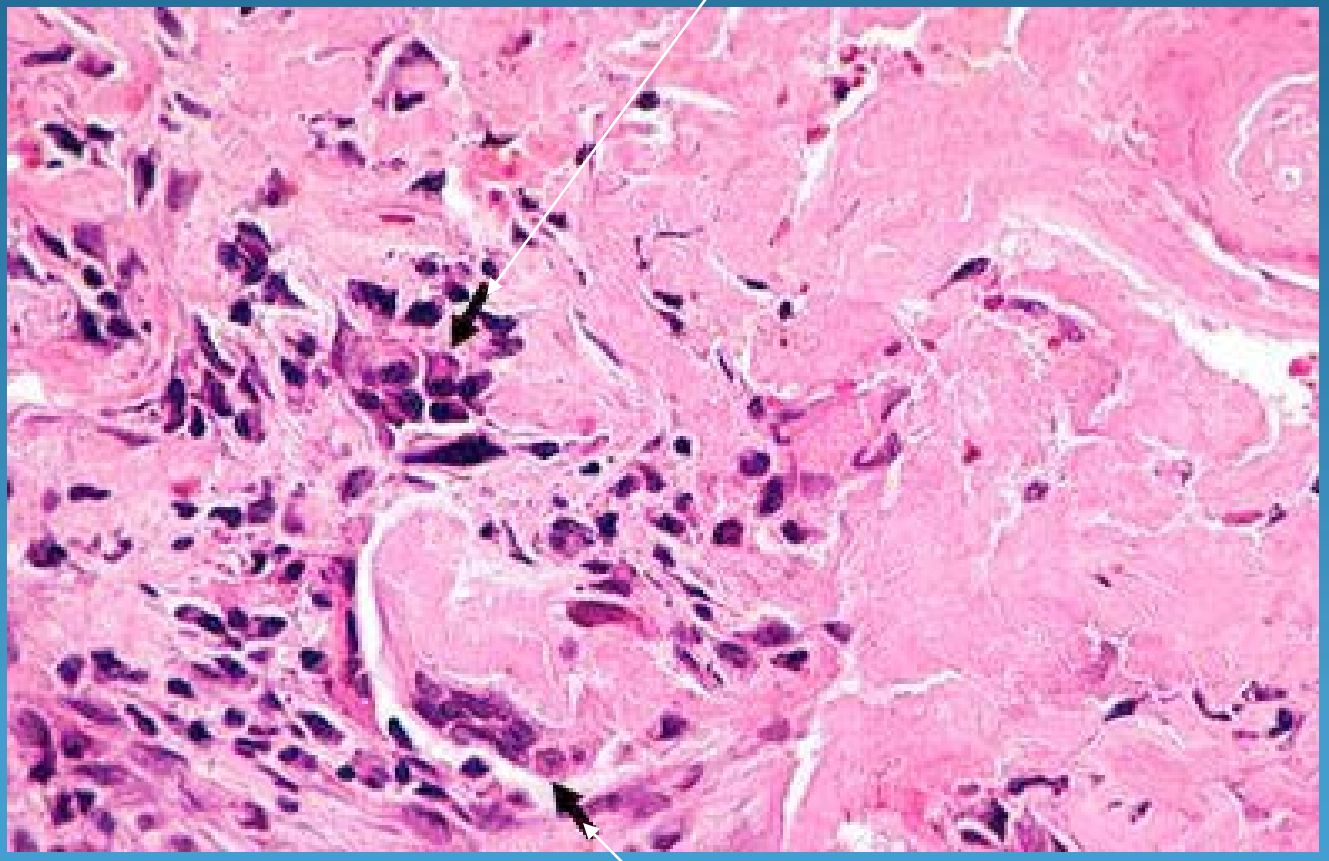


Amyloid Electron Microscopy

Histology: Systemic Amyloidosis

- **H&E:**
- dermal and subcutaneous pink, fissured, amorphous masses
- deposits in vessel walls, fat, and surrounding eccrine glands and other mesenchymal tissues
- Amyloid Rings: distinctive amyloid deposits around individual fat cells
- No associated inflammation

Amyloidosis



Histology: Systemic Amyloidosis

- **Biopsy of:**
  - **Clinically normal skin** is positive in ~50% of primary systemic forms
  - **Rectum** is positive in 75% of primary systemic forms

- **FNA of abdominal fat pad is most sensitive**
  - 95% positive in primary and myeloma-associated
  - 65% positive in secondary forms

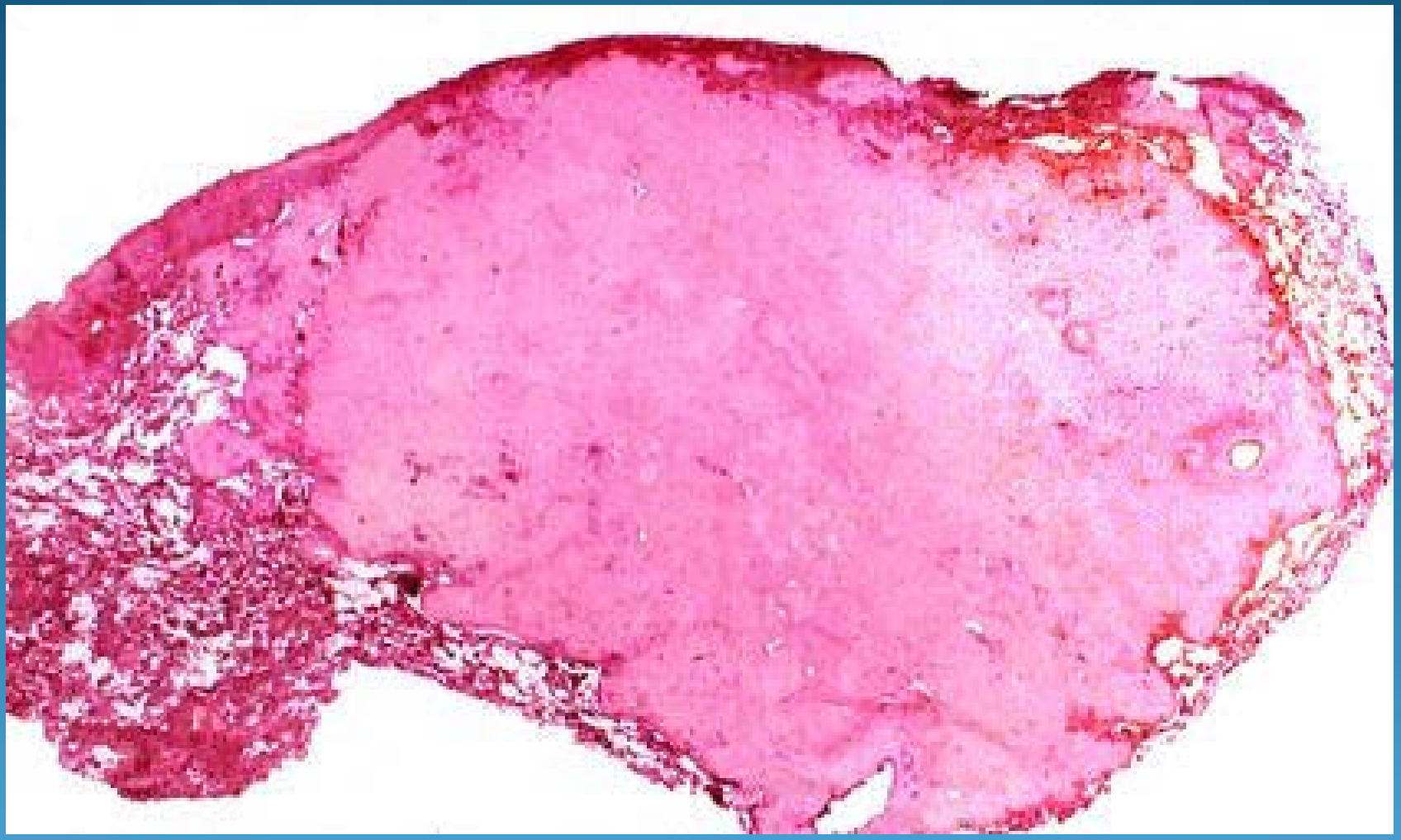
Histology: Systemic Amyloidosis

- Although skin is grossly uninvolved in secondary systemic amyloidosis, amyloid deposits in the deep dermis around adnexae, blood vessels, and fat cells are seen in 50%

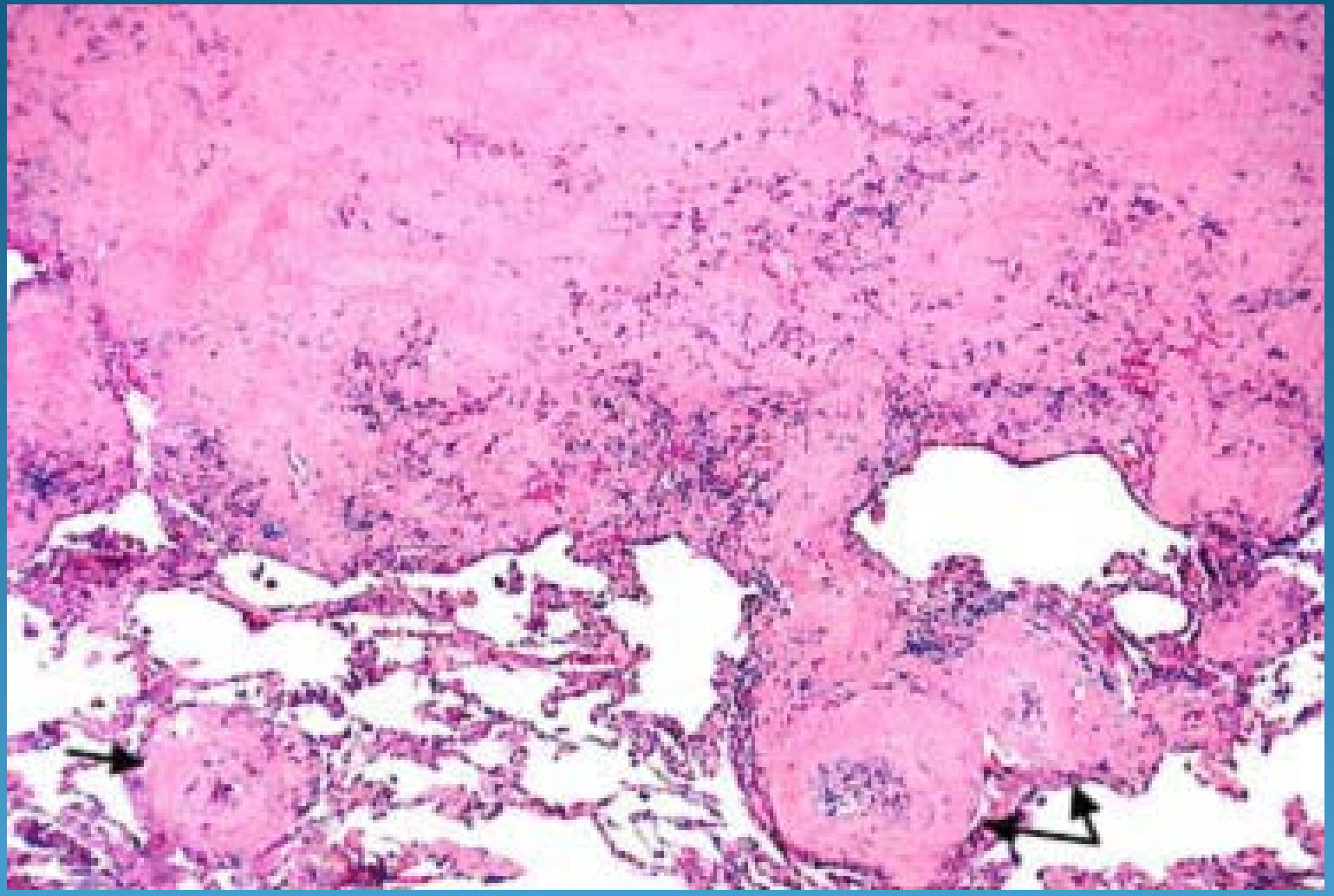
- **Distinguish AA from AL amyloid with**:
  - Indirect IF with anti-amyloid A antiserum
  - Potassium permanganate reaction

Histology: Localized Amyloidosis

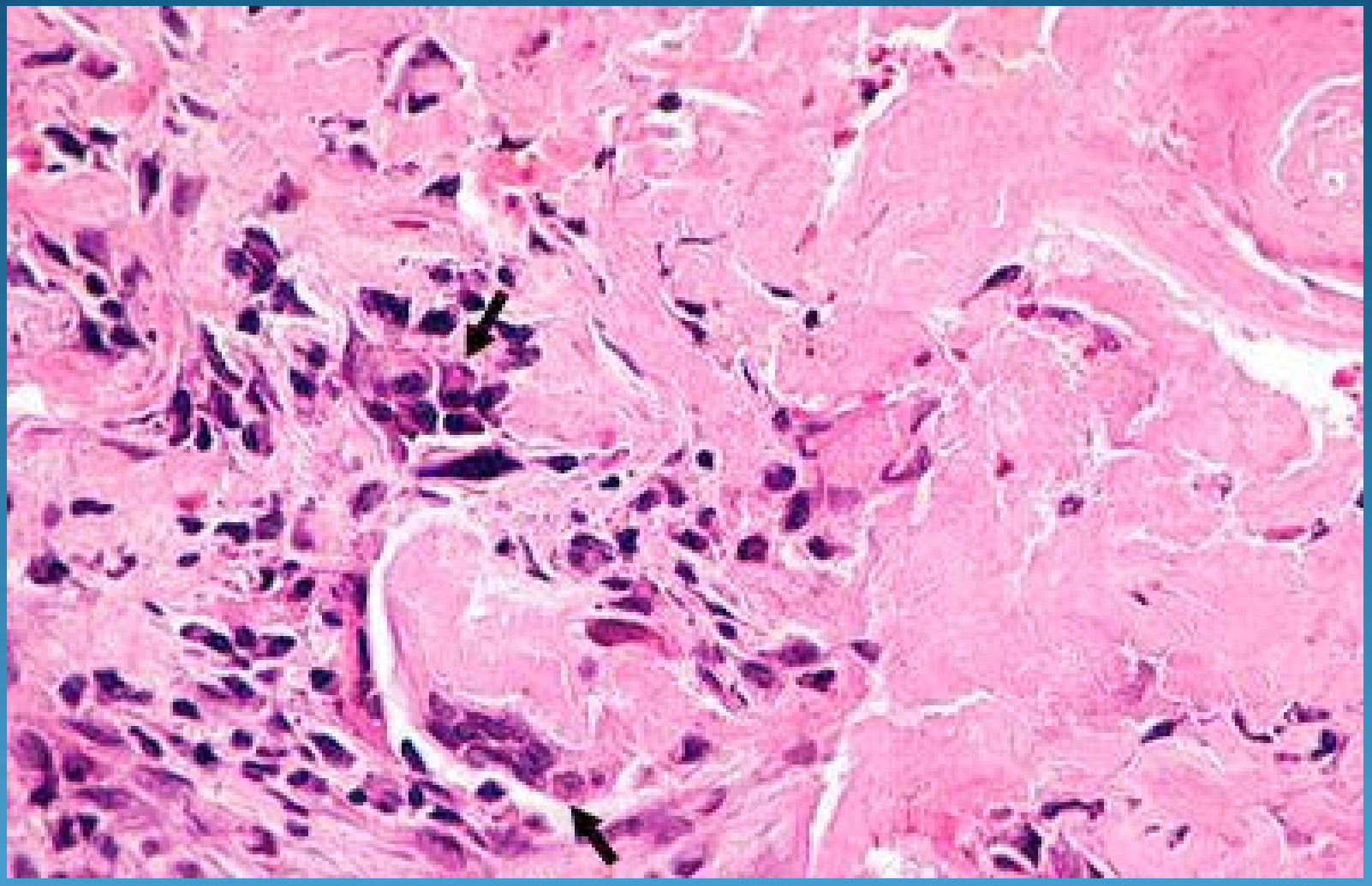
- **Nodular Amyloid**
- Atrophic epidermis overlies large amorphous masses extending from the dermis into the fat
- Deposits surround BV, adnexae, and fat cells
- ***Inflammatory infiltrate with plasma cells, Russell bodies, and giant cells is present***
- Plasma cells lie at the periphery of amyloid



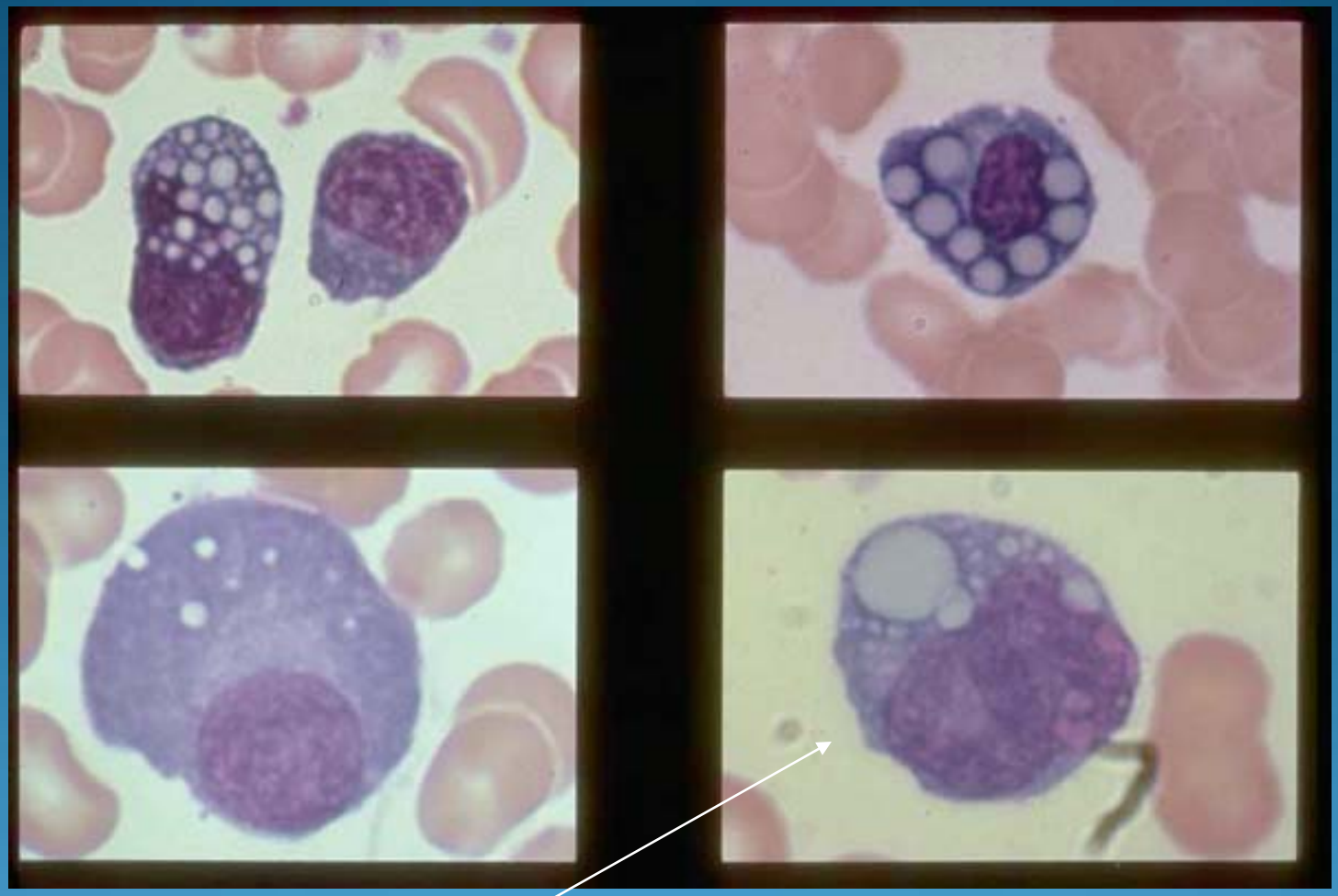
Nodular Amyloid



Amyloid encases blood vessels



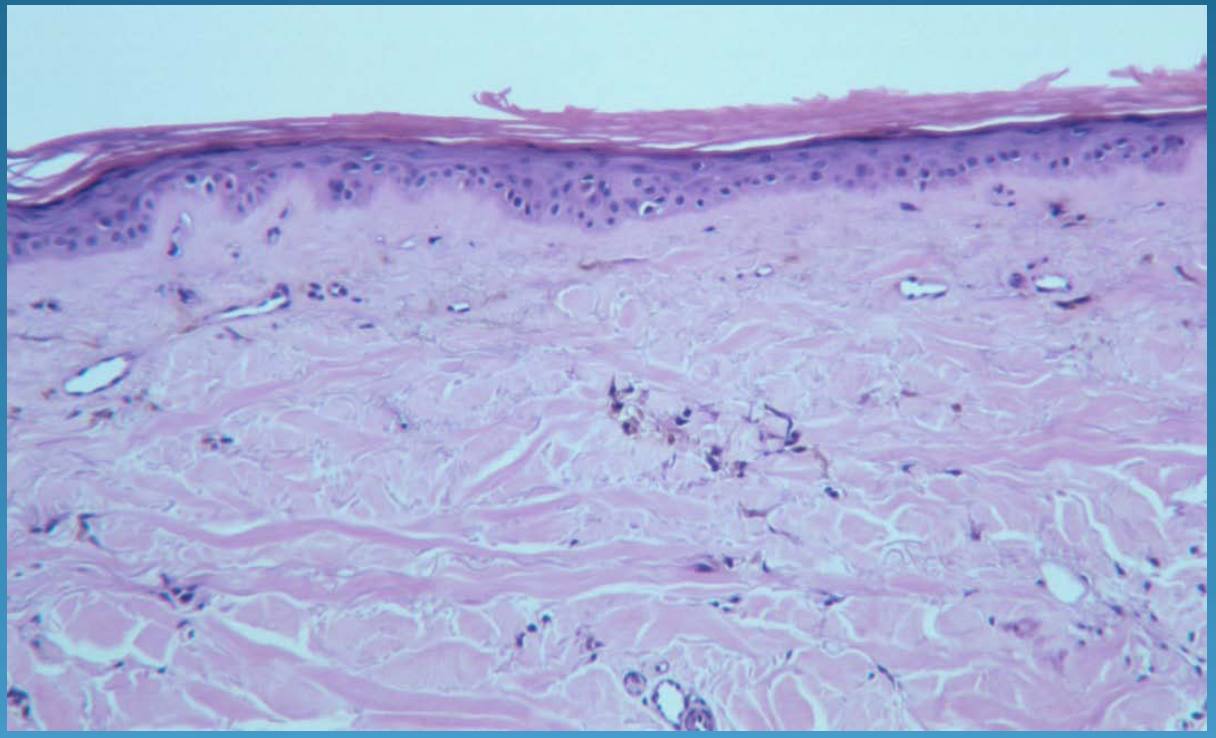
Plasma cells and giant cells



Russell Bodies:
plasma cells with vacuoles representing stored Ig

Histology: Localized Amyloidosis

- **Lichen and Macular Amyloid**
- Amyloid deposits in papillary dermis
- Pigment incontinence, hemorrhage, and hemosiderin in papillary dermis
- EM: amyloid composed of amyloid filaments, normal and degenerated tonofilaments, and lysosomes
- Monoclonal anti-keratin antibodies react with the deposits



Amyloidosis: Treatment

Treatment: Primary Systemic Amyloidosis

- **Cytotoxic chemotherapy**
  - Melphalan, prednisone, colchicine, penicillamine, azathioprine, vincristine, cyclophosphamide
- **Supportive Care**
  - Dialysis; cardiac and renal transplant
- **Bone Marrow Transplantation**
- **Dimethyl Sulfoxide (DMSO)**
  - Nontoxic antiinflammatory solvent may inhibit synthesis or promote degradation of amyloid

Treatment: Secondary Systemic Amyloidosis

- Treatment of the underlying disorder may improve the secondary amyloid deposits

- Specific Therapies:
  - Juvenile RA: chlorambucil
  - Familial Med. Fever: colchicine

Treatment: Localized Amyloidosis

- **Nodular Amyloid**
  - Excision; CO_2 Laser; ED&C
  - Recurrences are expected
- **Lichen Amyloid**
  - Topical DMSO, dermabrasion, oral retinoids
  - Topical steroids and antipruritics are usually ineffective
- **Macular Amyloid**
  - UVB

Satisfactory treatment overall is lacking for all forms of amyloidosis