Inflammatory skin disease every pathologist should know

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General Concepts

- Pattern recognition
  - Epidermal predominant vs. dermal predominant
    - Epidermal changes trump dermal changes
  - Distribution of the inflammatory infiltrate
    - Superficial vs. superficial and deep
    - Location: perivascular, interstitial, nodular
  - Nature of inflammatory infiltrate
    - Mononuclear (lymphocytes and histiocytes)
    - Mixed (mononuclear and granulocytes)
    - Granulocytic
- Correlation with clinical presentation
- Never diagnose “chronic nonspecific dermatitis”

Principle Patterns: Epidermal Changes Predominant

- Spongiotic pattern
- Psoriasiform pattern
  - Spongiotic and psoriasiform often co-exist
- Interface pattern
  - Basal vacuolization
    - Perivascular infiltrate

      or
    - Lichenoid infiltrate

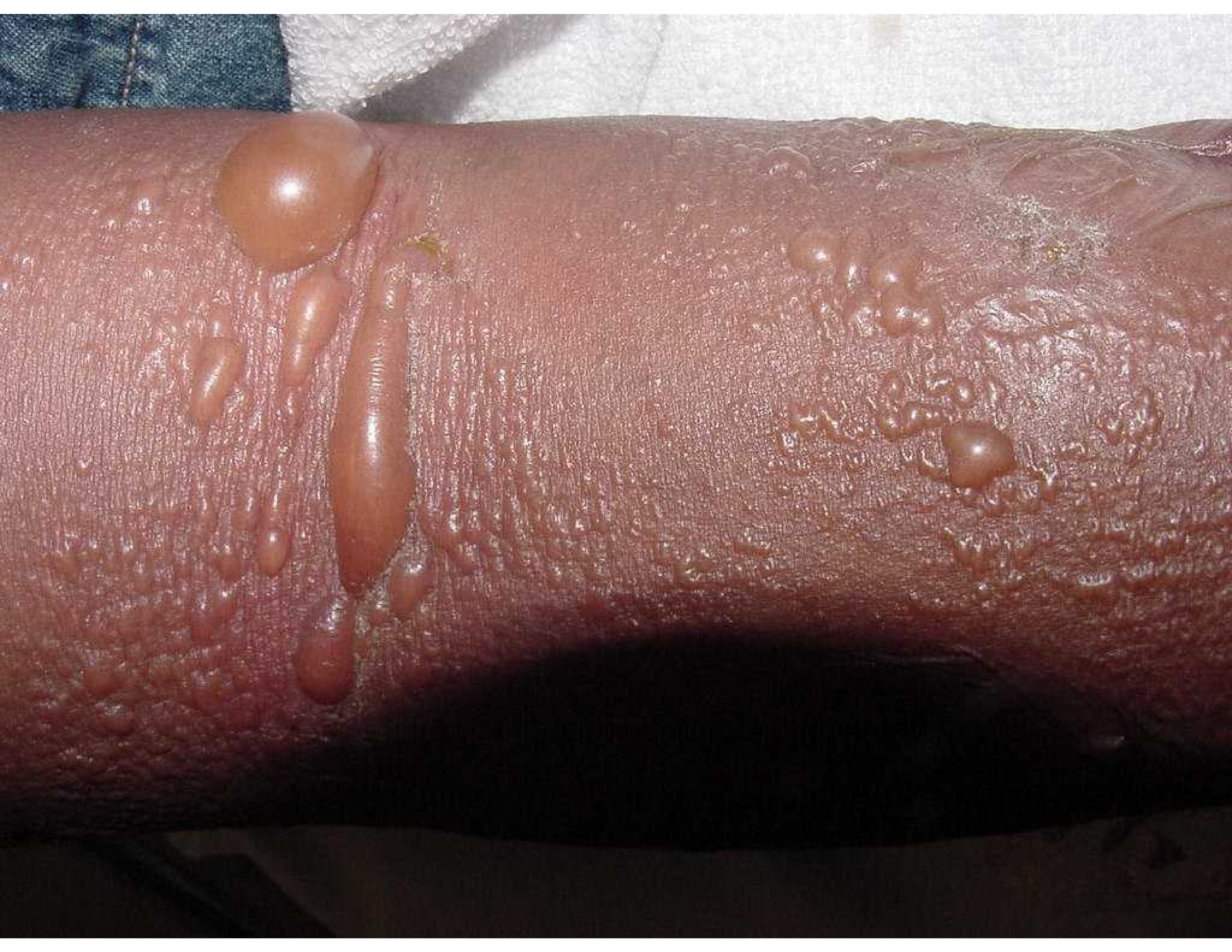
Principle Patterns: Dermal Changes Predominant

- Superficial perivascular
- Superficial and deep perivascular
- Interstitial pattern
  - Palisading granulomatous
  - Nodular and diffuse
- Sclerosing pattern

- Panniculitis
- Bullous disease
- Miscellaneous

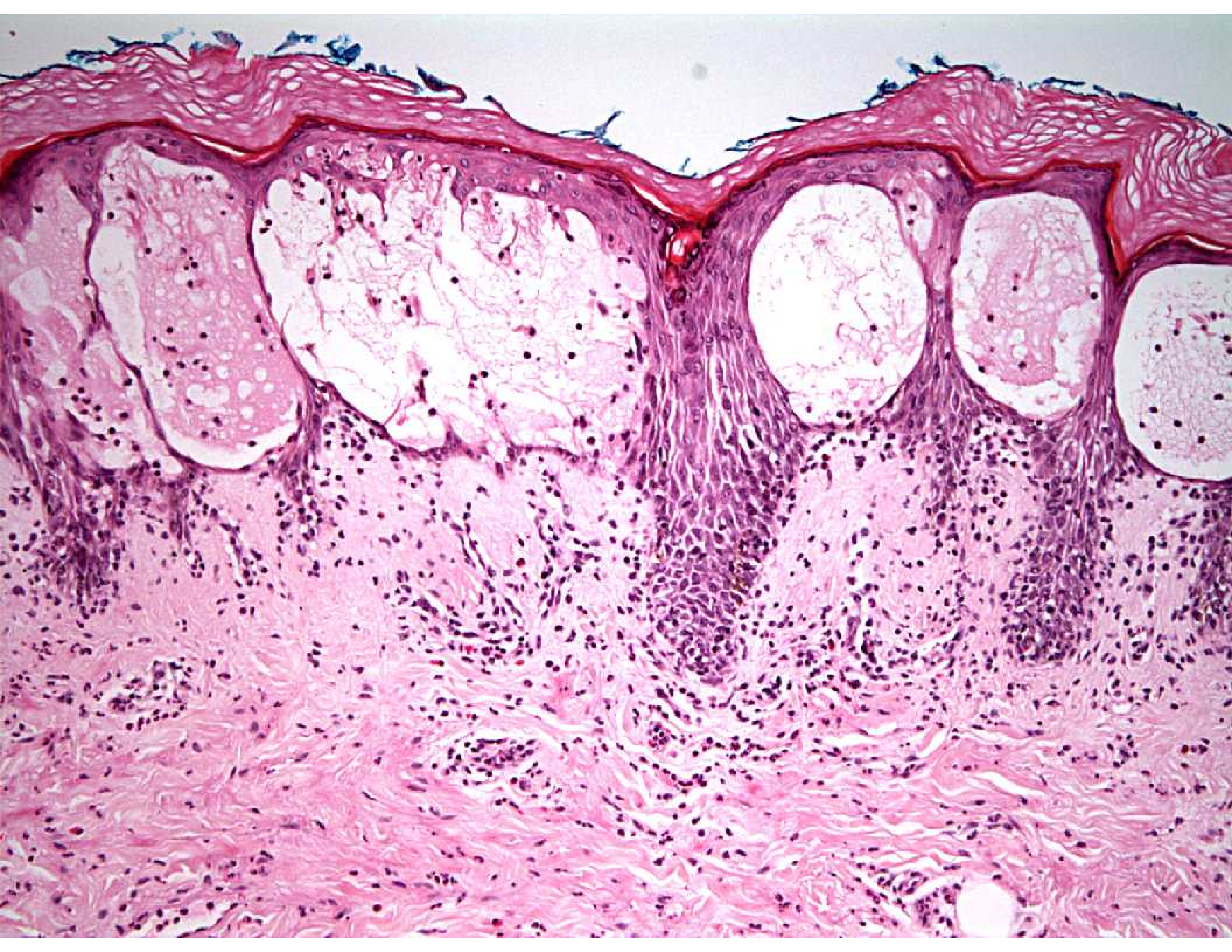
Spongiotic Dermatitis

- Three phases
  - Acute
  - Subacute
  - Chronic
- Different but overlapping histologic features



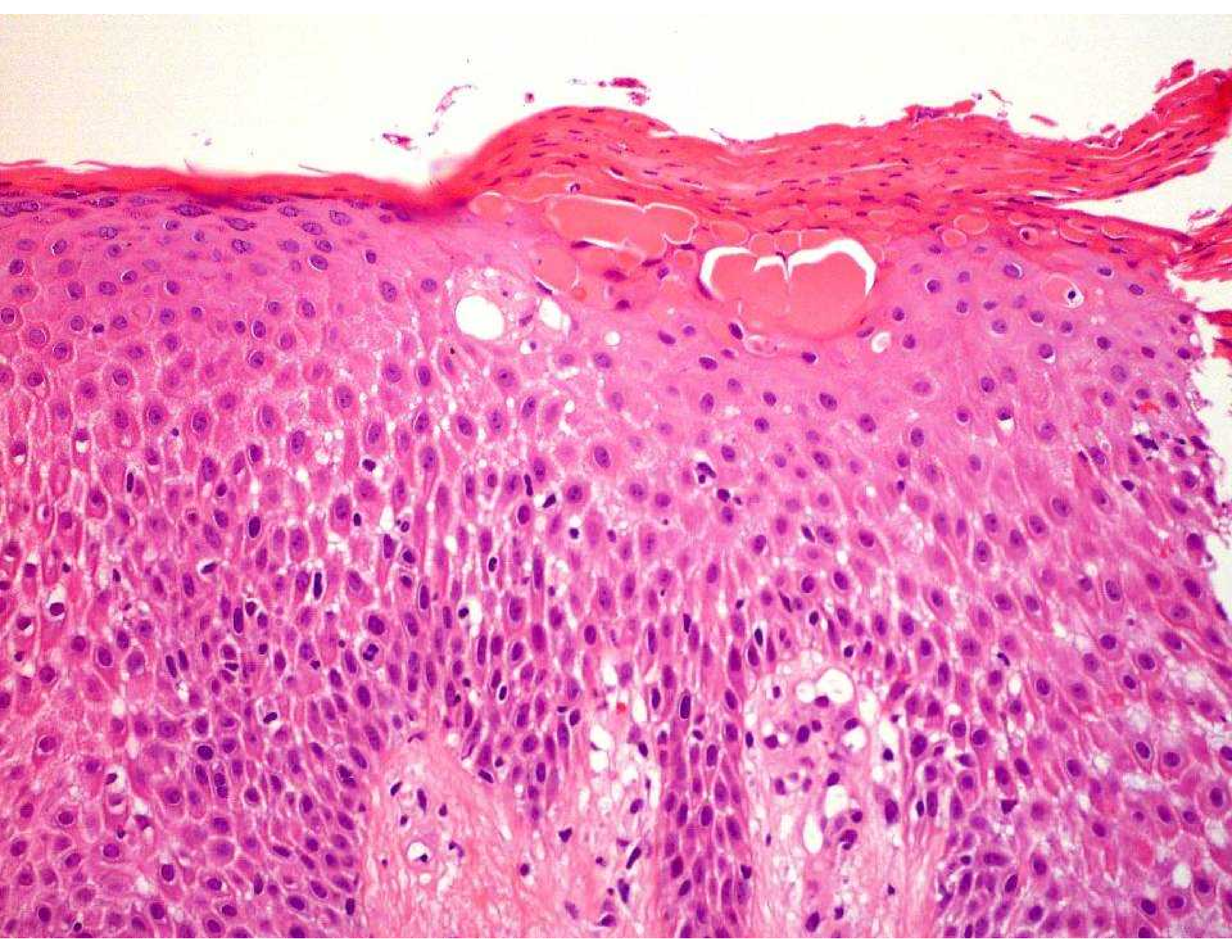
Spongiotic Dermatitis

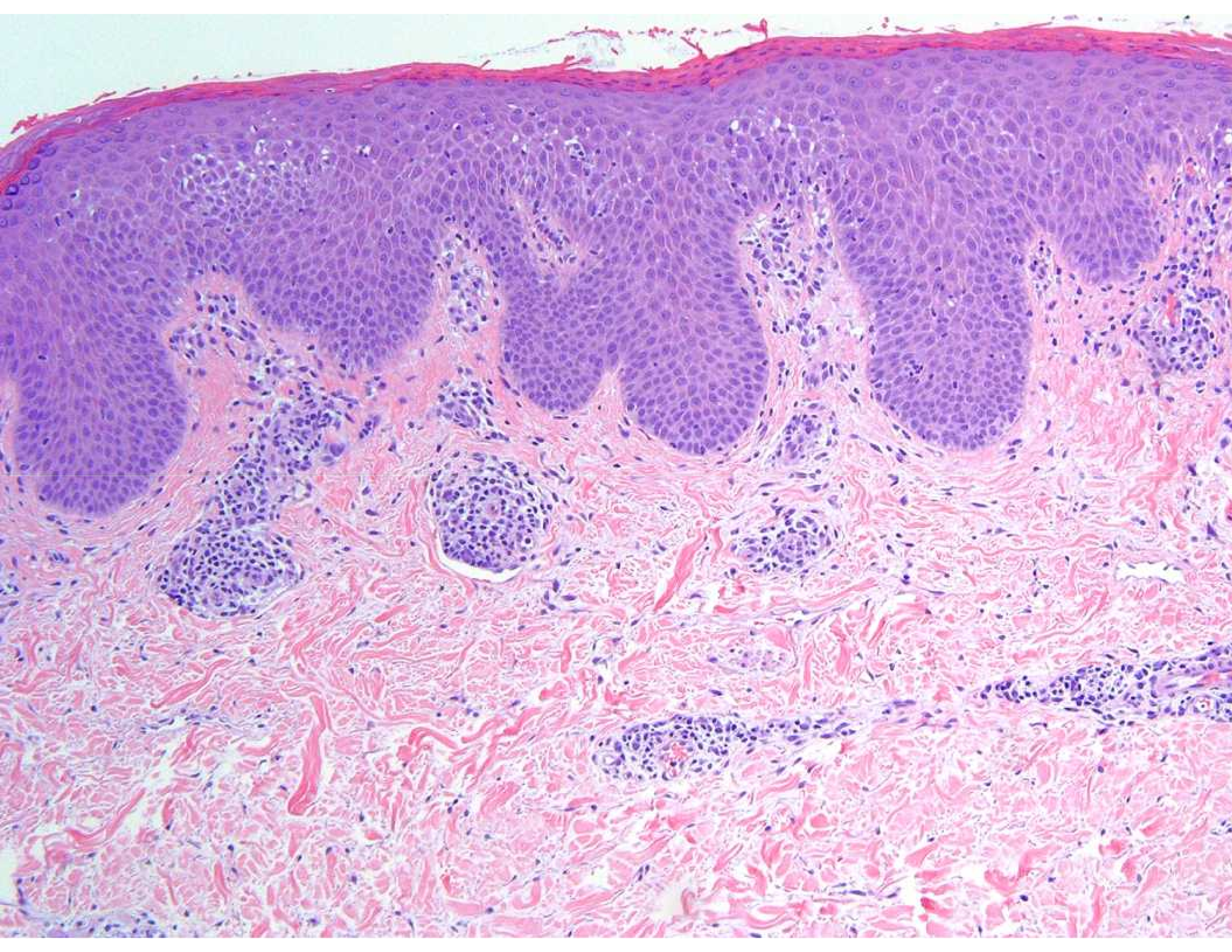
- Acute spongiotic dermatitis
  - Normal “basket-weave” stratum corneum
  - Pale keratinocytes
  - Spongiosis
  - Spongiotic vesicles (variable)
  - Papillary dermal edema
  - Variable superficial perivascular infiltrate of lymphocytes often with some eosinophils
  - Rarely biopsied in acute phase



Spongiotic Dermatitis

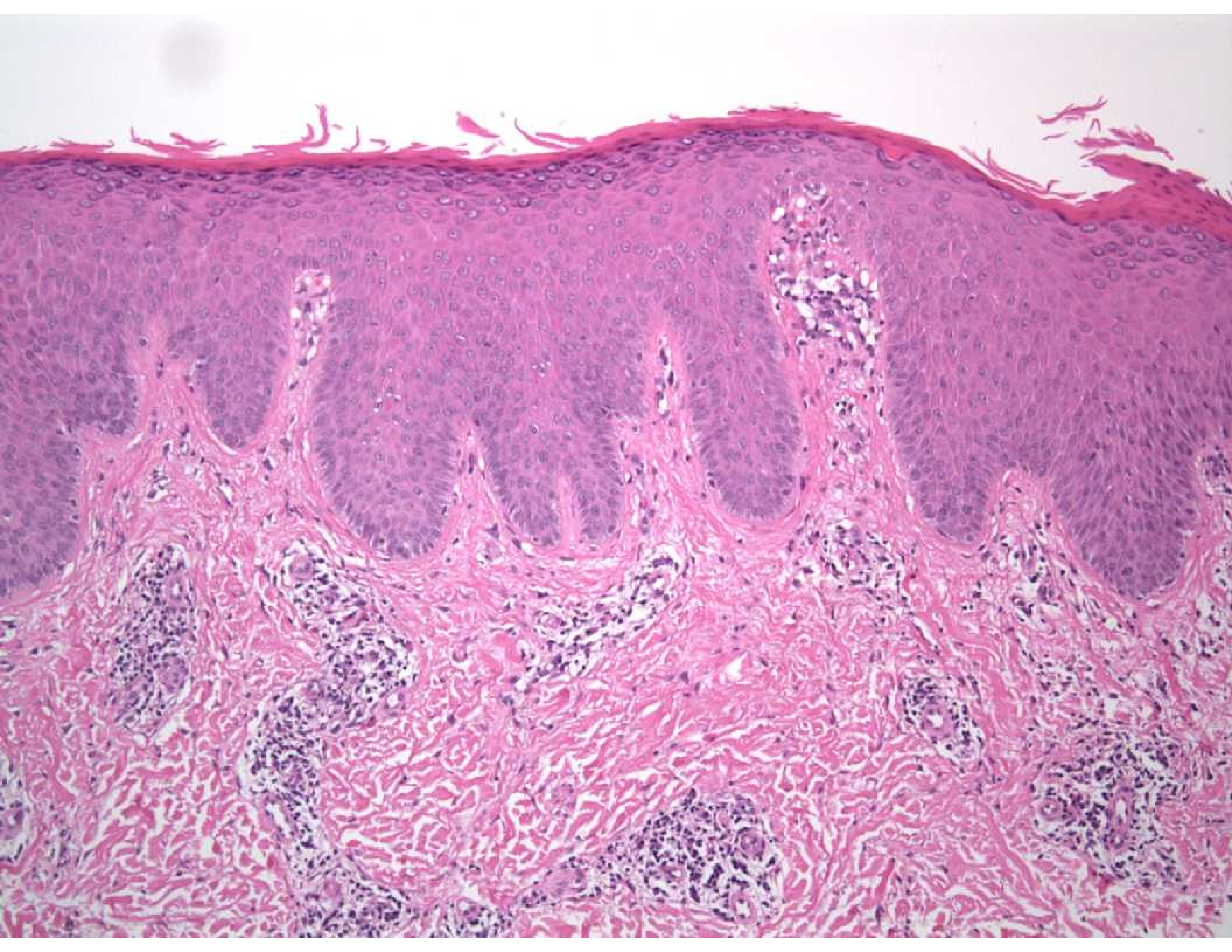
- Subacute spongiotic dermatitis
  - Parakeratosis often with serum (wet scale)
  - Diminished granular layer
  - Spongiosis
  - Acanthosis (overlap with psoriasiform pattern)
  - Variable superficial perivascular infiltrate of lymphocytes often with some eosinophils
  - Less edema





Spongiotic Dermatitis

- Chronic spongiotic dermatitis
  - Hyperkeratosis
  - Parakeratosis
  - Irregular granular layer
  - Acanthosis (overlap with psoriasiform)
  - Minimal to mild spongiosis
  - Variable perivascular infiltrate, often with eosinophils
  - Dermis may be fibrotic



Common Clinical Types of Spongiotic Dermatitis

- Eczema Dermatitis Family
  - Atopic dermatitis
  - *Contact dermatitis*
  - *Nummular dermatitis*
  - Dyshidrotic dermatitis (hand/foot dermatitis)
  - Id reaction (autoeczematization)
  - Eczematous drug eruption

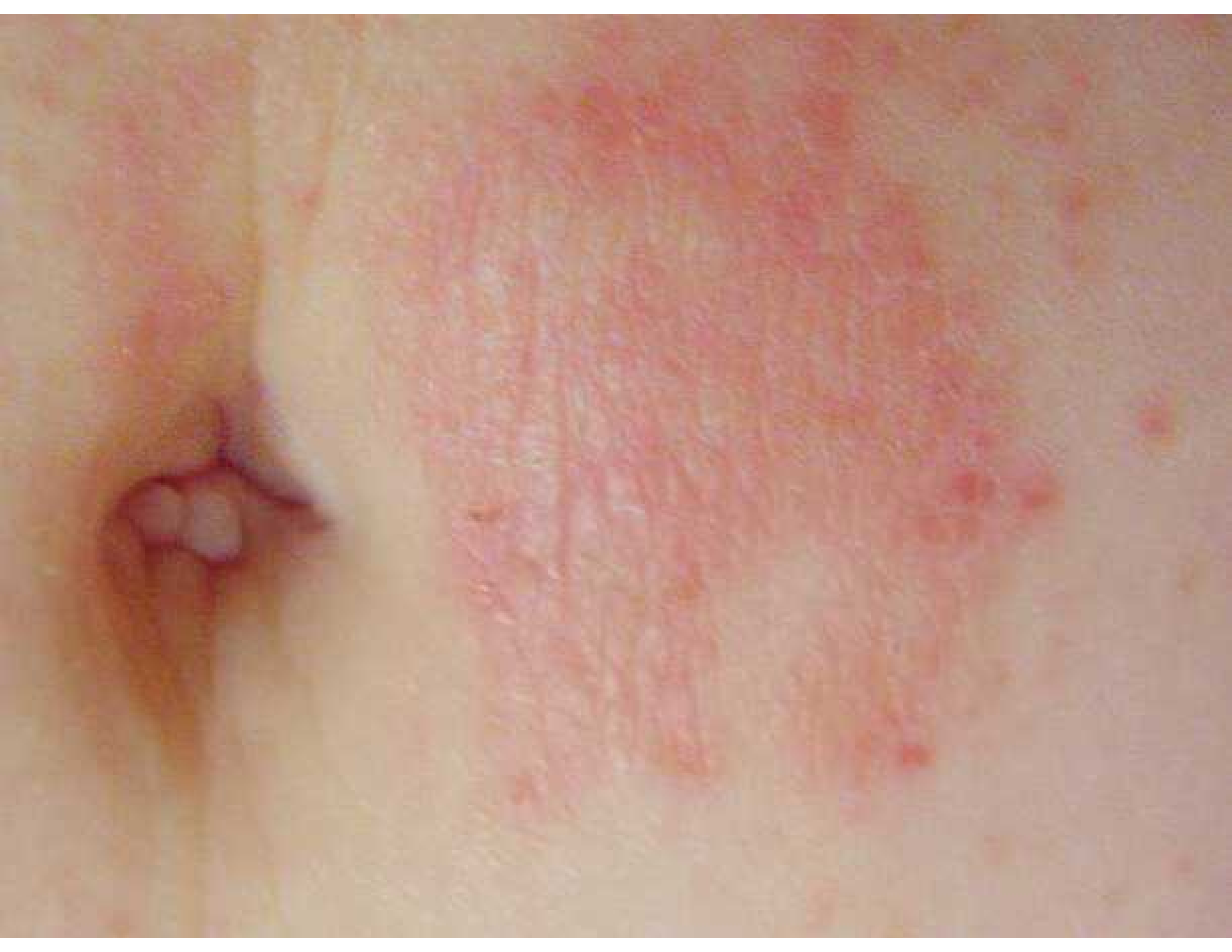
Eczema

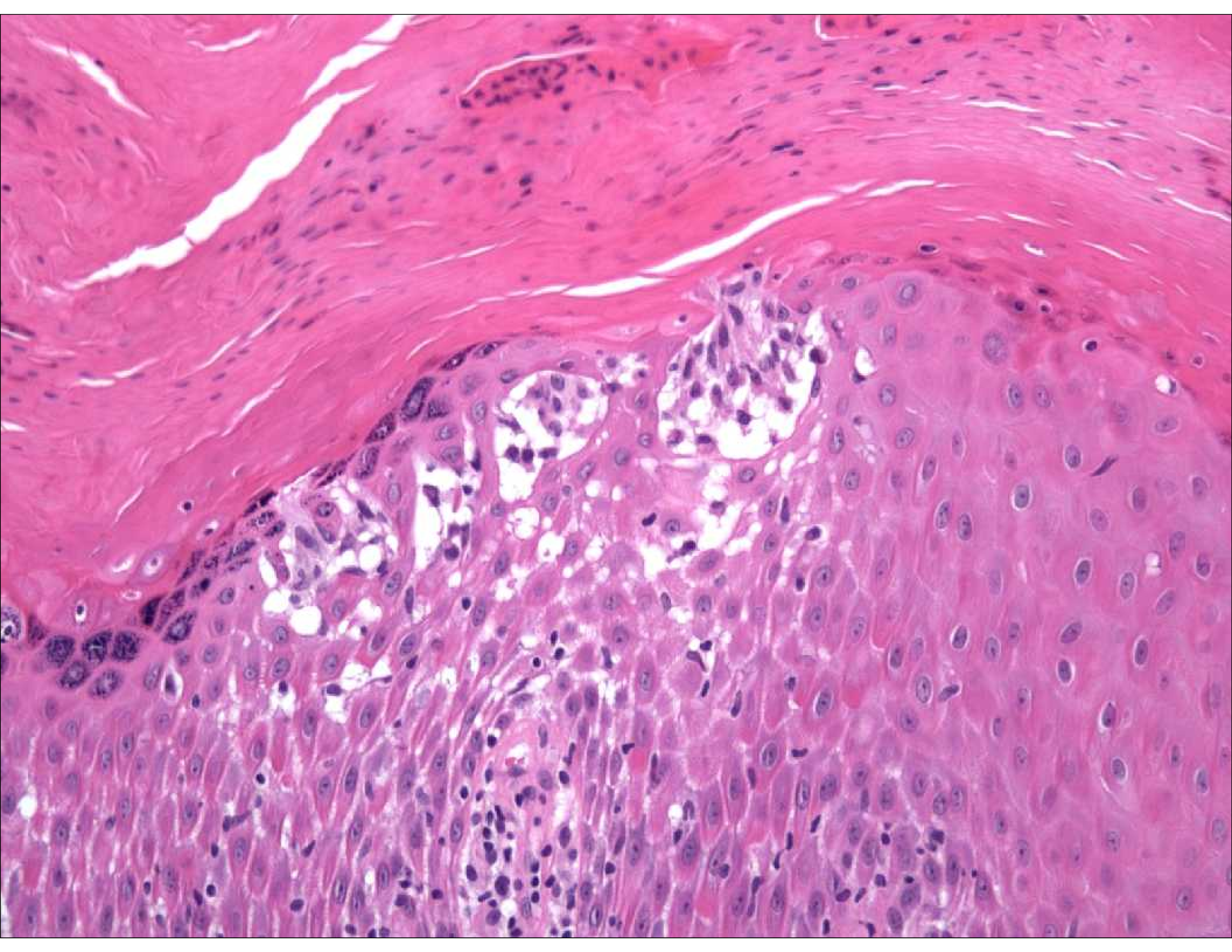
- Clinical term
- Histologically spongiotic dermatitis
- Specific diagnosis dependent on correlation with clinical presentation

- CLINICAL SUBTYPES ARE HISTOLOGICALLY INDISTINGUISHABLE

Allergic Contact Dermatitis

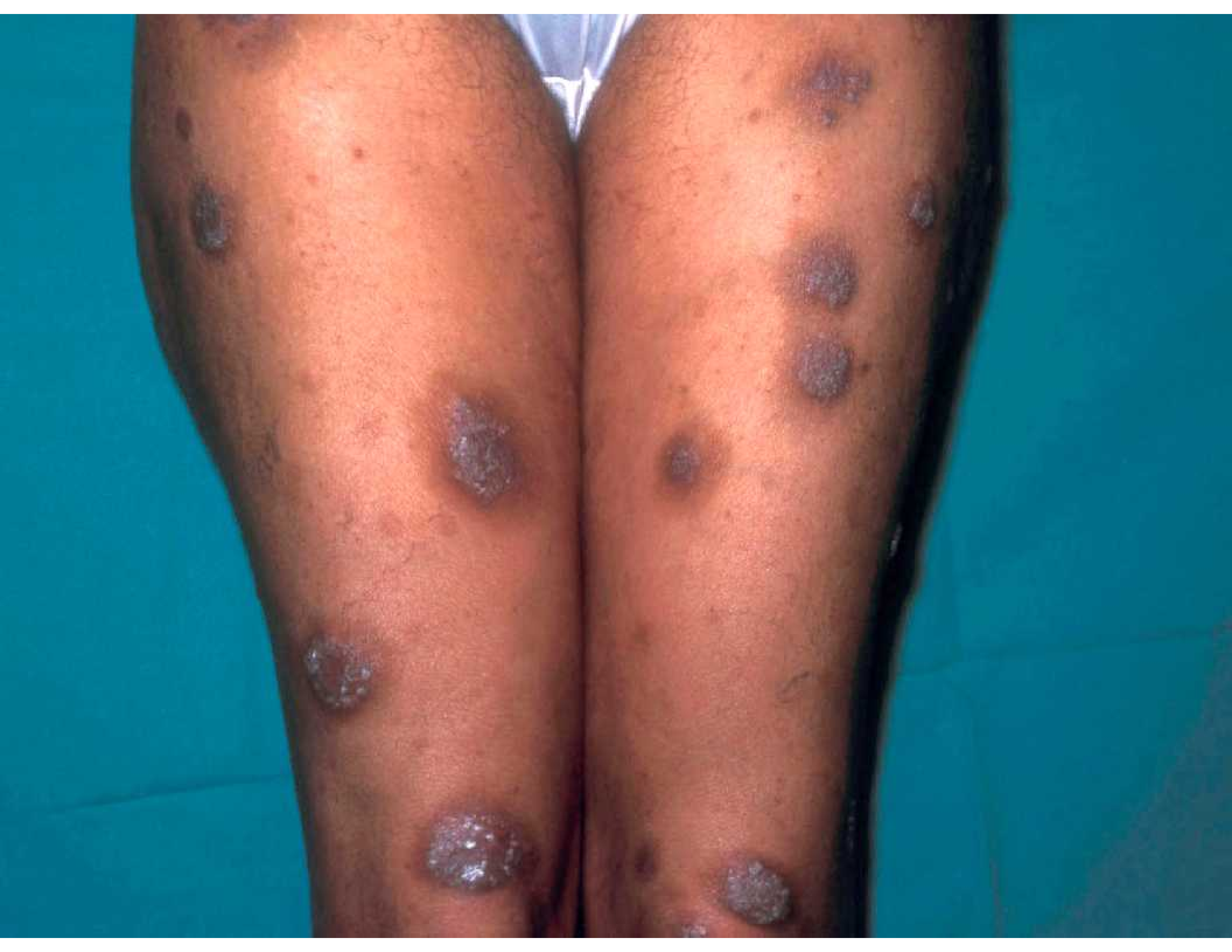
- Clinical
  - Erythematous papules, plaques and sometimes vesicles
  - May have linear pattern
  - Secondary to type IV delayed hypersensitivity reaction
  - Examples: nickel allergy, poison ivy
- Microscopic
  - Typical spongiotic dermatitis
  - May have Langerhans cell microabscesses

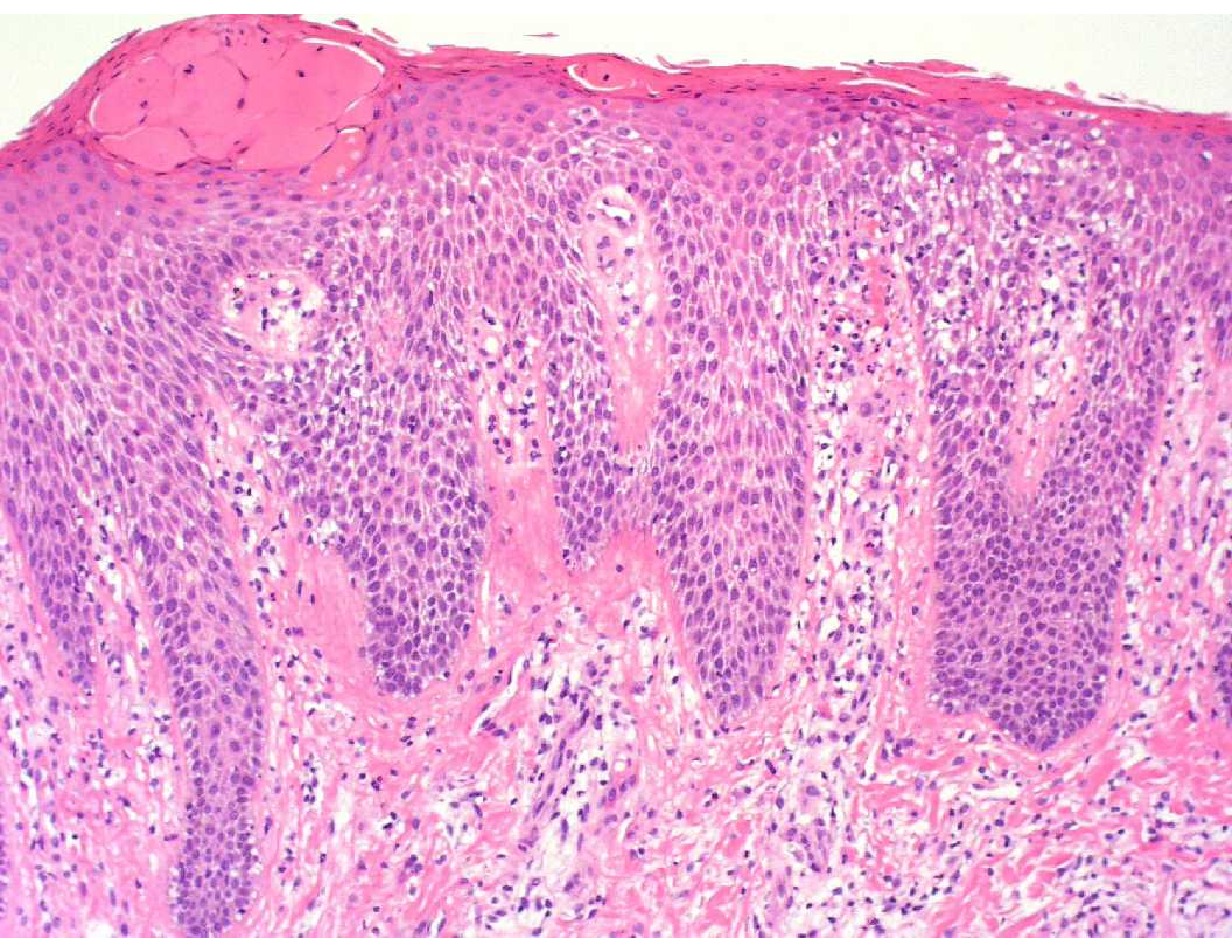




Nummular Dermatitis

- Common form of eczema that is biopsied
- Clinical
  - Pruritic round to oval patches and plaques
  - Often on extremities
- Microscopic
  - Psoriasiform and spongiotic
  - Can be classified as psoriasiform dermatitis
- Differential diagnosis
  - Psoriasis





Practical Tips for Eczematous Dermatitis

- Dx: "spongiotic dermatitis, see note"
- (Dx in cases with acanthosis: "spongiotic psoriasiform dermatitis, see note")
- Note: "The histologic features are compatible with an eczematous dermatitis. The DDx could include….. Clinicopathologic correlation is recommended."
- Tips
  - Eliminate where possible more specific entities
  - Neutrophils in stratum corneum or epidermis: exclude dermatophytosis or psoriasis
  - Clinical history can be helpful
  - Langerhans cell microabscess: suggest contact dermatitis

Stasis Dermatitis

- Clinical
  - Lower extremities associated with venous insufficiency
  - May develop ulcers
- Microscopic
  - Subacute to chronic spongiotic dermatitis
  - Variable acanthosis
  - Lobular proliferation of thick-walled dermal vessels
  - Extravasated erythrocytes, siderophages, perivascular lymphocytes
  - Variable dermal fibrosis

Initial presentation of stasis dermatitis mimicking solitary lesions: A previously unrecognized clinical scenario

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- 37 cases of stasis dermatitis presenting as solitary lesion
- 33/37 no history of venous stasis
- 33% mistaken for SCC; 24% mistaken for BCC

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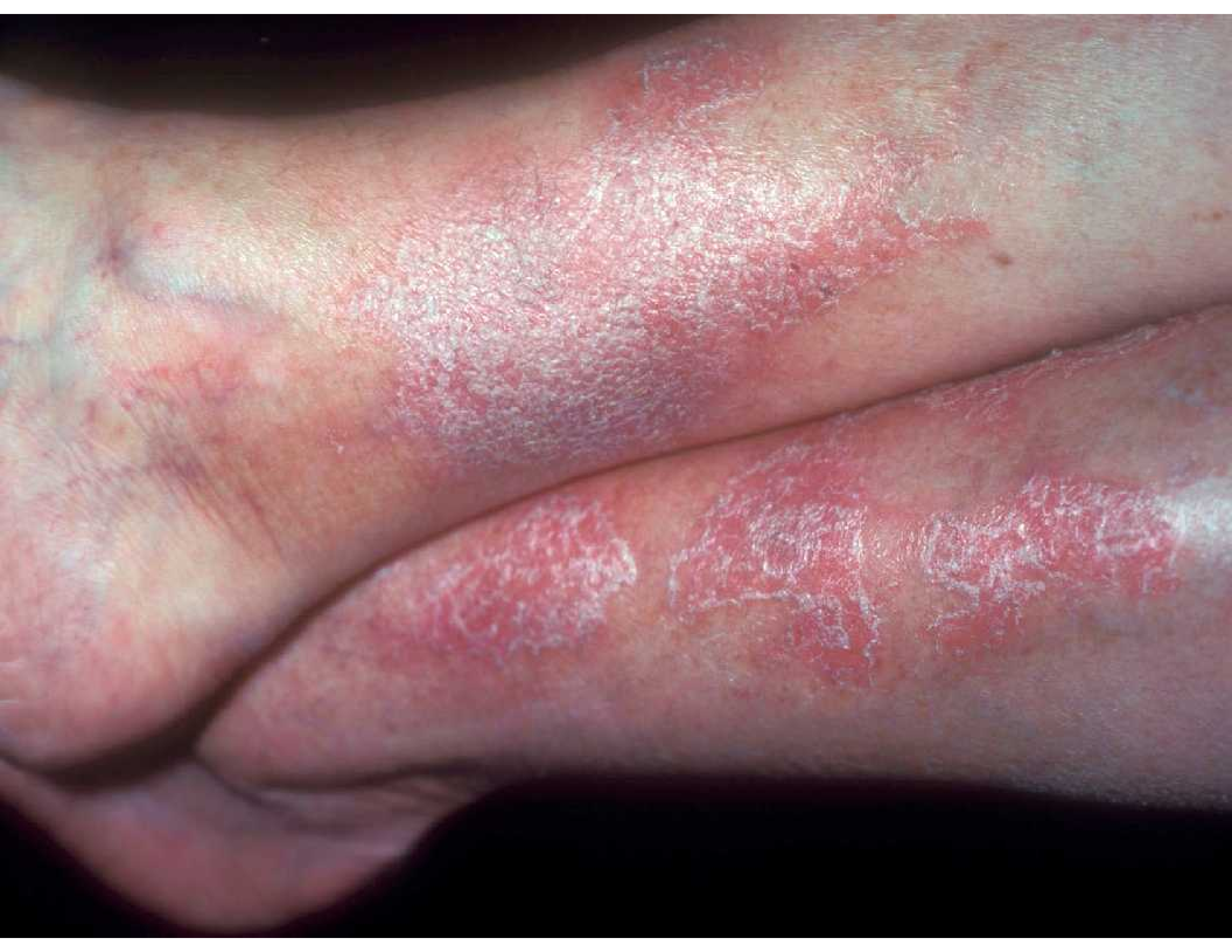
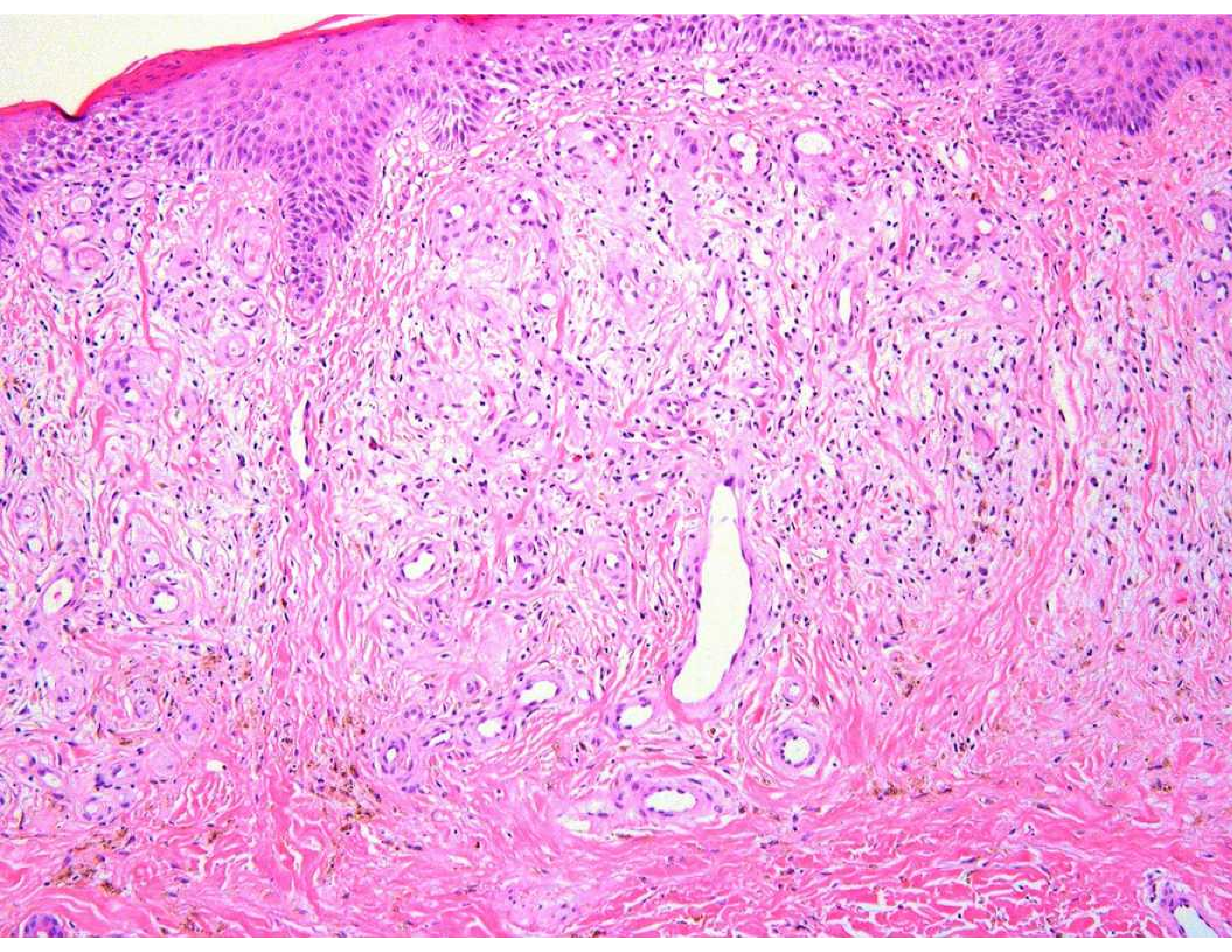
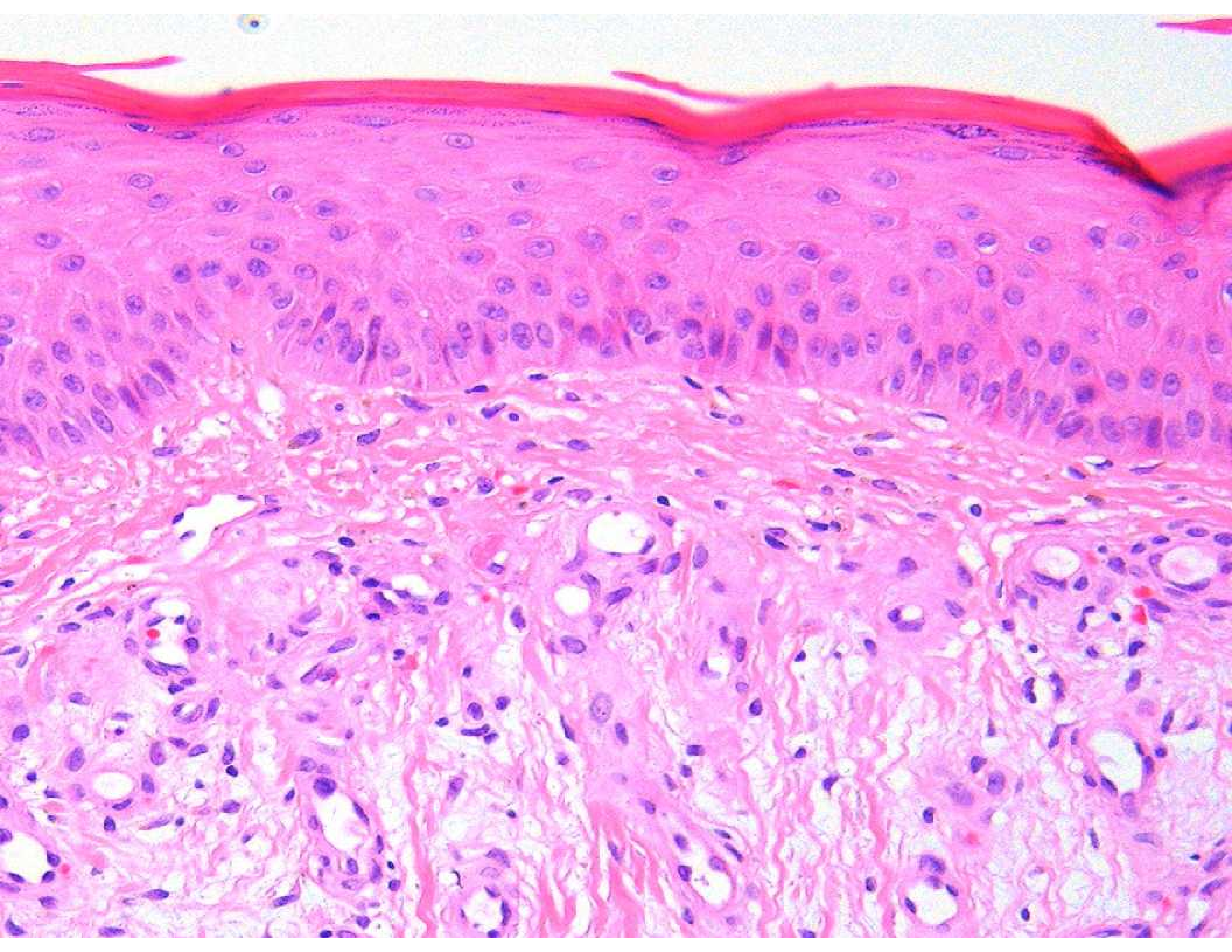
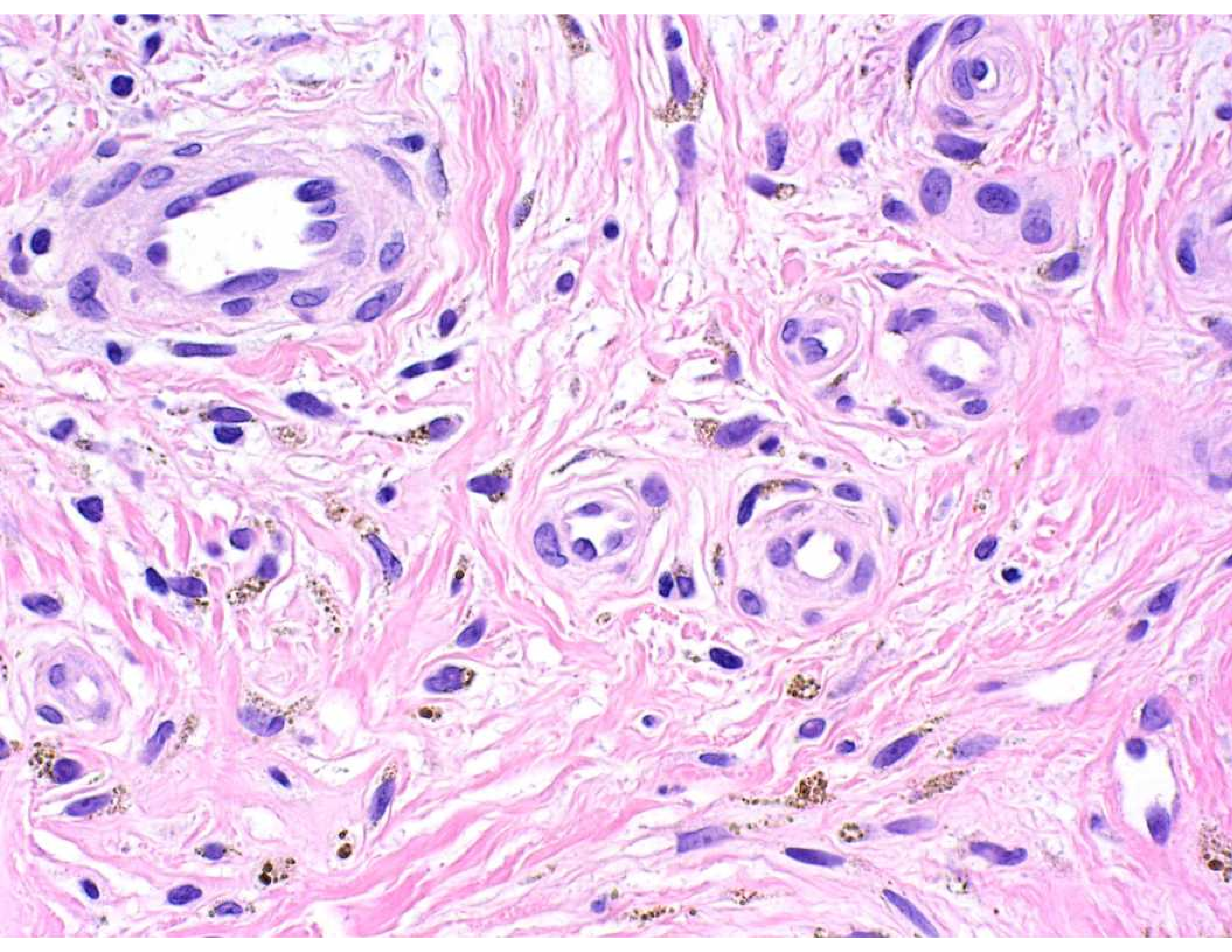
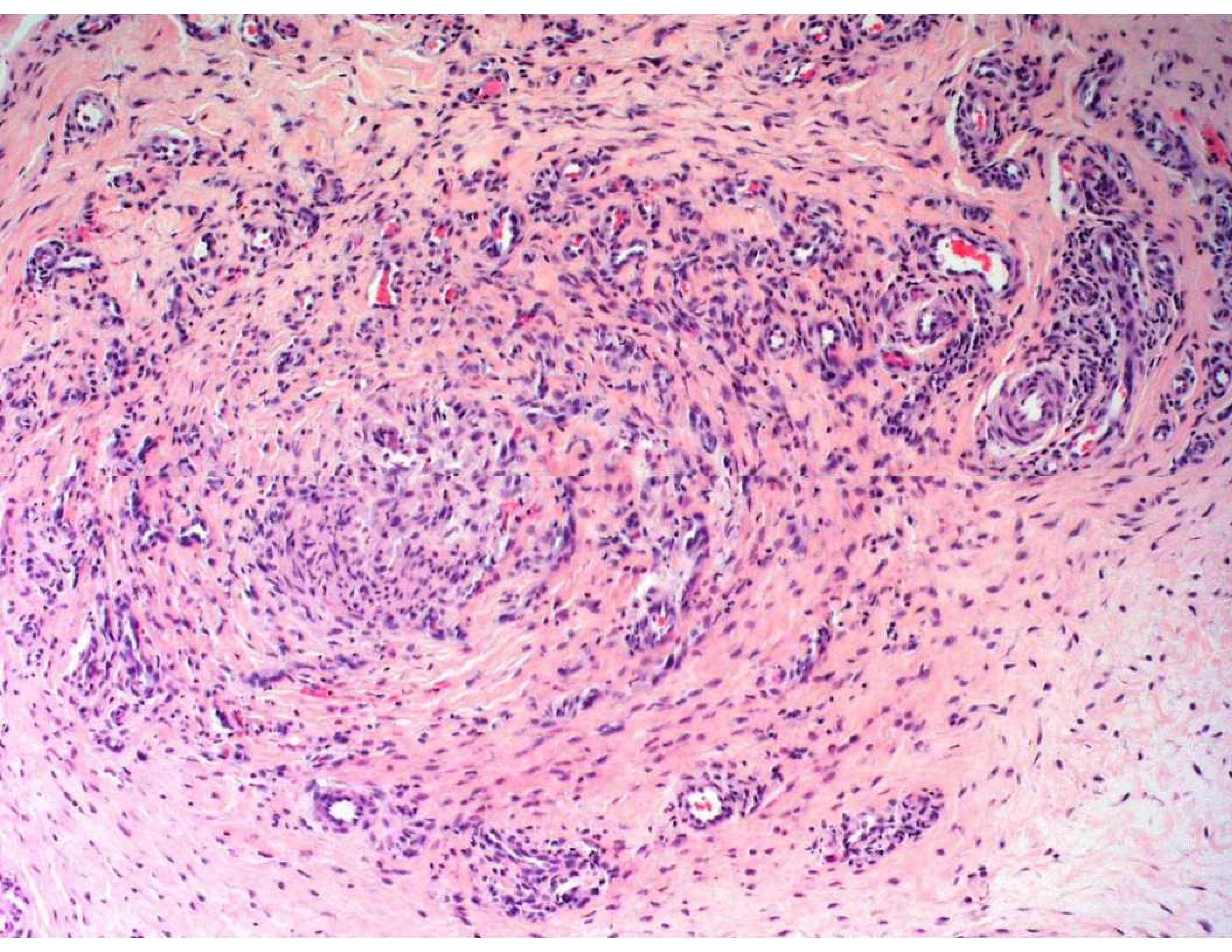










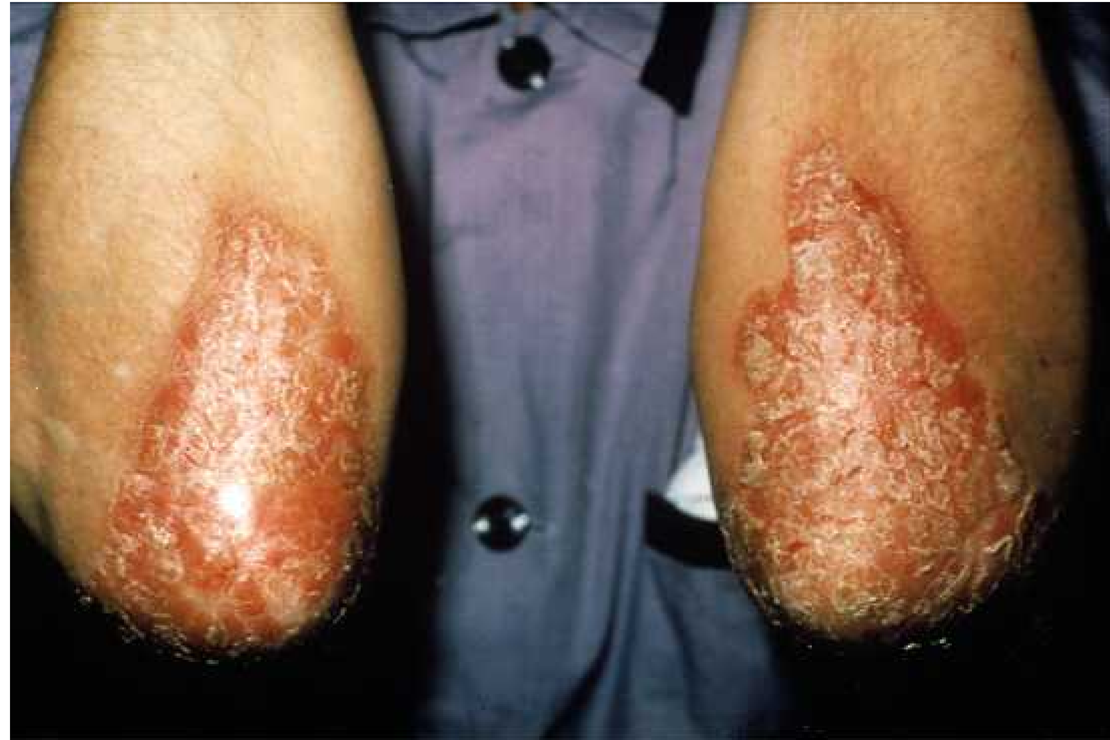
Stasis Dermatitis

- Differential diagnosis
  - Eczematous dermatitis
  - Kaposi sarcoma (acroangiodermatitis)
- Tips
  - High index of suspicion
  - Vascular changes key feature
  - Sometimes clinically mimics neoplasm: consider deeper levels
  - Can have other form of eczematous dermatitis on stasis background (descriptive dx: spongiotic dermatitis and stasis change)

Psoriasis

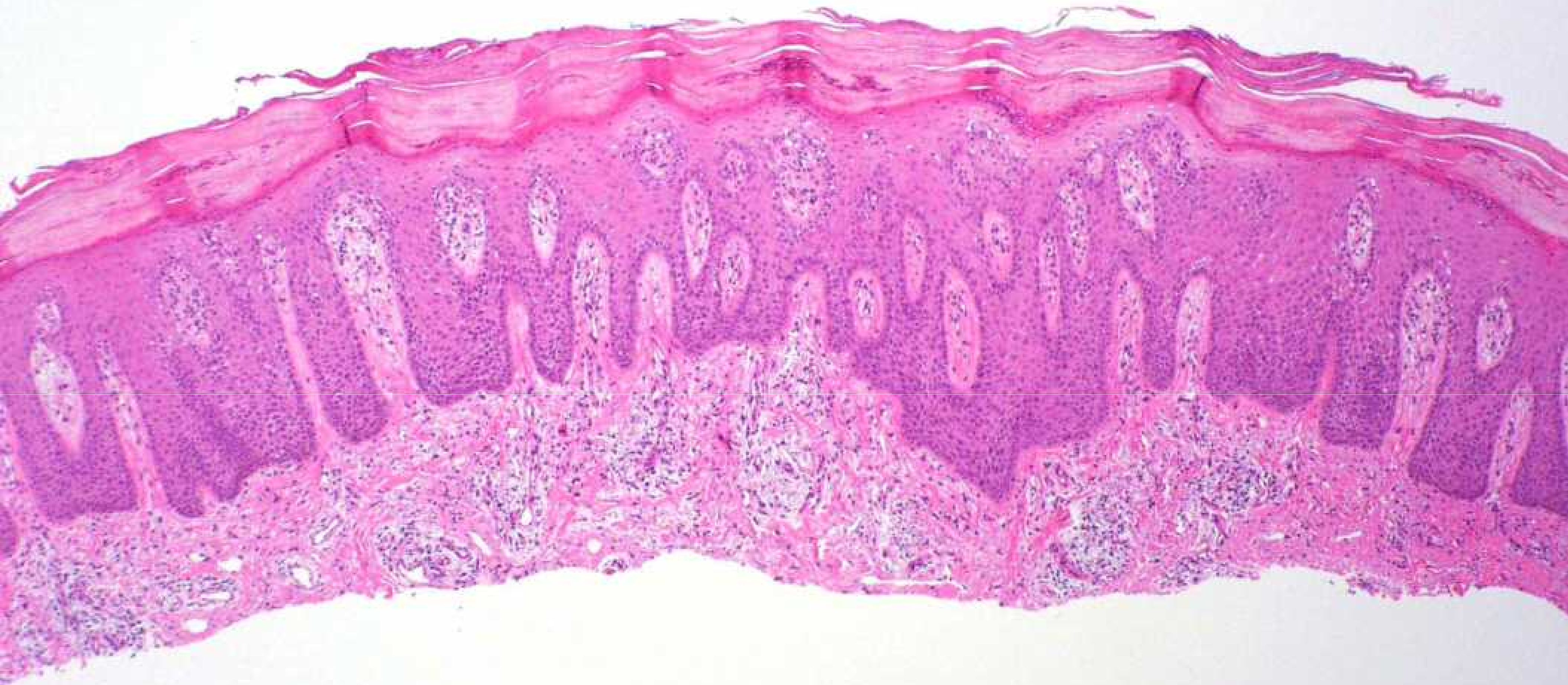
Psoriasis vulgaris

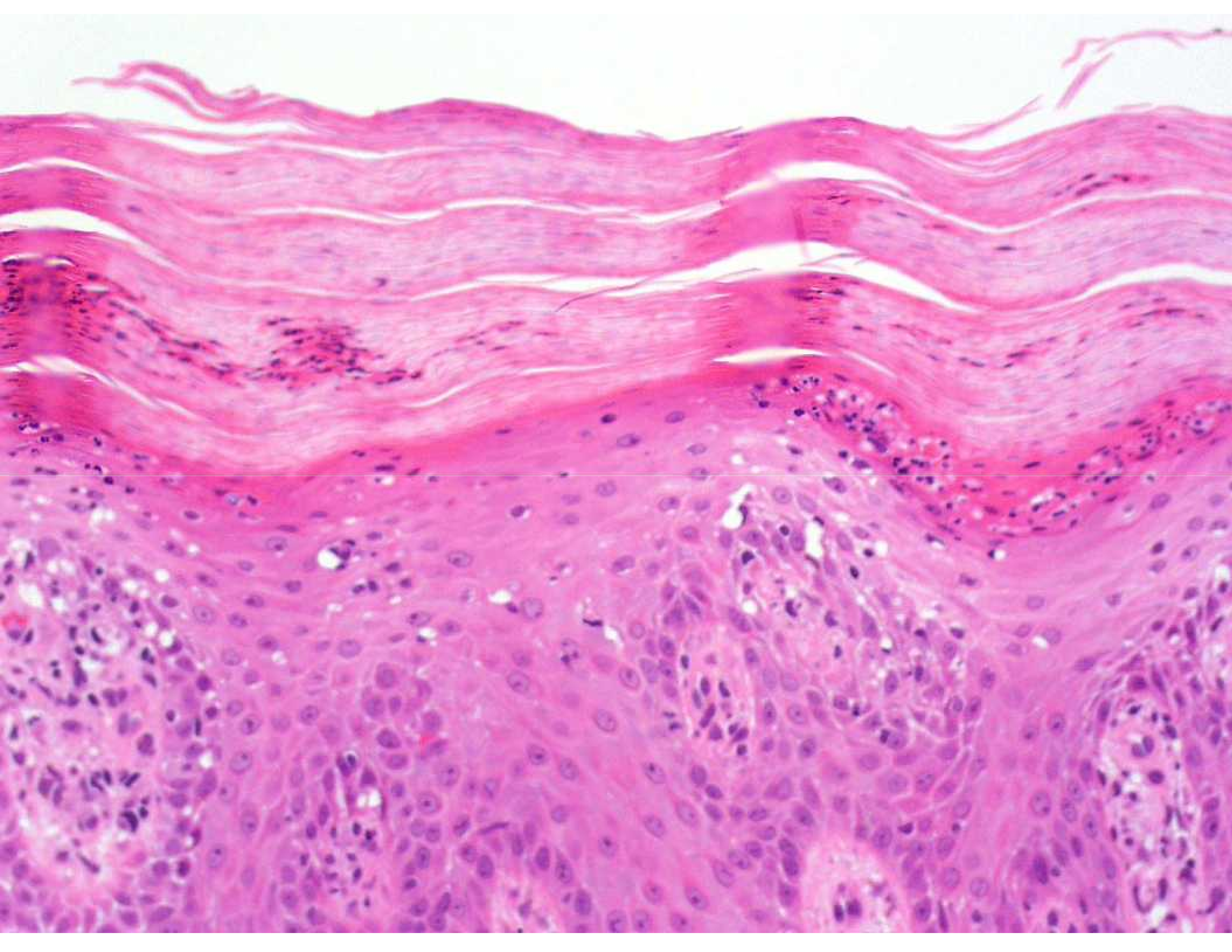
- Clinical
  - Usually presents in 2nd-3rd decades
  - Erythematous plaques with silvery scale
  - Extensor surfaces, scalp, gluteal cleft, glans penis
  - Nail pitting and yellow discoloration
  - Arthritis 1-5%

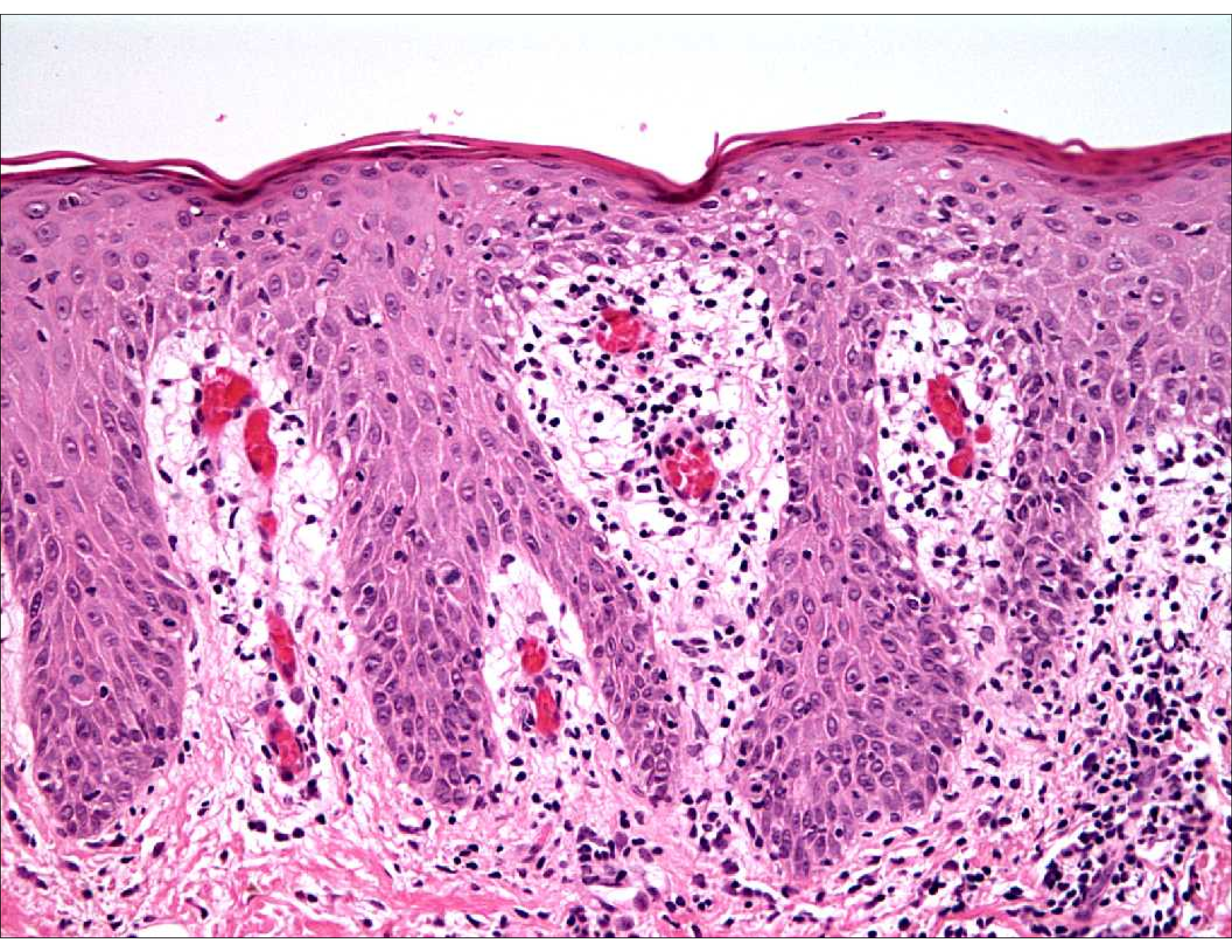


Psoriasis Vulgaris

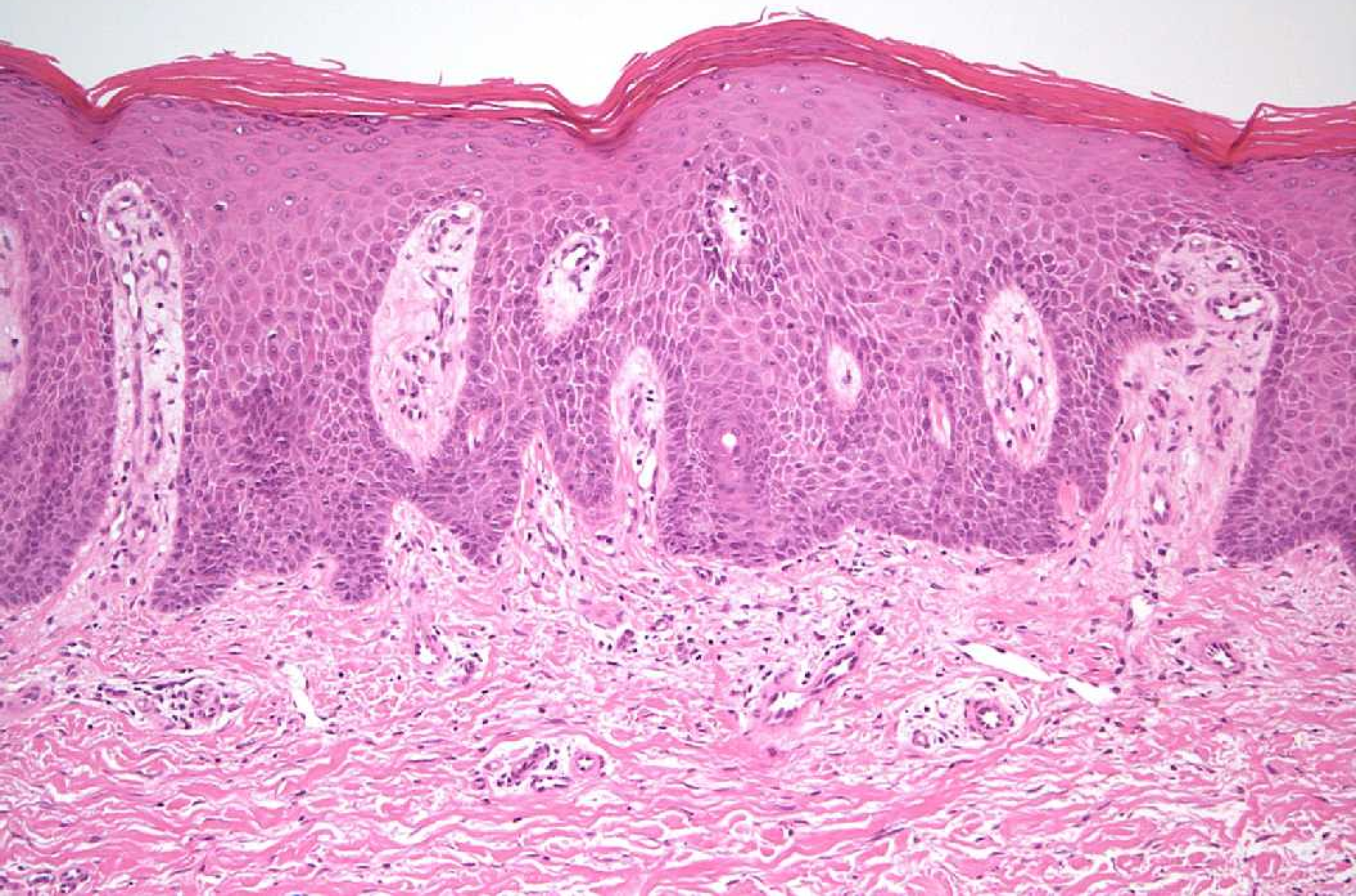
- Microscopic
  - Uniform acanthosis with elongated rete ridges
  - Absent (diminished) granular layer
  - Prominent parakeratosis (dry scale)
  - Neutrophils in stratum corneum (Munro's microabscess) and/or epidermis (pustules of Kogoj)
  - Suprapapillary plate thinning
  - Dilated, tortuous papillary dermal vessels
  - No eosinophils







Partially treated psoriasis

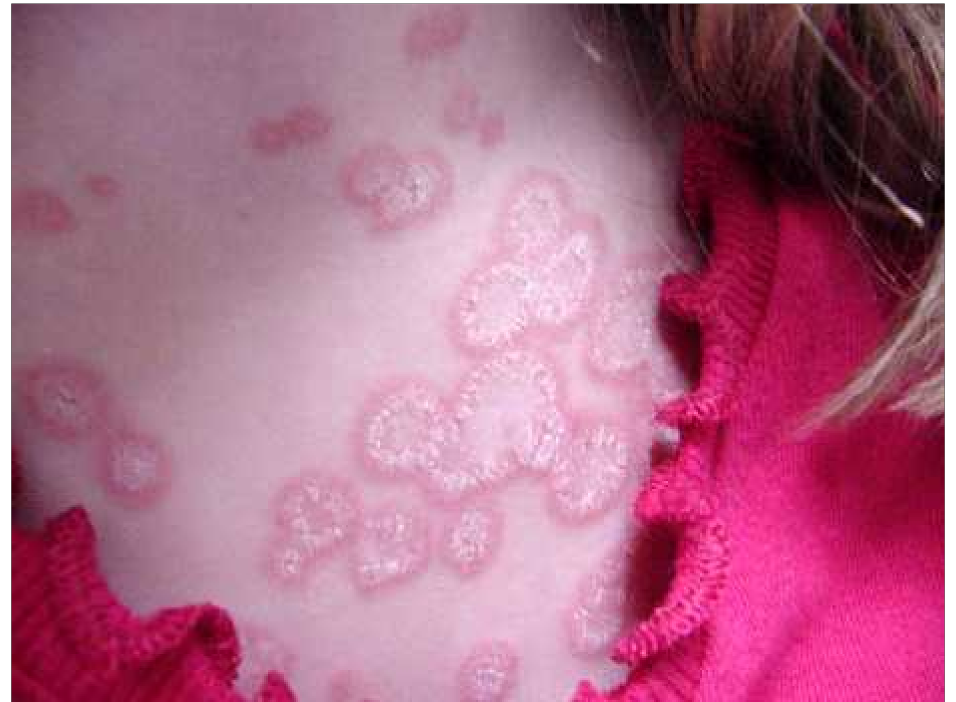


Psoriasis Vulgaris

- Differential Diagnosis
  - Nummular dermatitis
    - Spongiosis, wet scale, often has eosinophils
  - Contact dermatitis
    - Spongiosis, wet scale, often has eosinophils, Langerhans cell microabscesses (+/-)
  - Dermatophytosis
  - Drug-induced psoriasis

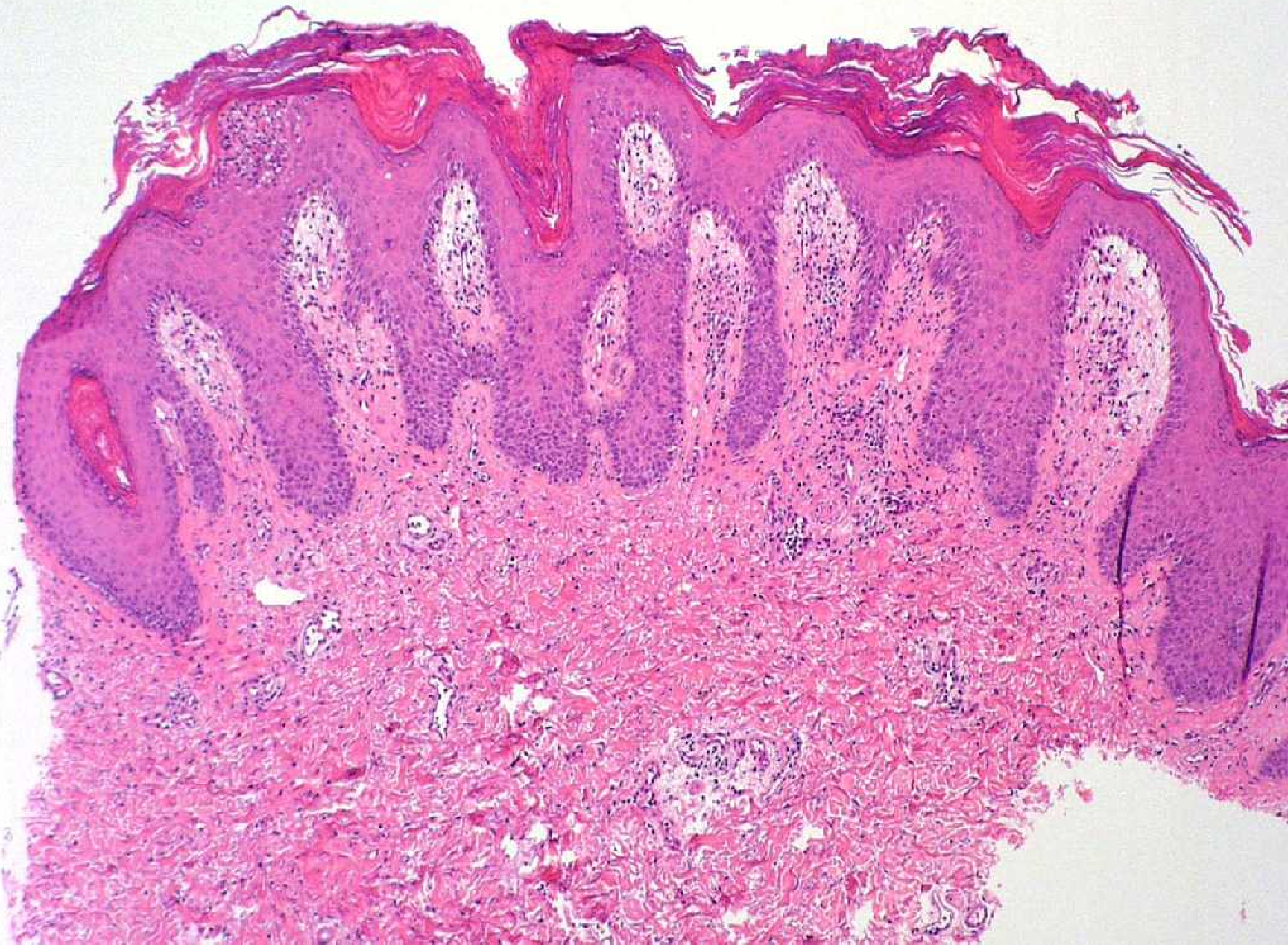
Dermatophytosis

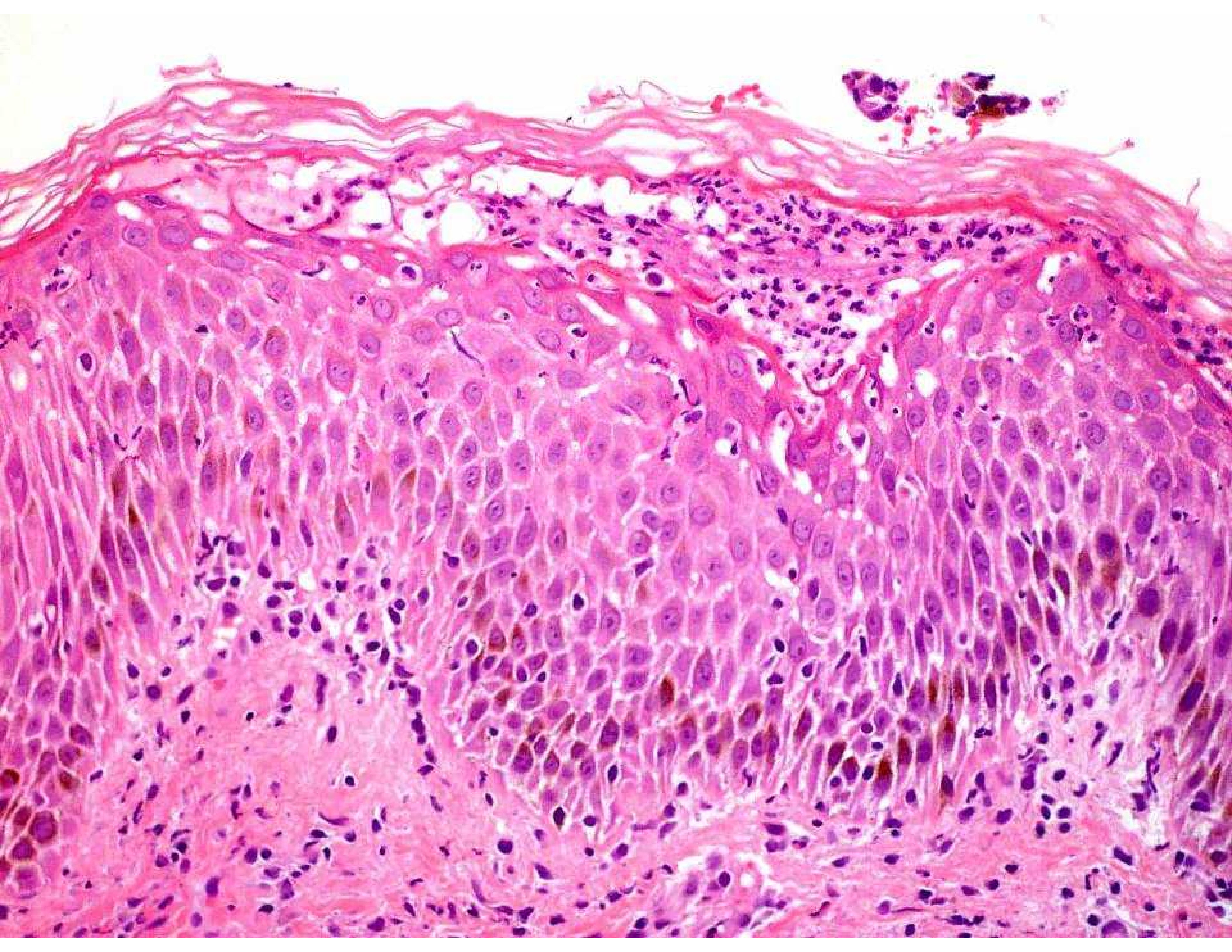
- Clinical
  - Annular scaly plaques with central clearing
  - Usually on trunk

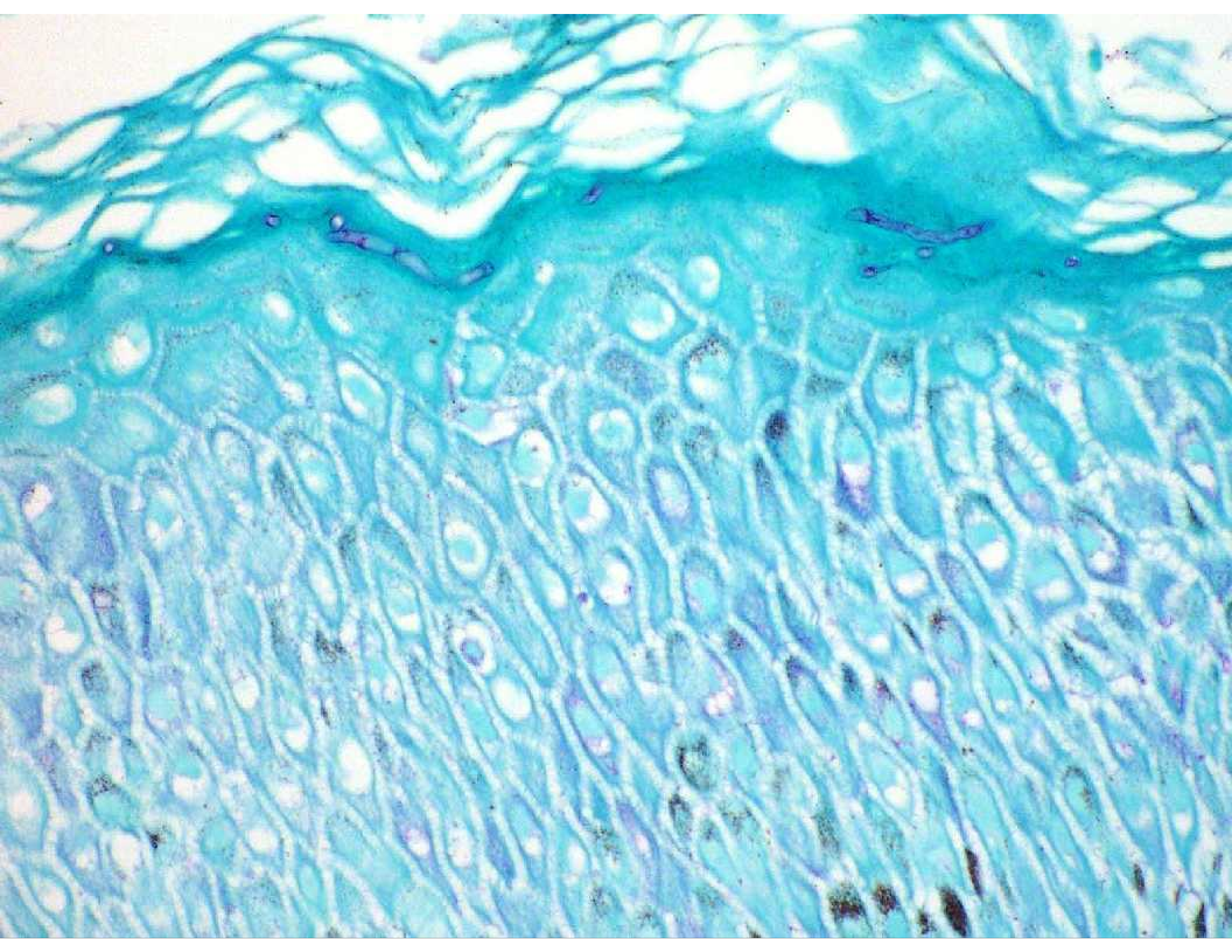


Dermatophytosis

- Microscopic
  - Neutrophils in stratum corneum
  - Parakeratosis
  - Hyphae in stratum corneum (usually seen with PAS or GMS stain)
  - Acanthosis
  - Variable spongiosis
  - Superficial perivascular infiltrate often with some eosinophils







Dermatophytosis

- Tips:
  - Neutrophils may be absent in lesions treated with topical steroids
  - Always get PAS or GMS stains if clinical history is “rash not responsive to topical steroids”
  - Look for fungi adjacent to neutrophils

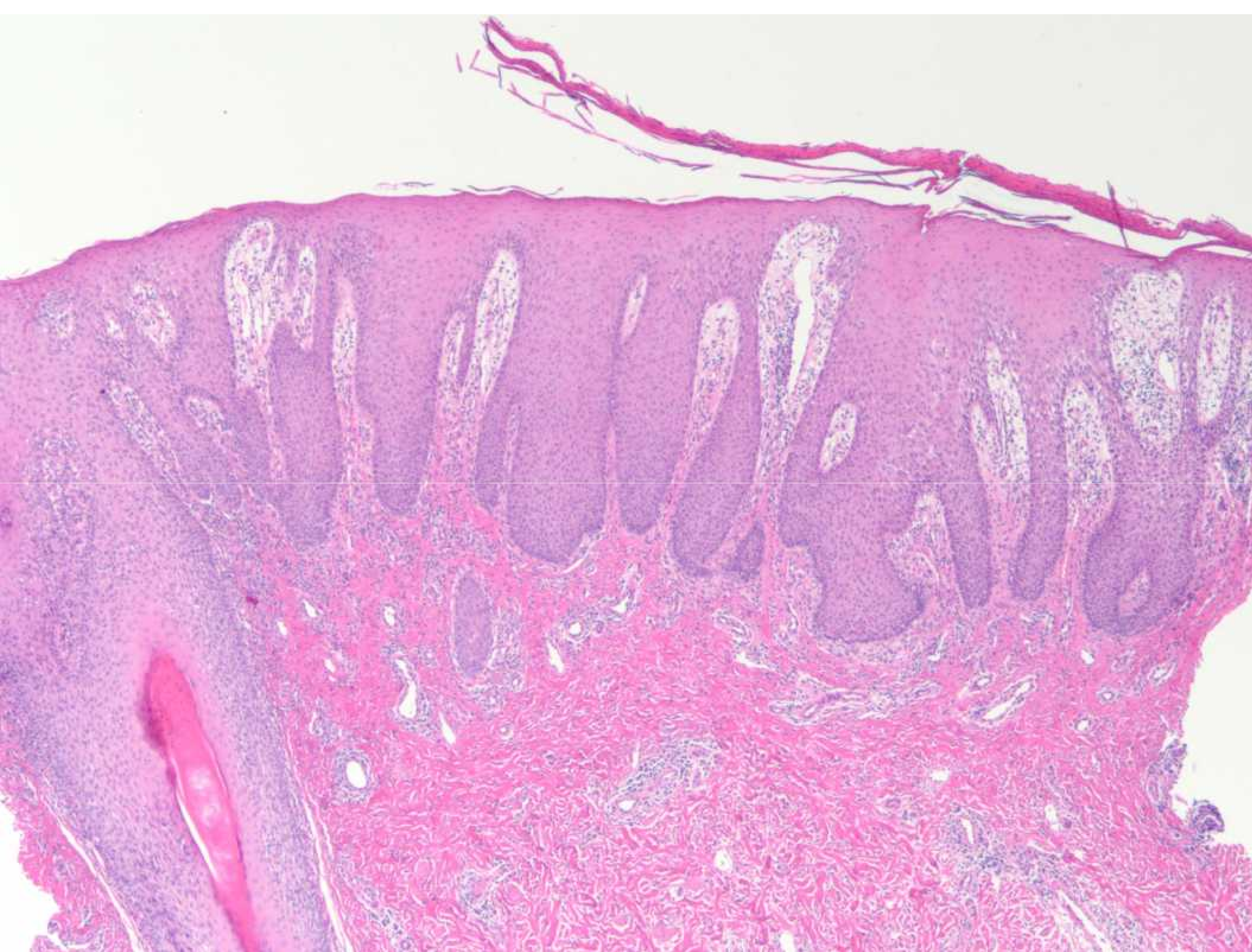
Drug-Induced Psoriasis

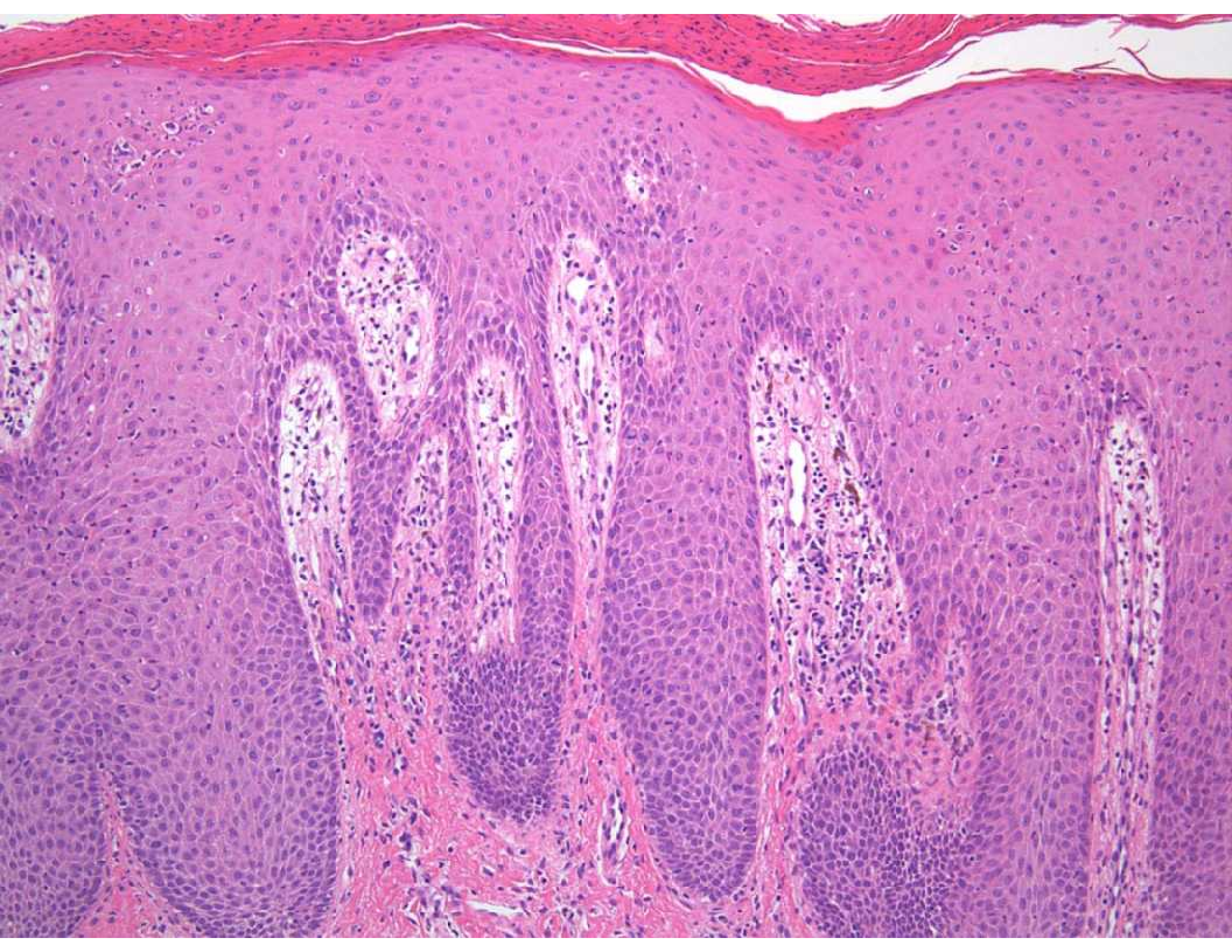
- Tumor necrosis factor- (TNF-) inhibitors can cause psoriasis-like rash
- Most commonly seen in patients with inflammatory bowel disease on TNF-inhibitors
- Looks like psoriasis vulgaris except with eosinophils in the dermis

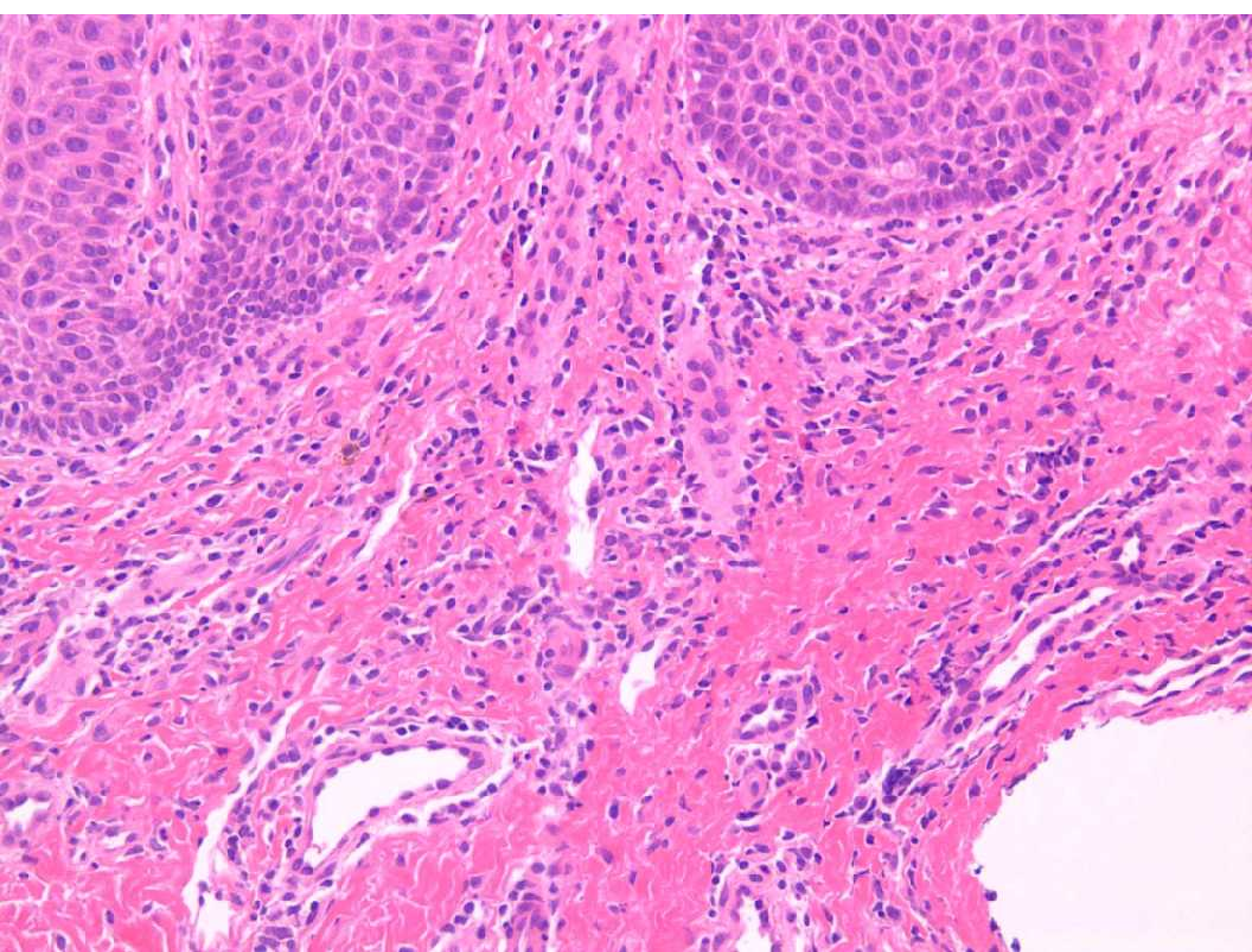
34-year-old woman with Crohn's disease

Presented with erythematous plaques involving vulva

Clinical diagnosis: cutaneous Crohn's disease





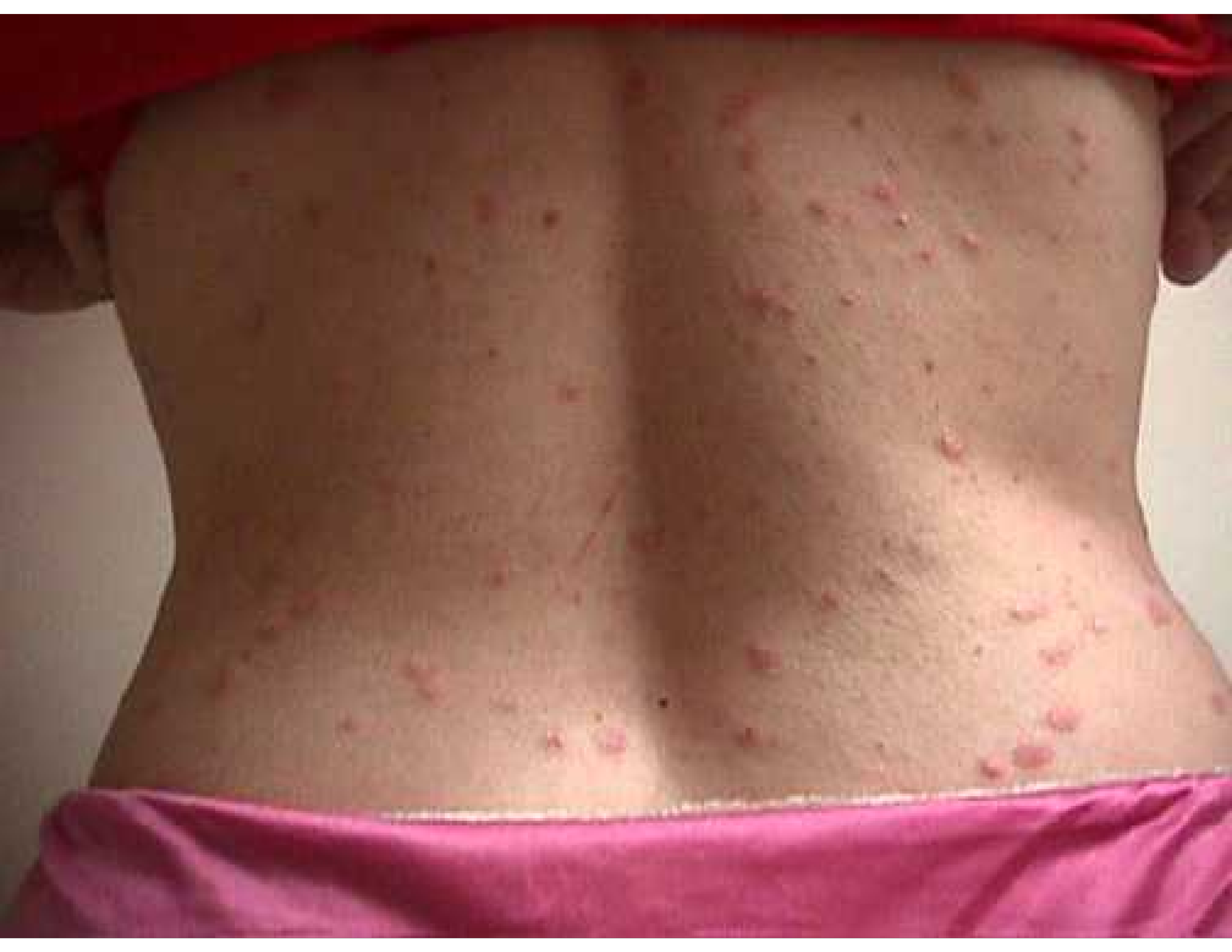


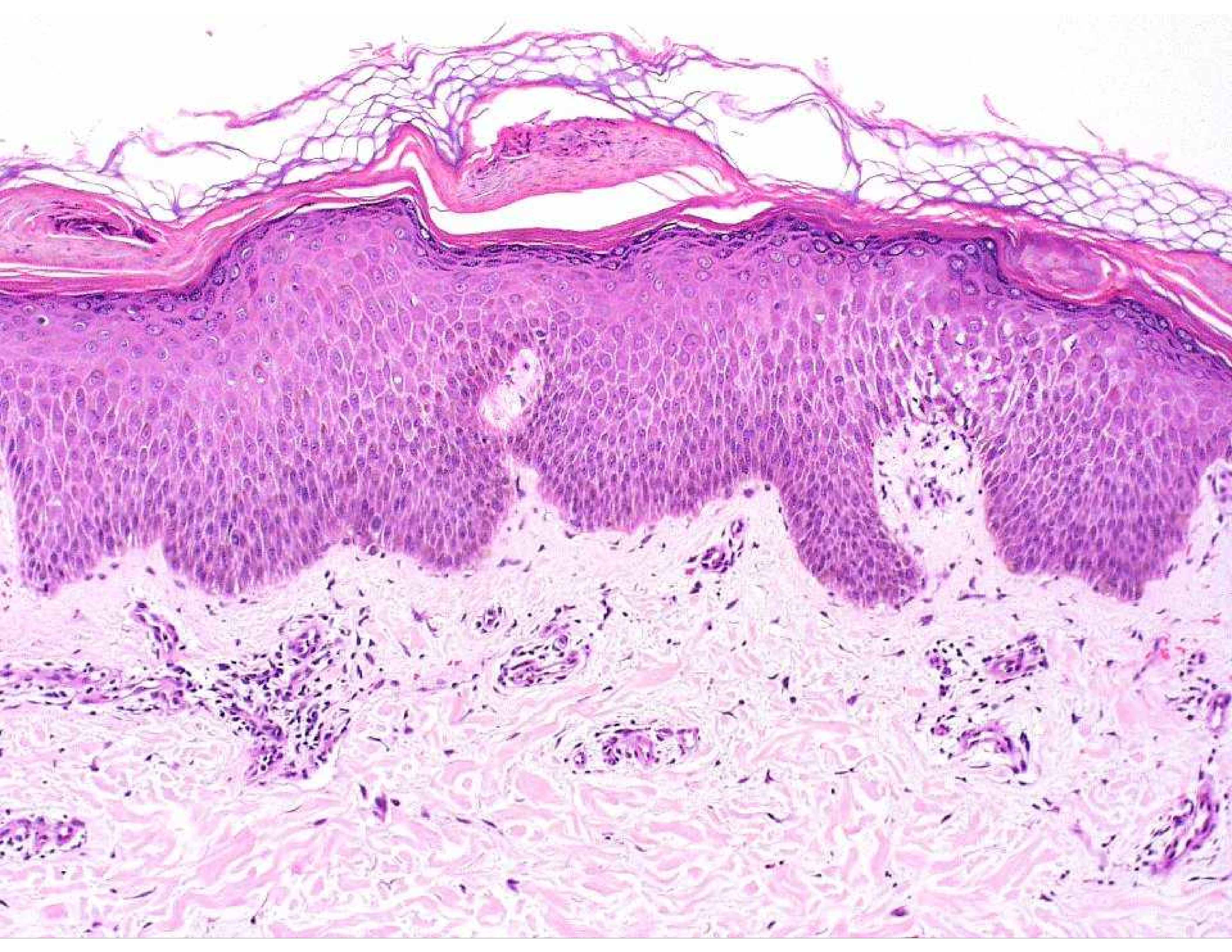
Psoriasis Vulgaris

- Practical tips
  - Eosinophils absent in psoriasis (except drug-induced; intravascular eosinophils don't count)
  - Epidermal hyperplasia not always uniform
  - Impetiginization not seen
  - Some features may be absent in partially treated psoriasis
  - Descriptive dx: psoriasiform dermatitis

Guttate Psoriasis

- Clinical
  - Rapid onset
  - Widespread disease
  - Small scaly plaques
  - Antecedent streptococcal infection
- Microscopic
  - Minimal acanthosis
  - Diminished granular layer (variable)
  - Focal mounds of parakeratosis with neutrophils (sometimes neutrophils absent)
- Differential Diagnosis
  - Pityriasis rosea, dermatophyte infection



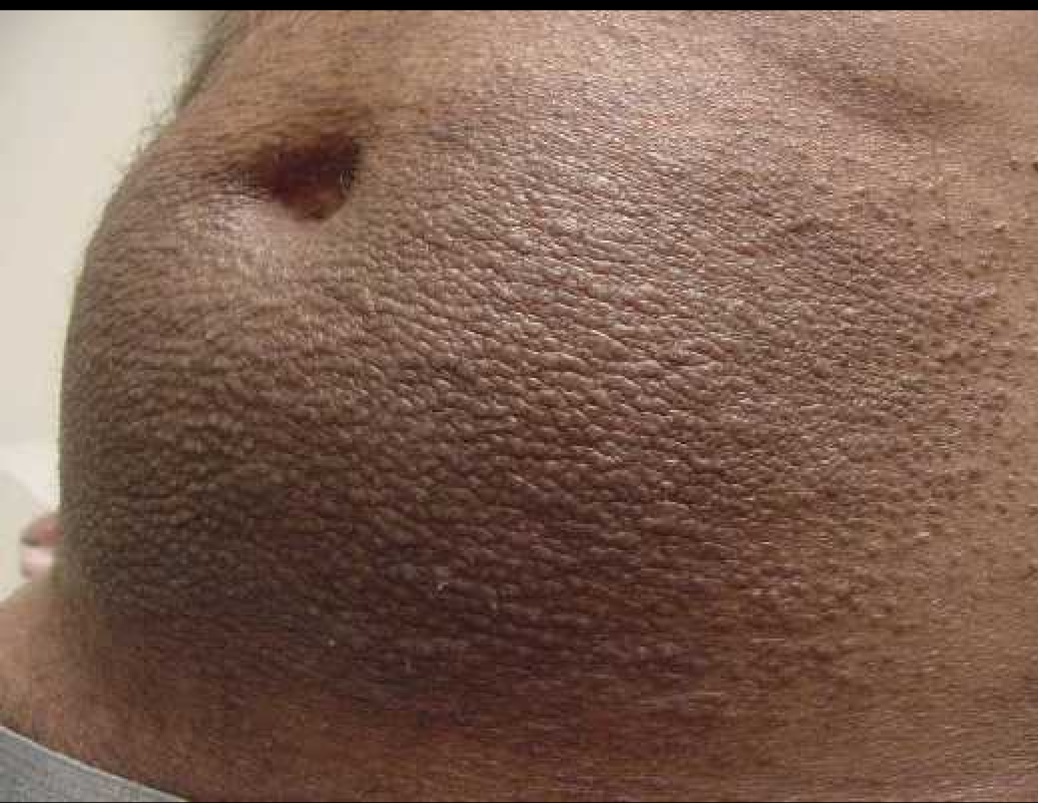
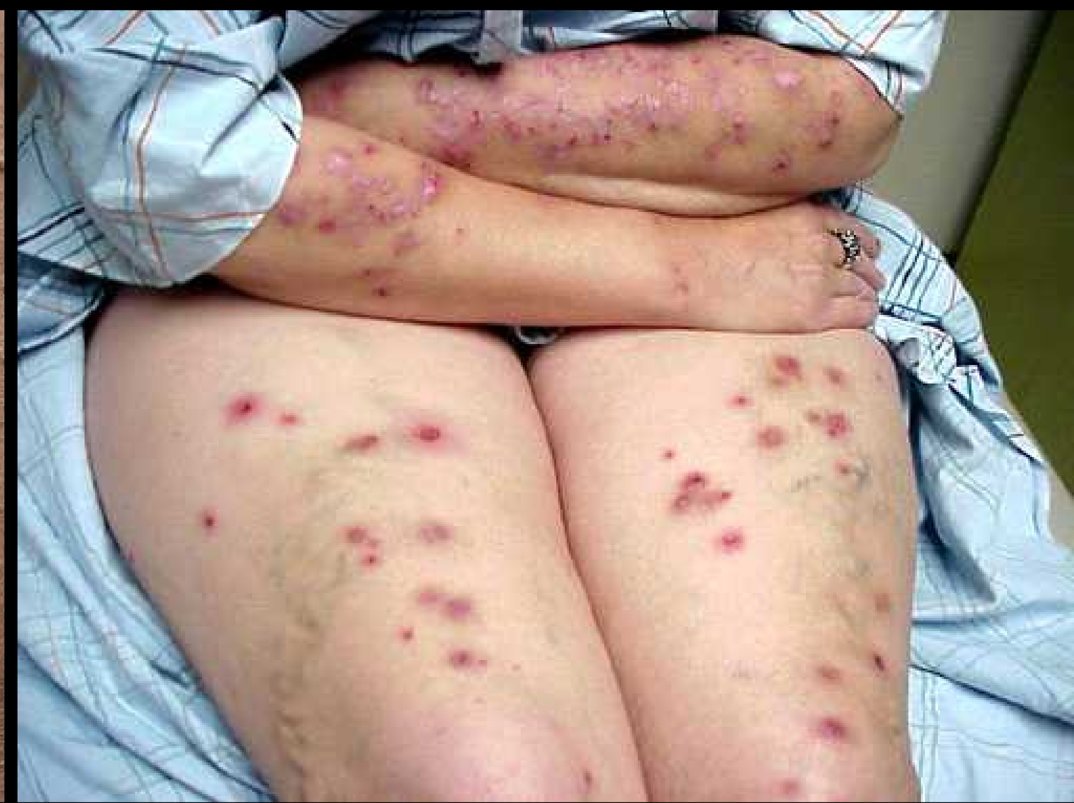


Guttate Psoriasis

- Practical tips
  - Clinical history
    - Rapid onset
    - Antecedent streptococcal infection 2/3
  - Neutrophils not always present
    - Descriptive diagnosis: Psoriasiform or spongiotic dermatitis, see note
    - Note: The mounds of parakeratosis suggest the possibilities of guttate psoriasis or pityriasis rosea

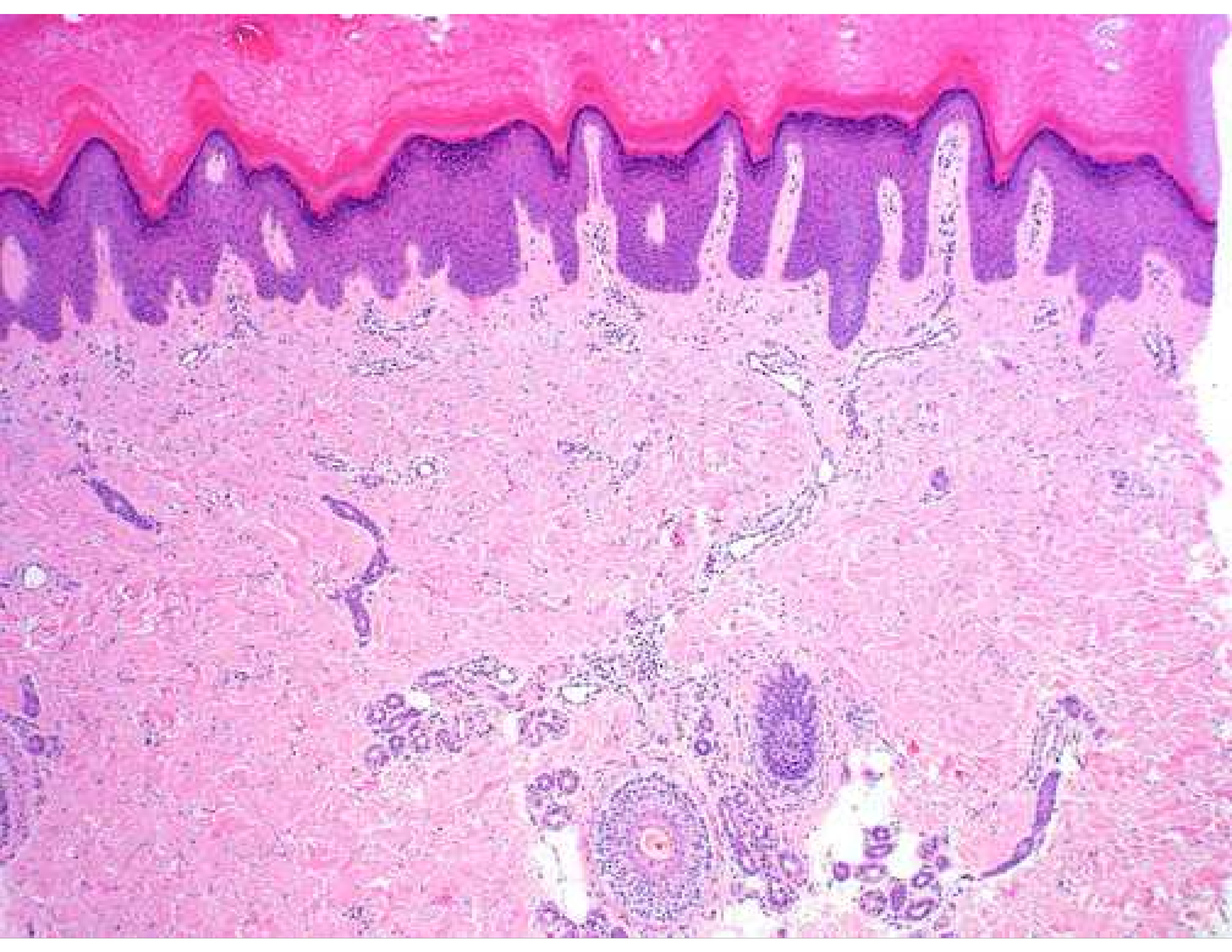
Lichen Simplex Chronicus and Prurigo Nodularis

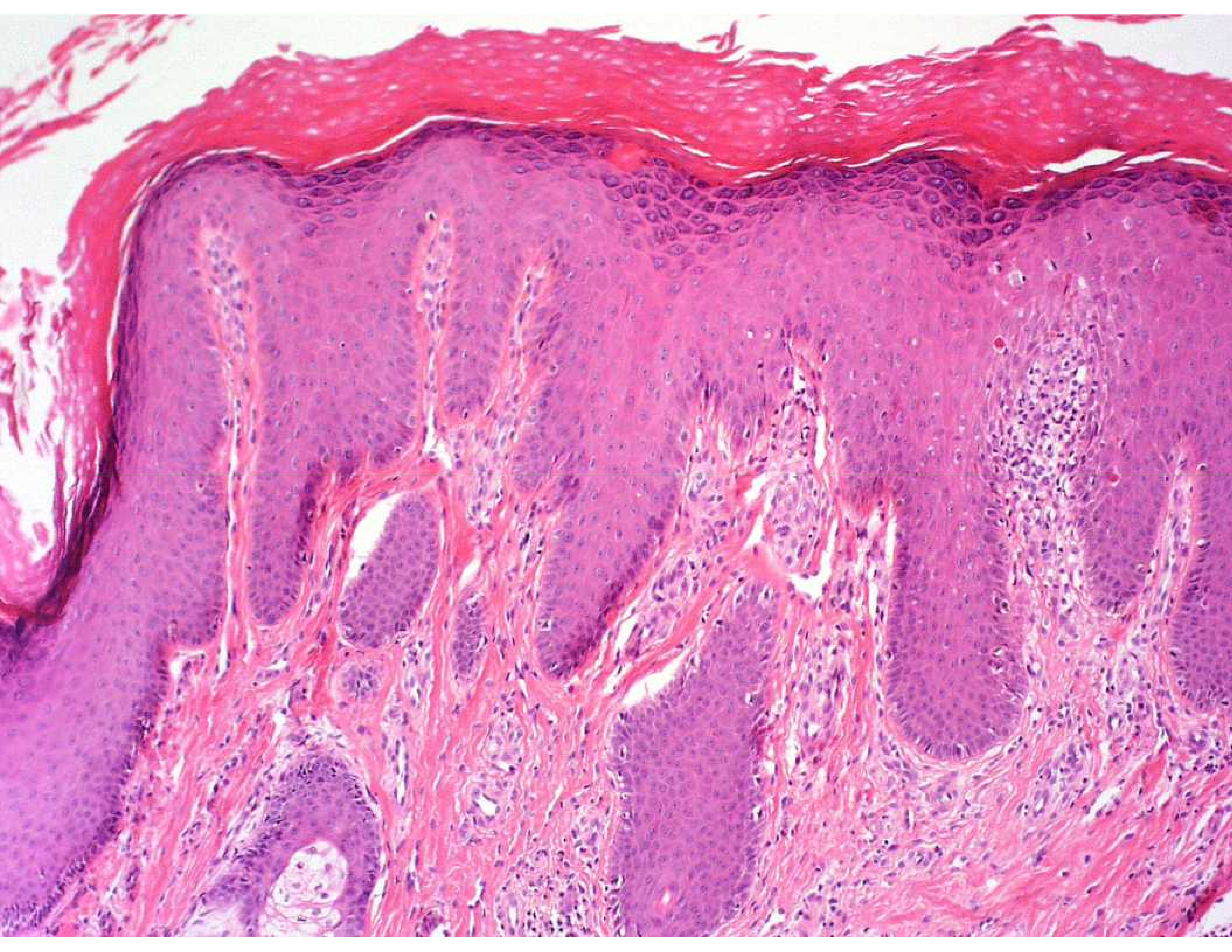
- Clinical
  - Spectrum of same dermatologic disease
  - Secondary to persistent rubbing/scratching
  - Lichen simplex chronicus presents as pruritic indurated plaques
  - Prurigo nodularis presents as pruritic nodules
  - Lesions occur only where the skin can be reached: posterior scalp, ankle, shin, forearm, anterior thigh, genitalia
  - Can develop as a secondary change in underlying dermatitis

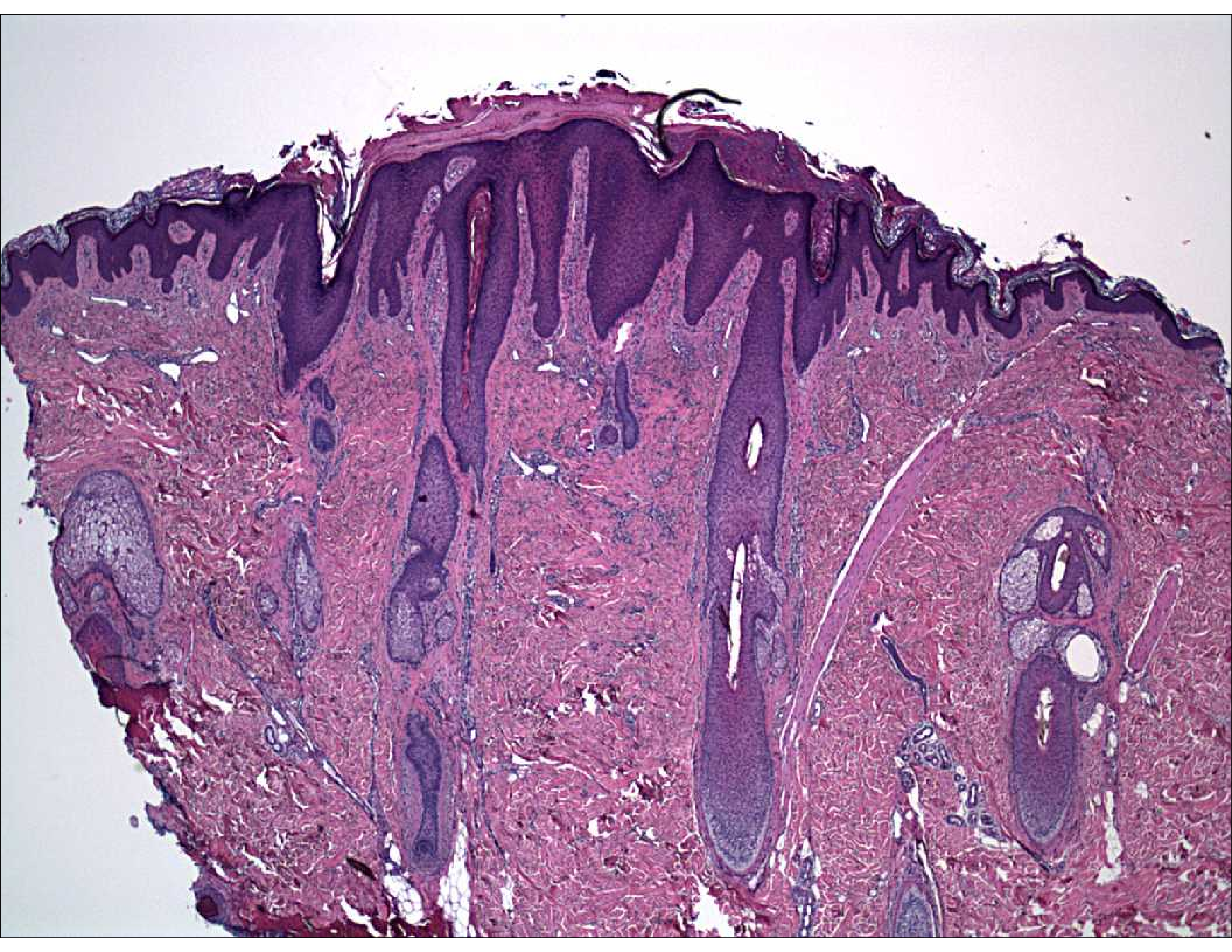



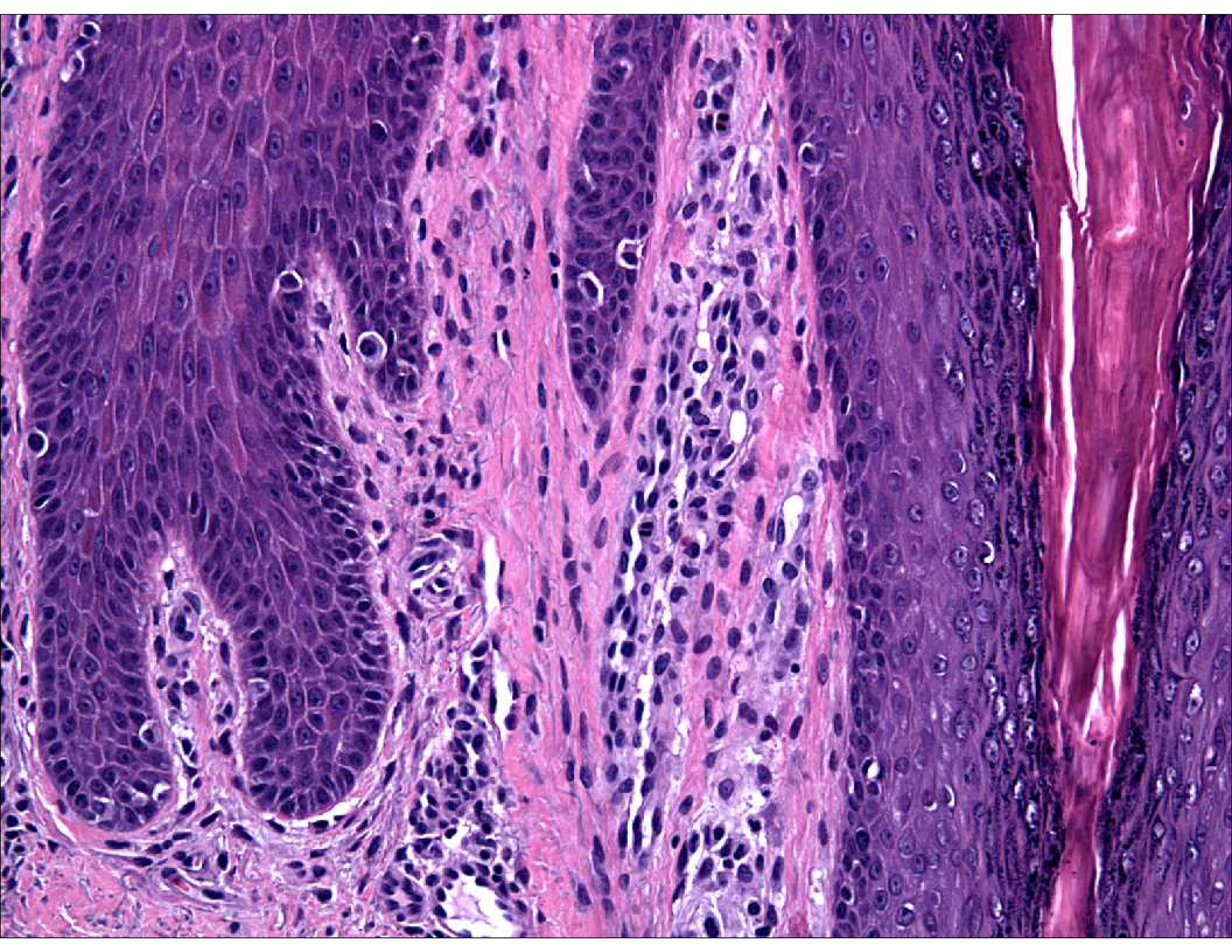
Lichen Simplex Chronicus and Prurigo Nodularis

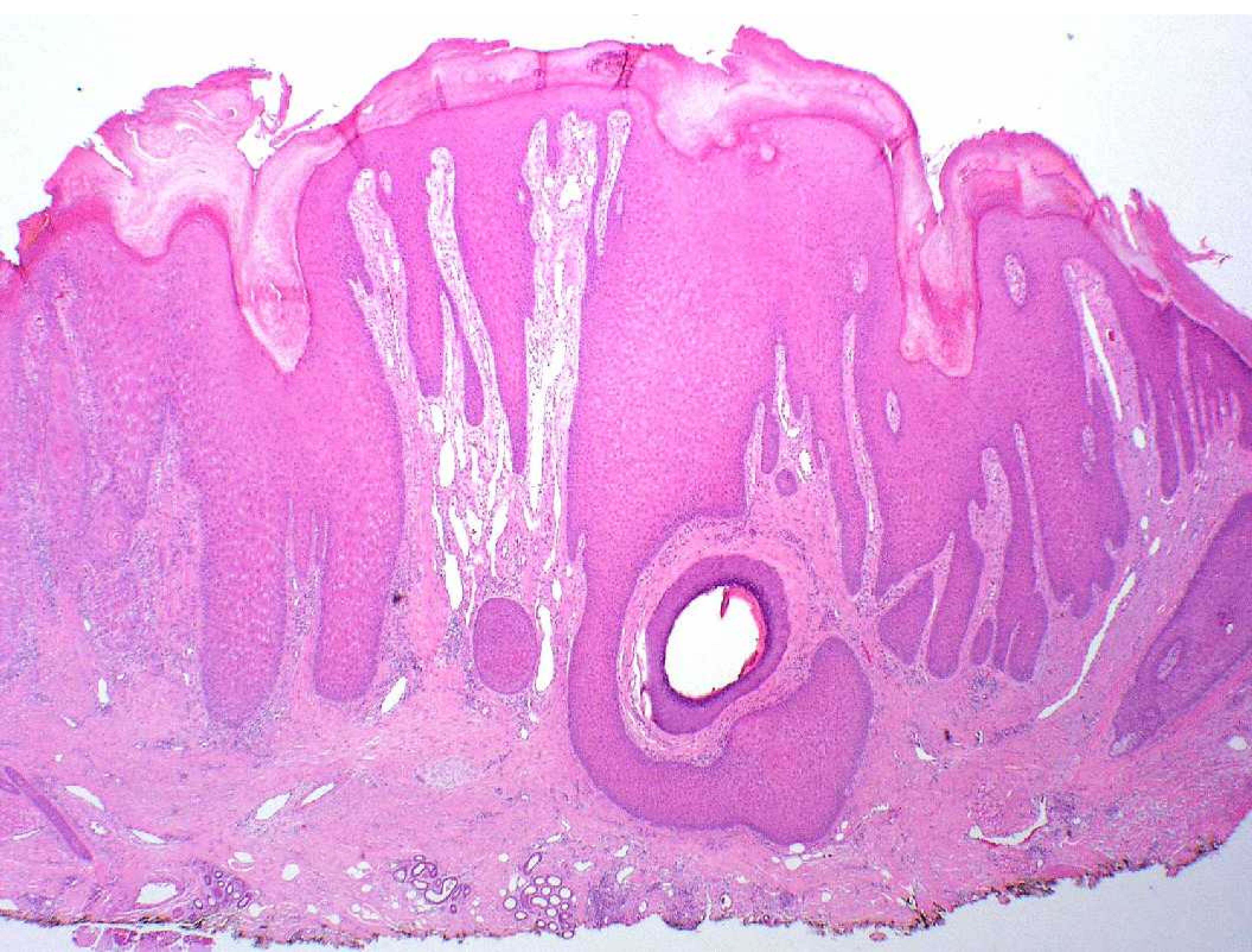
- Microscopic:
  - Prominent compact hyperkeratosis
  - Variable parakeratosis
  - Thickened granular layer
  - Acanthosis, sometimes with pseudoepitheliomatous pattern
  - Vertical fibrosis of papillary dermis
  - Mild perivascular lymphocytic infiltrate
  - Looks like acral skin (hairy palm sign)









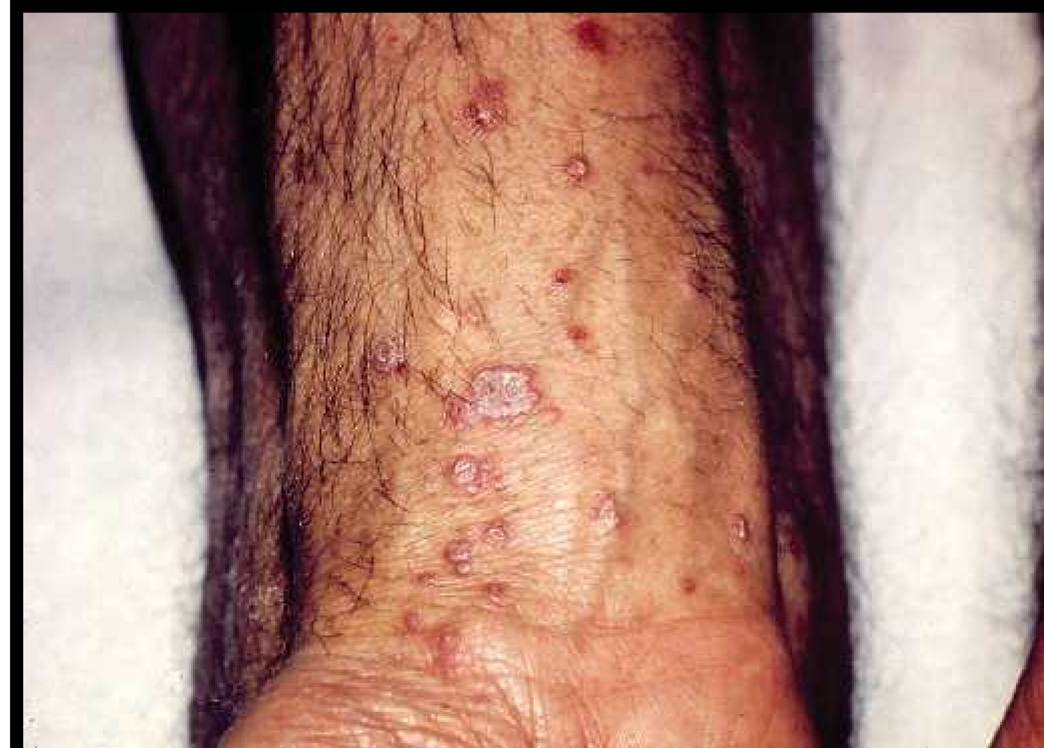


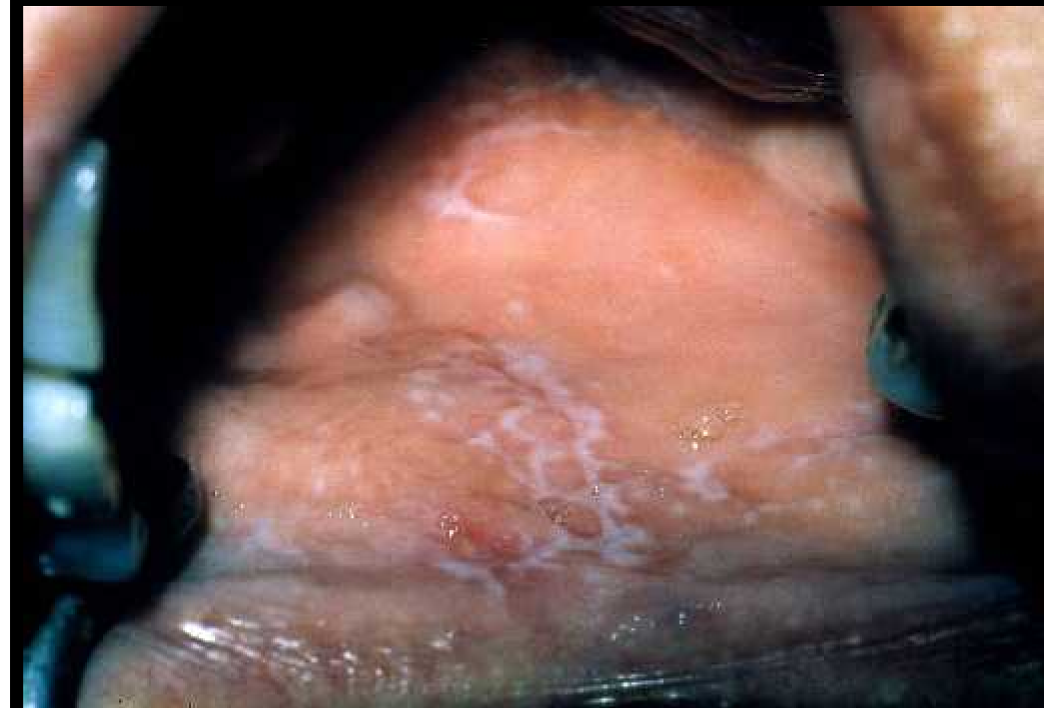
Practical Tips

- Acral skin in non-acral location
- "Hairy palm" sign
- Clinical history: is it itchy?
- Descriptive diagnosis
  - Psoriasiform dermatitis with f/o LSC/PN
- May be superimposed on chronic spongiotic dermatitis
  - Spongiotic dermatitis with superimposed features of LSC

Lichen Planus

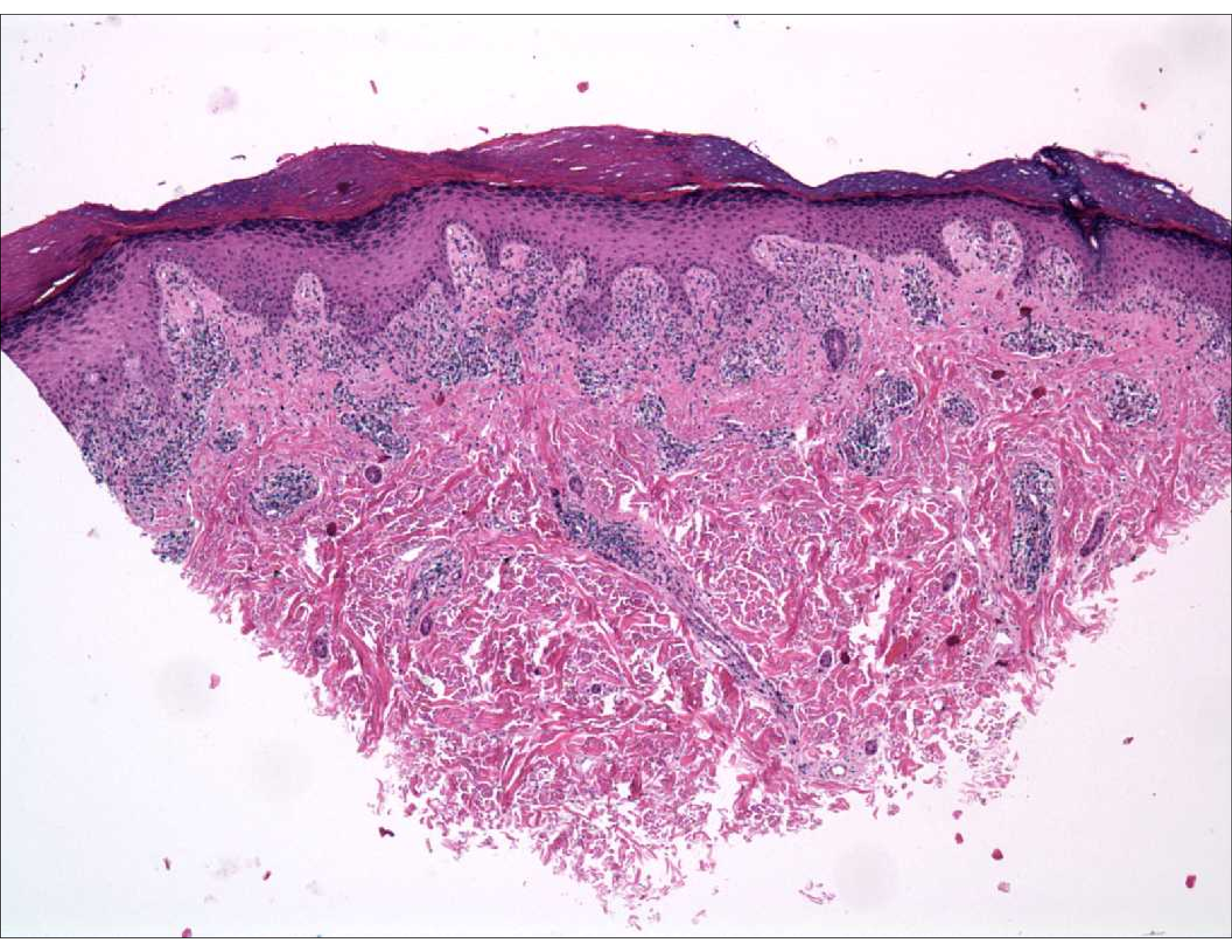
- Clinical
  - Pruritic violaceous, polygonal papules
  - Predilection for flexural surfaces of wrists and ankles
  - May be widespread
  - Oral: lace-like pattern

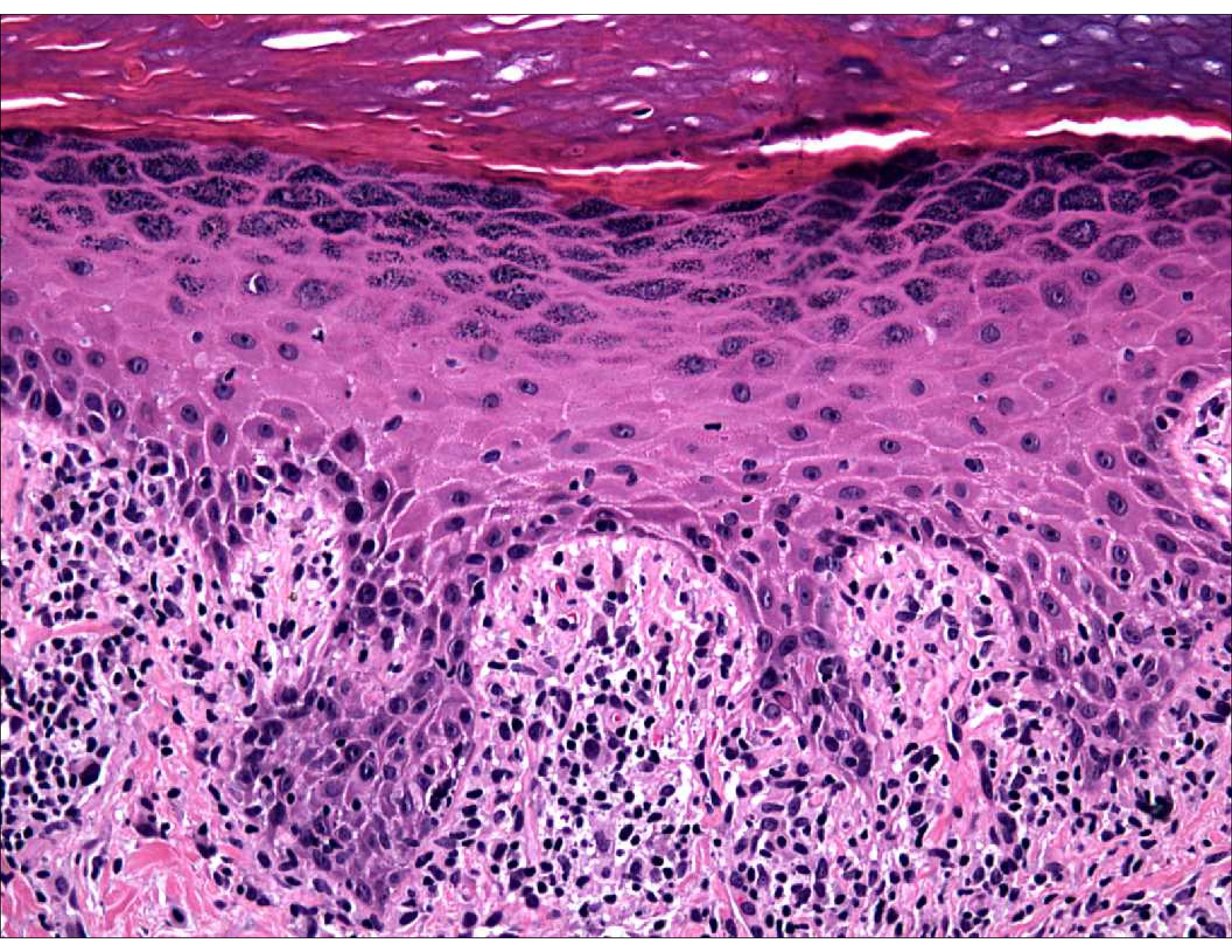


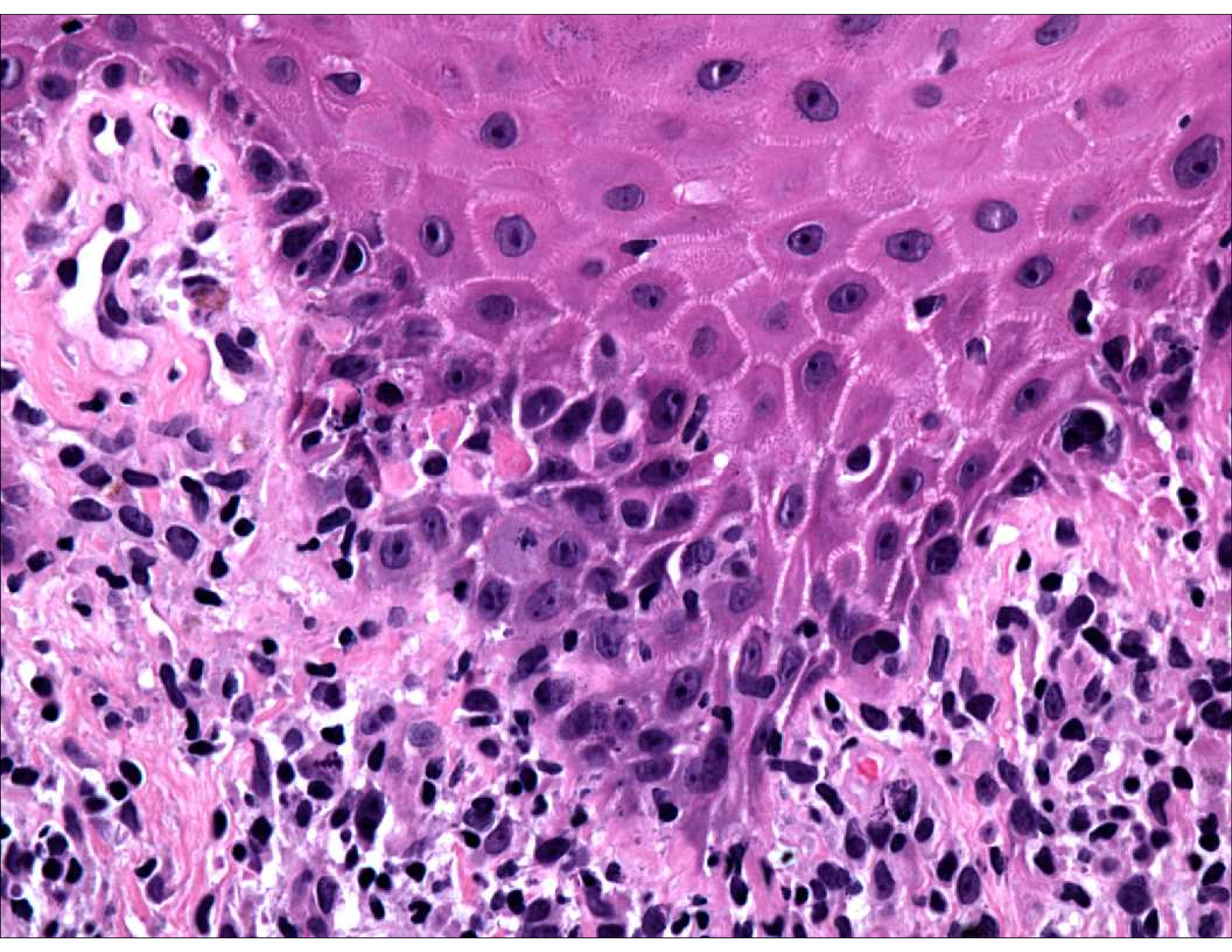


Lichen Planus

- Microscopic features
  - Hyperkeratosis without parakeratosis
  - Acanthosis with wedge-shaped hypergranulosis
  - Interface change with dense band-like lymphocytic infiltrate (rare eosinophils acceptable)
  - “Saw-tooth” rete pegs
  - Scattered dyskeratotic cells

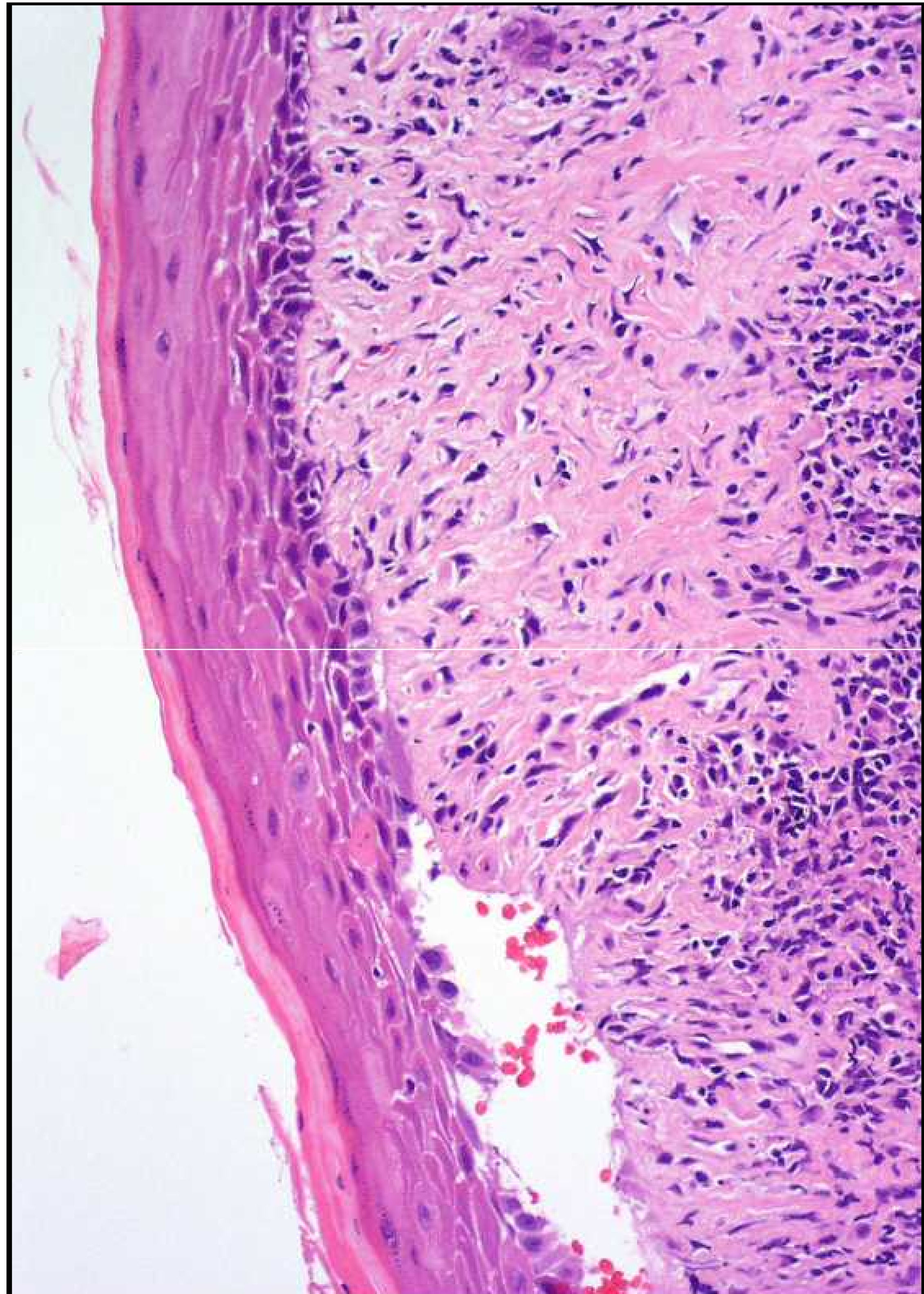






Oral Lichen Planus

- Absent or subtle granular layer
- Parakeratosis
- Lichenoid infiltrate (sometimes less prominent)
- “Saw-toothing” not usually present



Lichen Planus

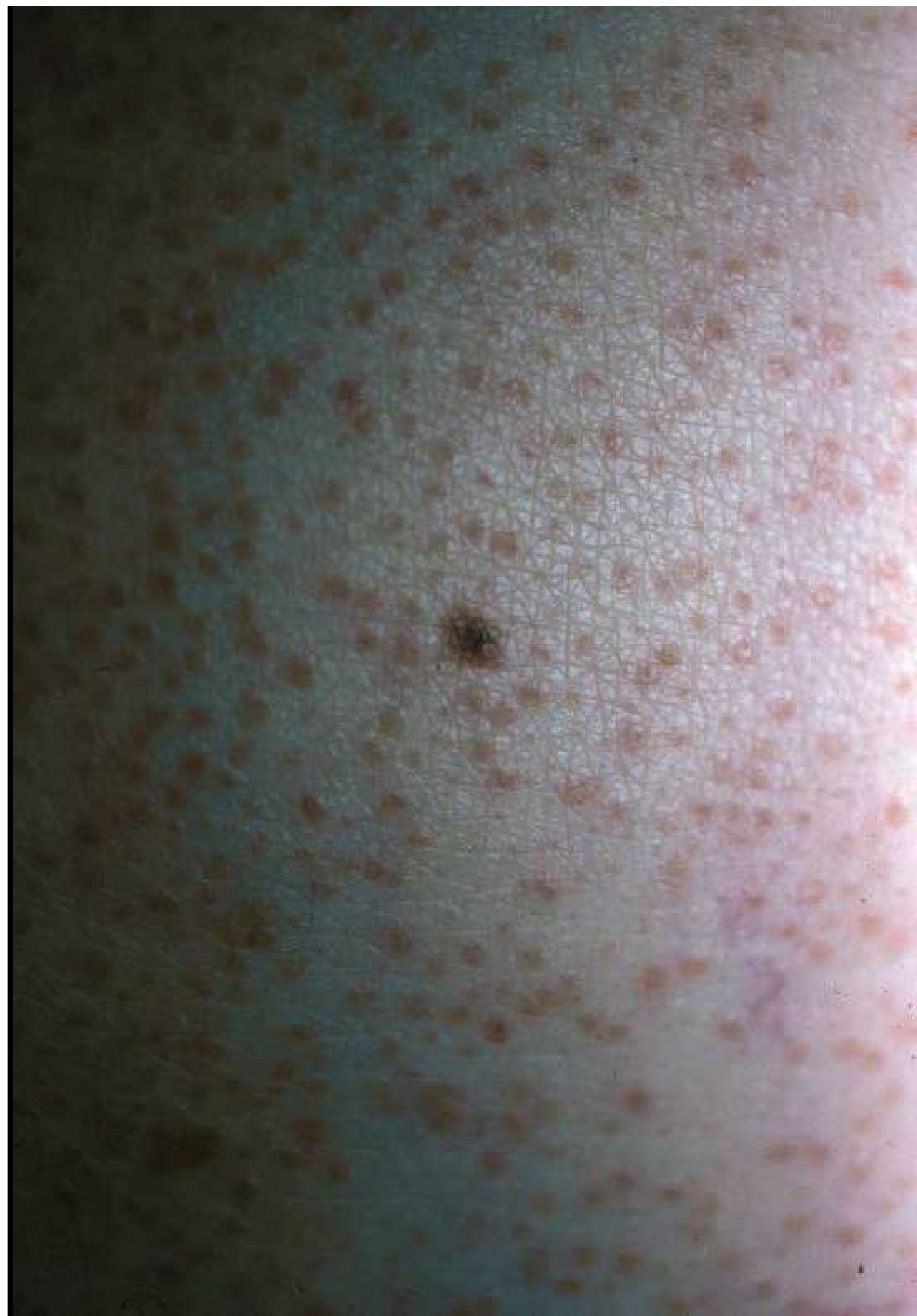
- Differential Diagnosis
  - Lichenoid benign keratosis
  - Lichenoid drug eruption
  - Lichenoid graft vs. host disease
  - Lupus erythematosus
  - Early lichen sclerosus

Lichenoid Benign Keratosis

- Solitary lesion
- Usually on trunk
- Middle-aged and older patients
- Clinically confused with basal cell carcinoma
- Looks like lichen planus or benign keratosis with lichenoid infiltrate

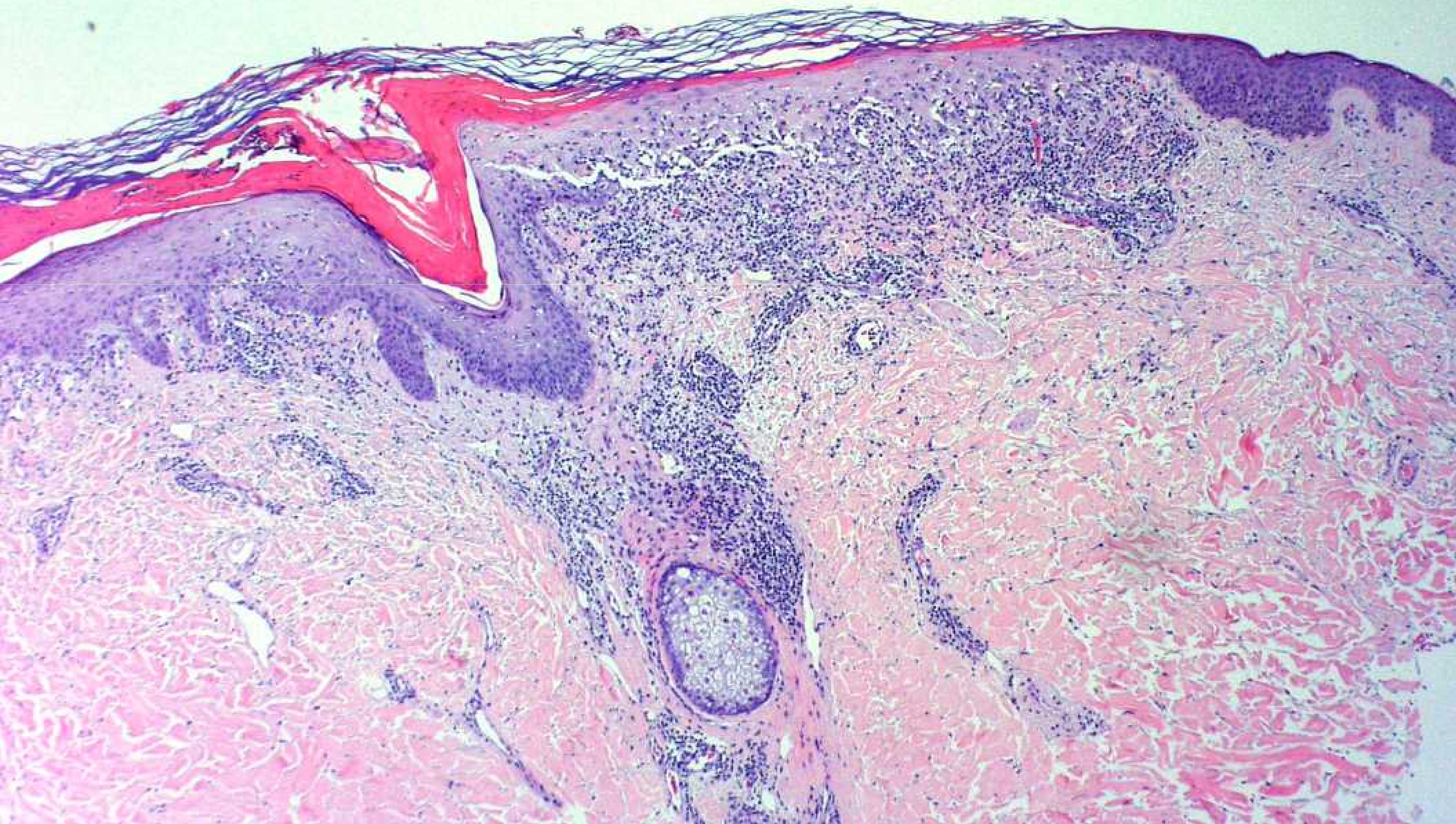
Lichenoid Drug Eruption

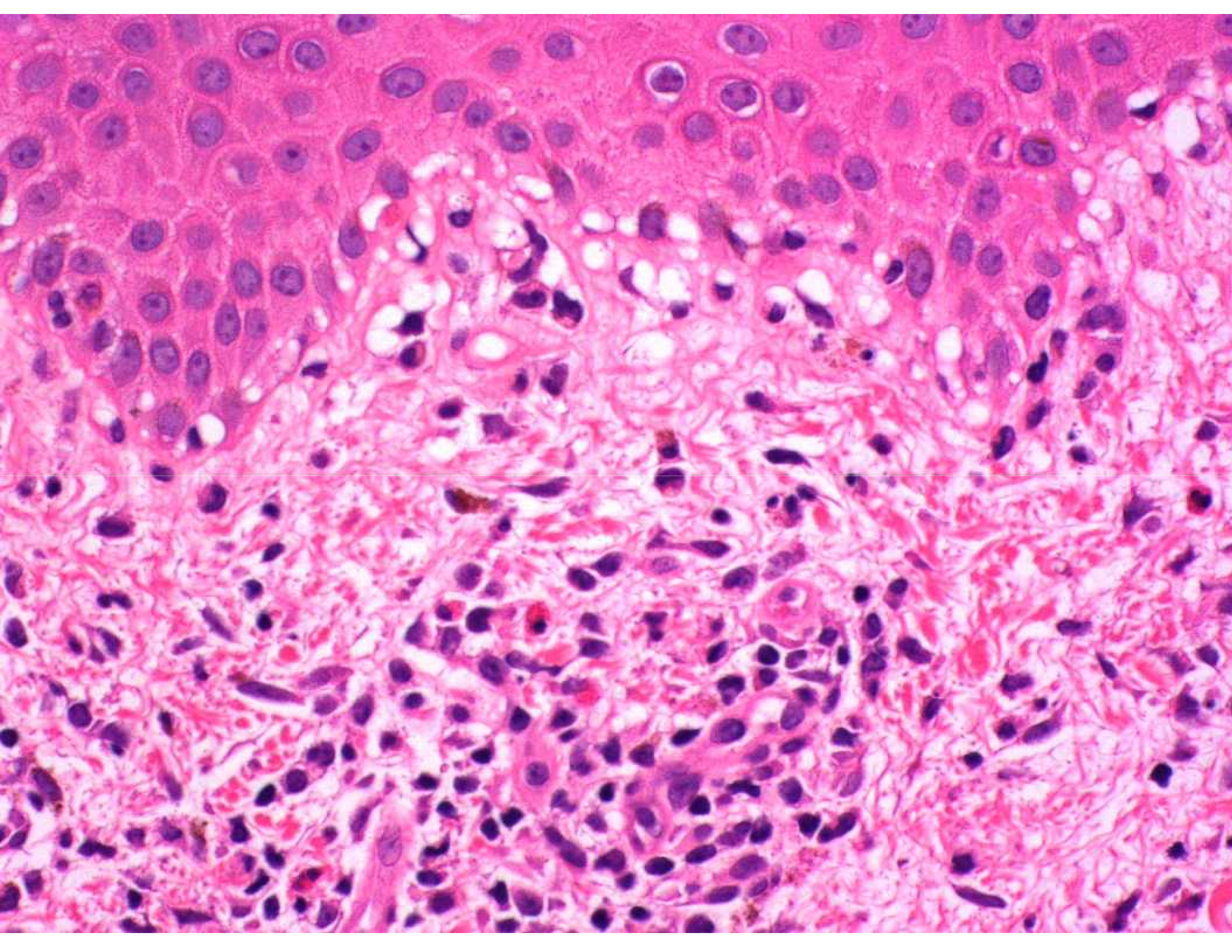
- Widespread violaceous papules
- May occur weeks to months after initiation of drug therapy
- May progress to exfoliative dermatitis



Lichenoid Drug Eruption

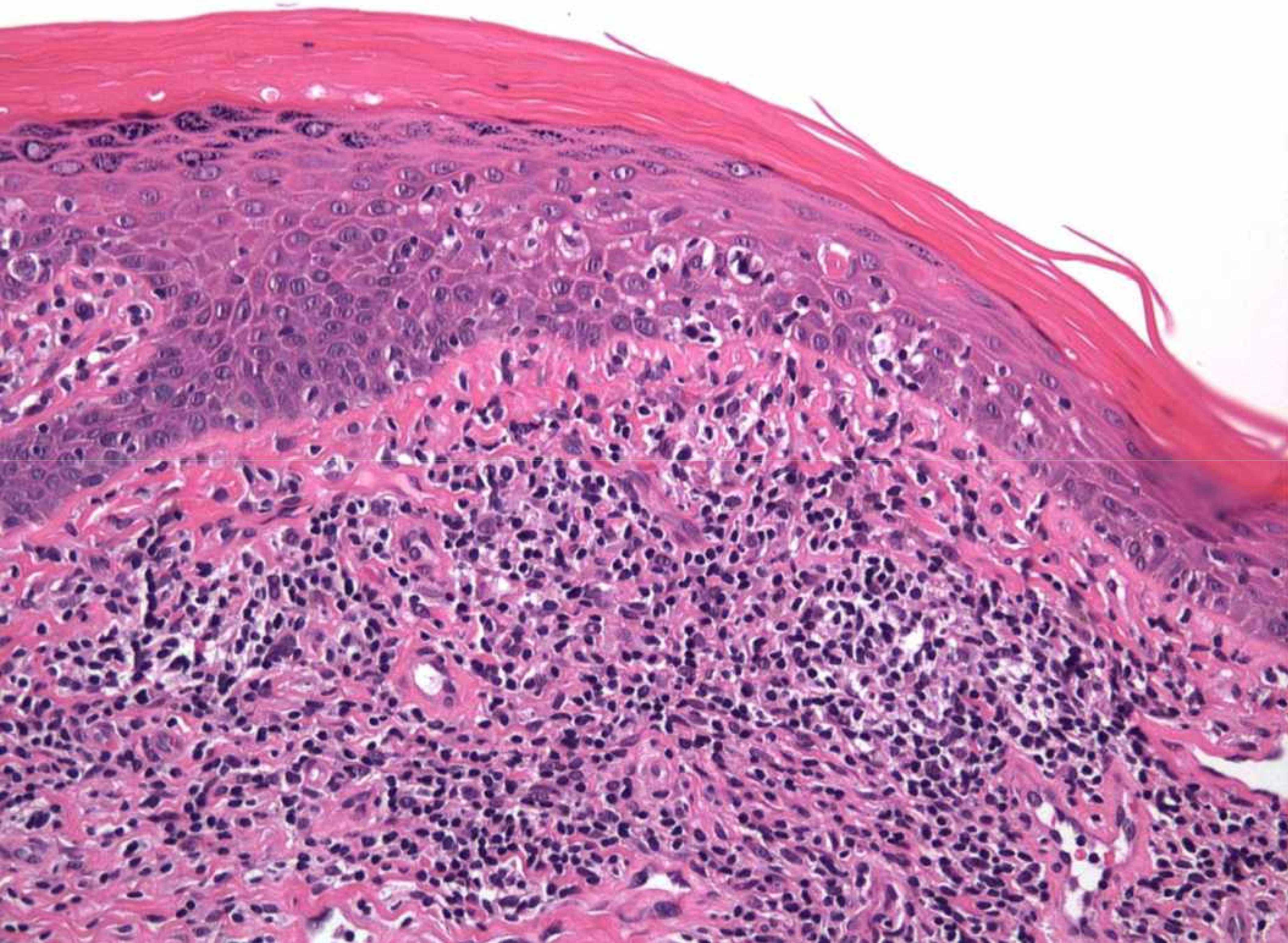
- Microscopic
  - Very similar to lichen planus
  - Occasional to frequent eosinophils
  - Often some parakeratosis
- Differential Diagnosis
  - Lichen planus, fixed drug eruption
- Practical tips
  - Look for eosinophils and parakeratosis





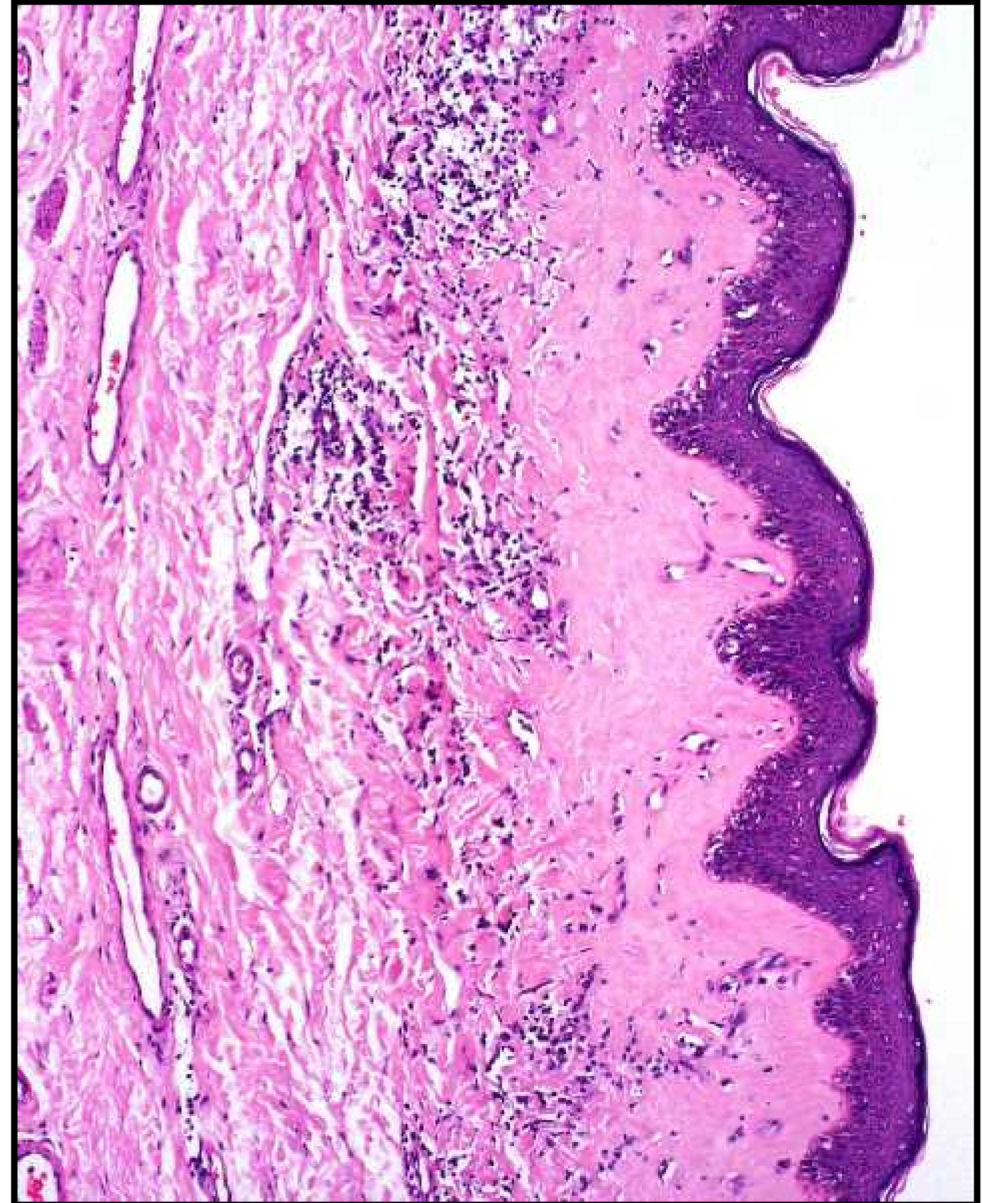
Lichen Sclerosus

- Early lesions:
  - Lichenoid infiltrate of lymphocytes and plasma cells with interface change
  - Psoriasiform epidermal hyperplasia may be present early
  - Basement membrane thickening may be present
  - Look for evidence of papillary dermal fibrosis



Lichen Sclerosus

- Established lesions
  - Homogenized or sclerotic papillary dermis
  - Scattered lymphocytes and plasma cells beneath altered collagen
  - Atrophic epidermis with compact hyperkeratosis and thickened granular layer



Practical Tips

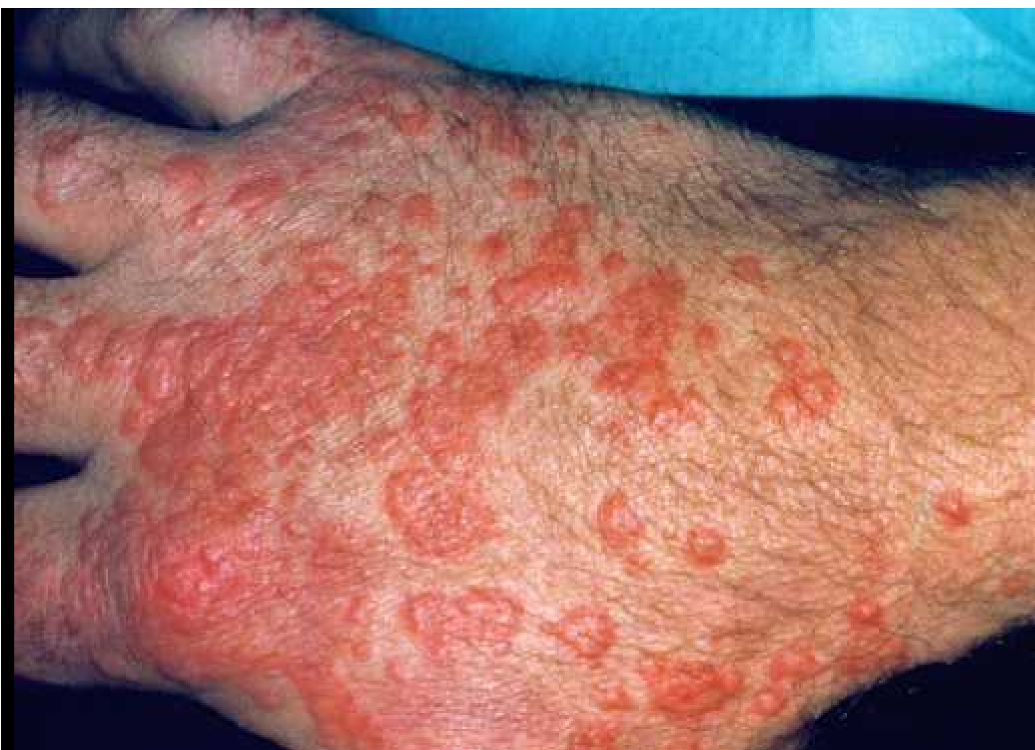
- Rare eosinophils acceptable in lichen planus
  - If numerous think lichenoid drug reaction
- Parakeratosis typically absent in lichen planus
  - Exception: oral lichen planus
- Solitary lesions that look like lichen planus: lichenoid benign keratosis
- Looks like lichen planus on genital skin:
  - Lichenoid interface dermatitis, see comment
  - Comment: the differential diagnosis includes lichen planus vs. early lichen sclerosus

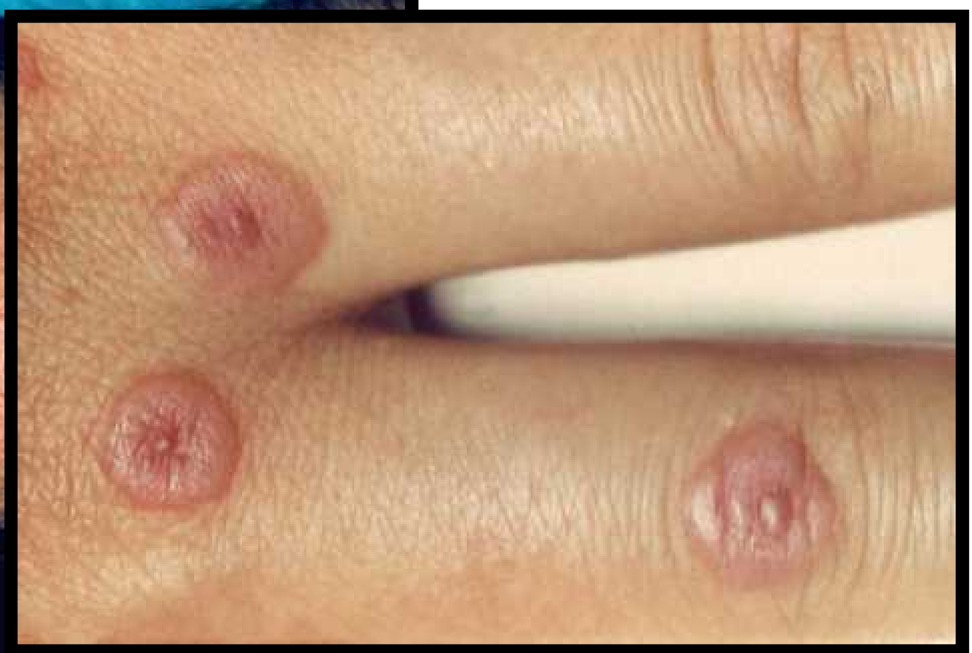
Erythema multiforme spectrum

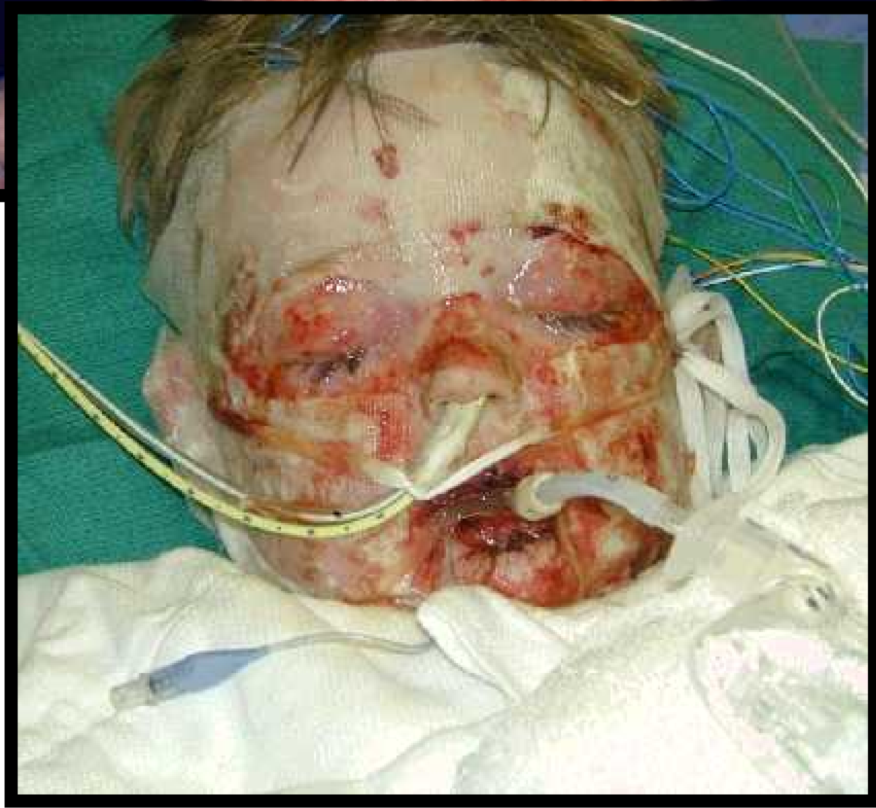
- Erythema multiforme
  - Self-limiting episodic eruptions
  - Erythematous macules, papules and targetoid lesions
  - Extensor surfaces, palms, soles, and oral mucosa
  - Associated with HSV, Mycoplasma, and drugs (sulfonamides)
- Stevens-Johnson syndrome: mucosal involvement <10% body surface area

Clinical Features

- Toxic epidermal necrolysis (TEN)
  - Widespread tender macular erythematous eruption with vesicles and bullae >30% body surface area
  - Associated with drugs
  - Mortality 25-50%
- Stevens Johnson-TEN overlap: 10-30% body surface area

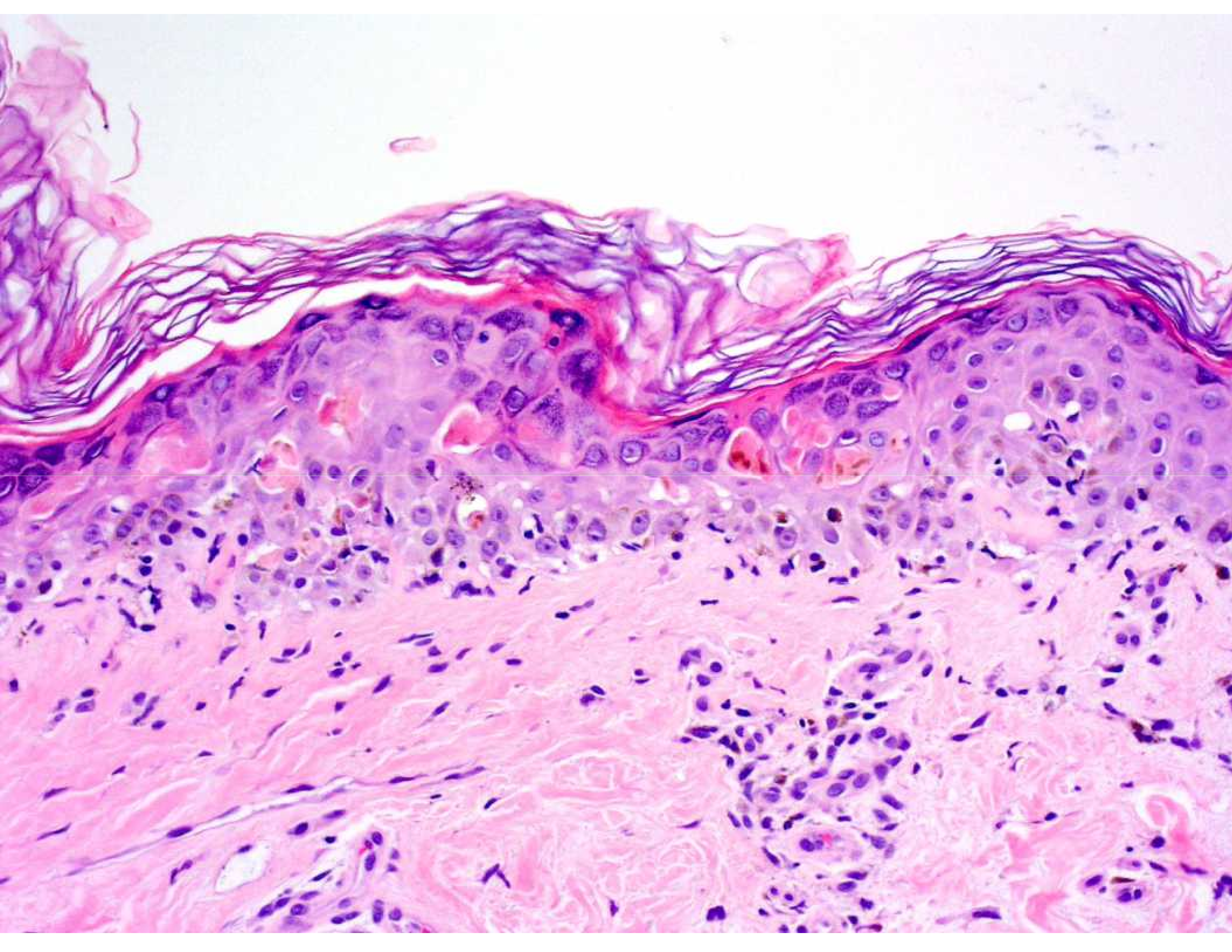


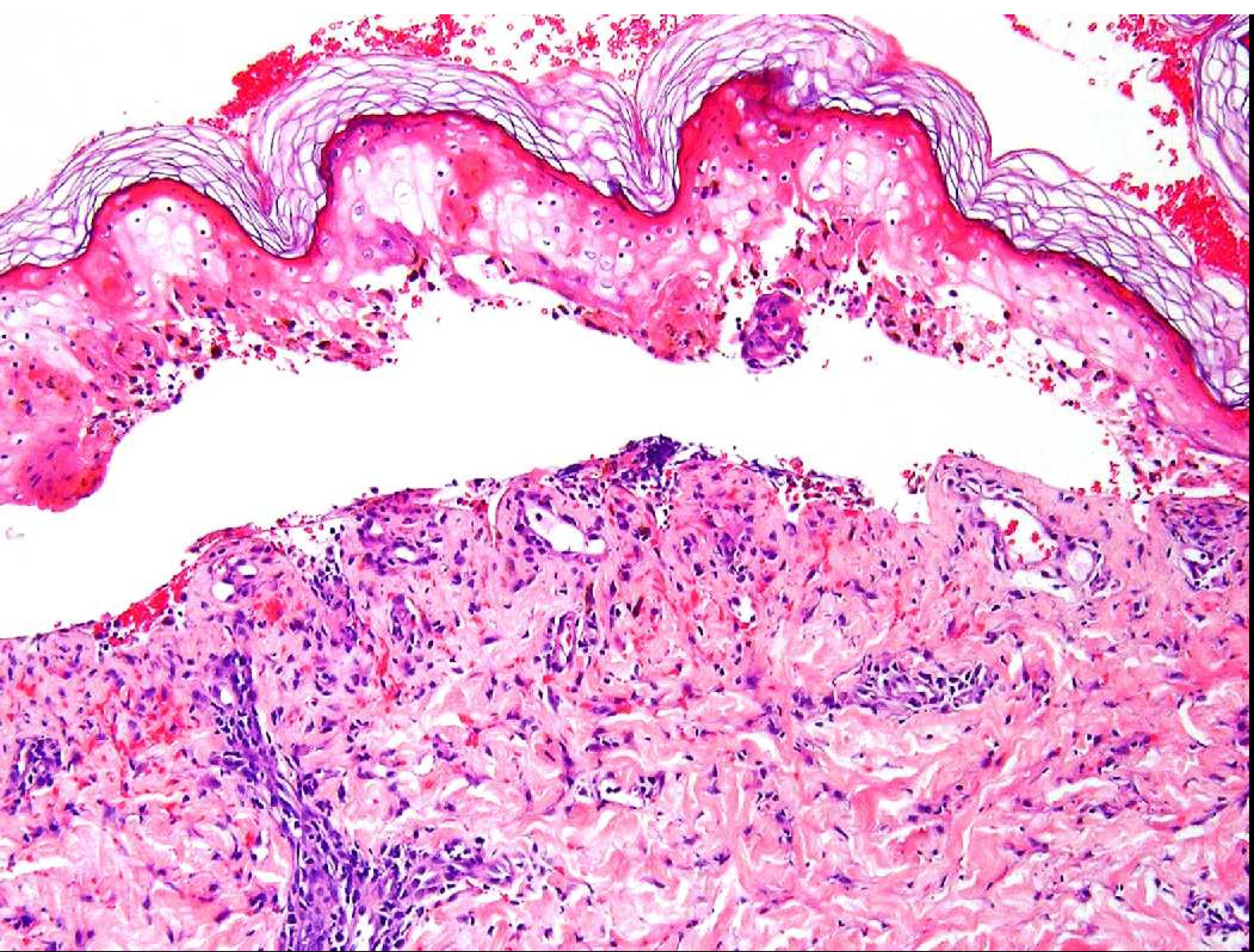




Erythema Multiforme/TEN

- Microscopic
  - Normal basket-weave stratum corneum
  - Spongiosis
  - Dyskeratotic cells at all levels of epidermis
  - Basal vacuolization
  - Mild superficial perivascular lymphohistiocytic infiltrate (sometimes eosinophils)
  - Exocytosis of lymphocytes
  - Epidermal necrosis (seen in older lesions)
    - More common in TEN





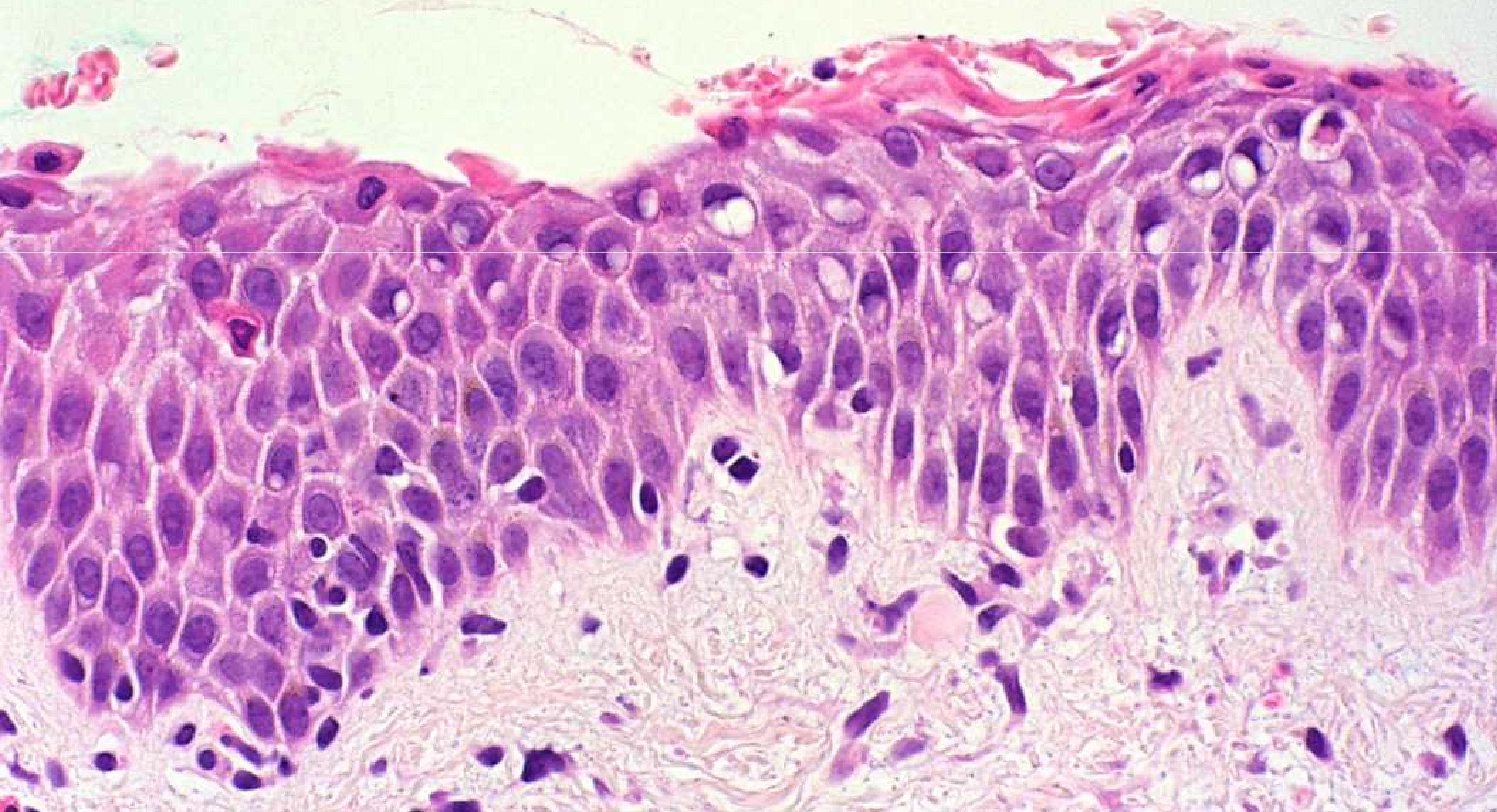
Differential Diagnosis

- Lupus erythematosus/dermatomyositis
  - More epidermal change
- Morbilliform drug eruption
  - Less epidermal damage
- Graft versus host disease
  - Clinical history

Practical Tips: EM and TEN

- Necrotic keratinocytes, normal stratum corneum
- Disproportionate epidermal damage for amount of inflammation
- Histologic distinction between EM and TEN requires clinical information
- SJS and TEN: medical emergency
- TEN clinical ddx: Staph scalded skin syndrome

Staph scalded skin syndrome

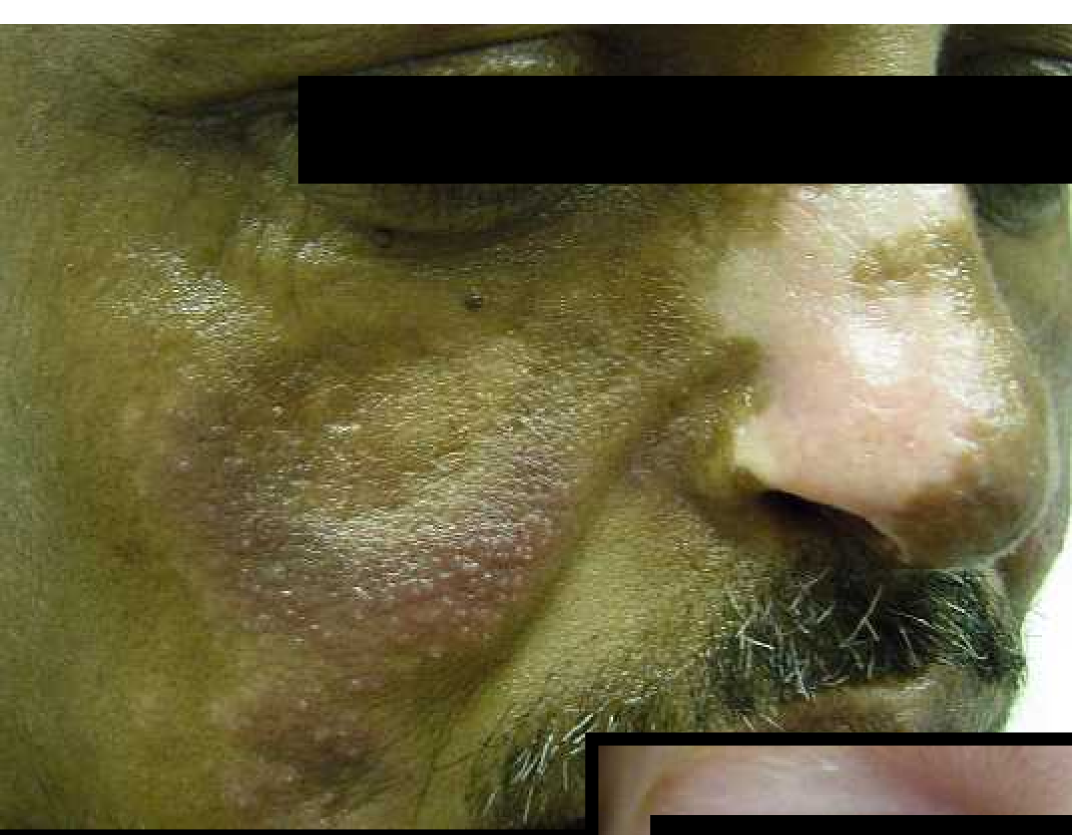
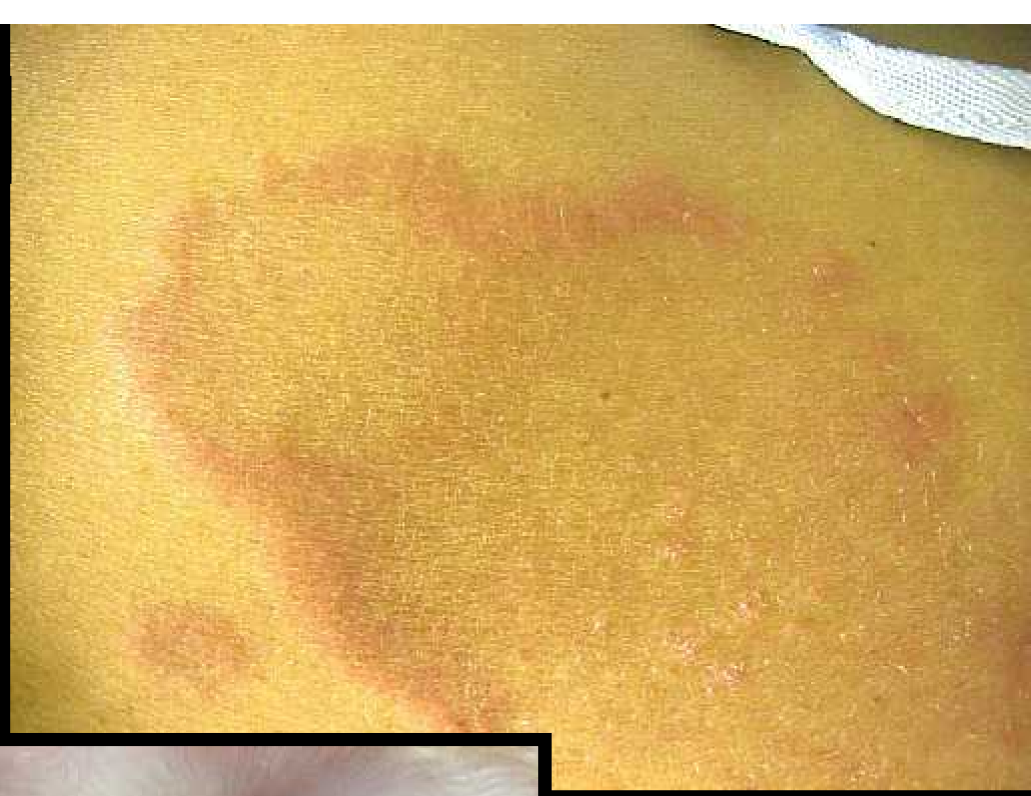
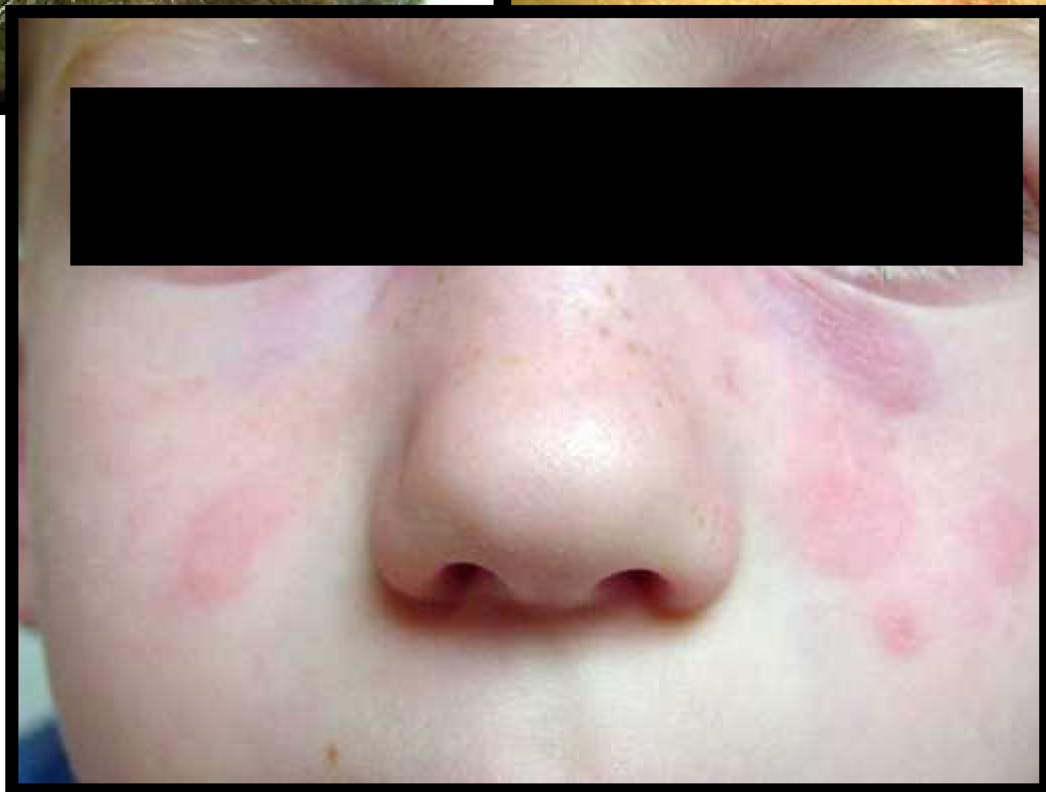


Lupus Erythematosus

- Clinical
  - Chronic (discoid)
    - Well-demarcated scaly plaques
    - Erythematous to hyper or hypopigmented
    - Usually on head/neck (sun-exposed skin)
    - Most patients with skin only disease
  - Subacute
    - Scaly erythematous, often annular plaques
    - Upper trunk, extensor surfaces of arms
    - Positive ANA 75%

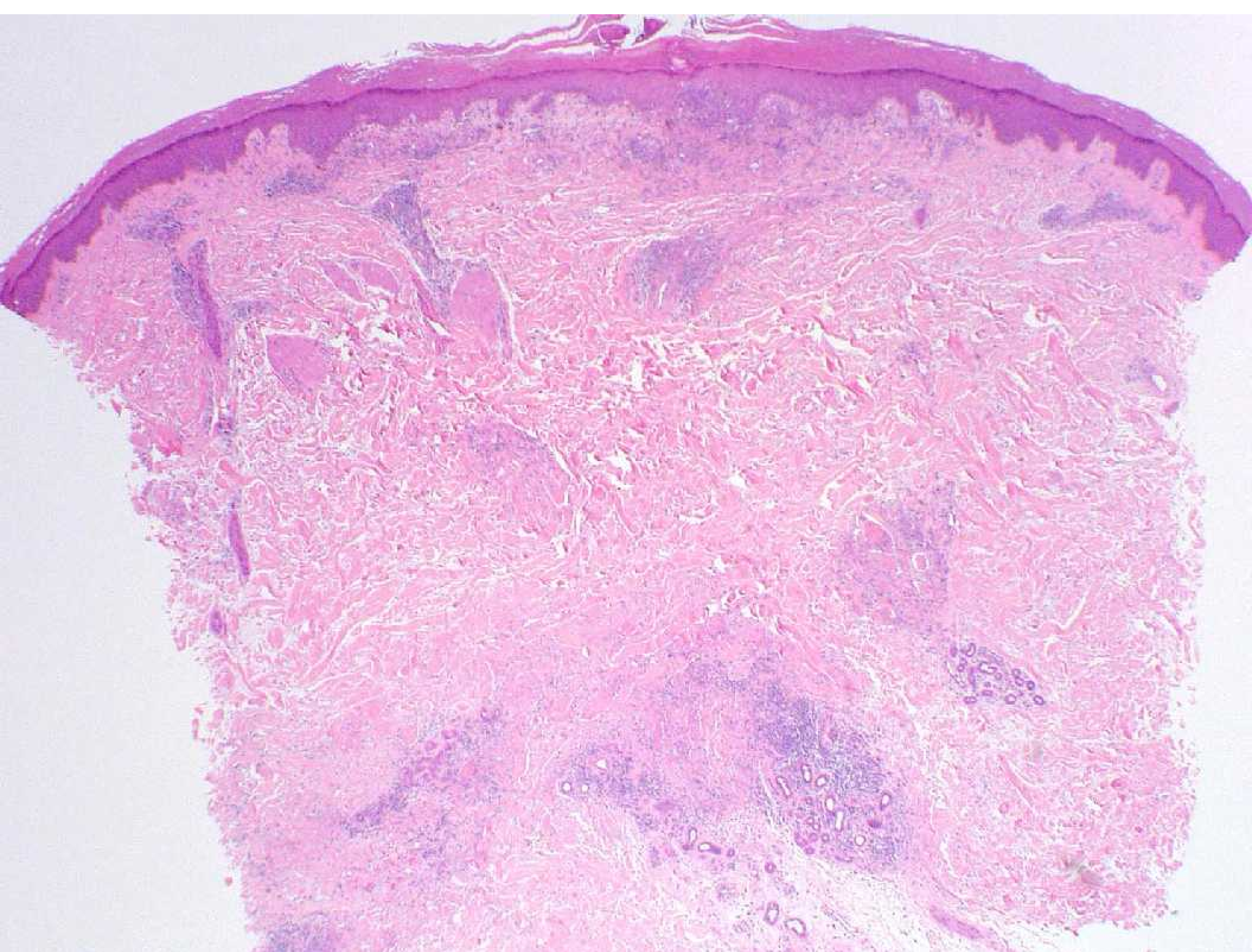
Lupus Erythematosus

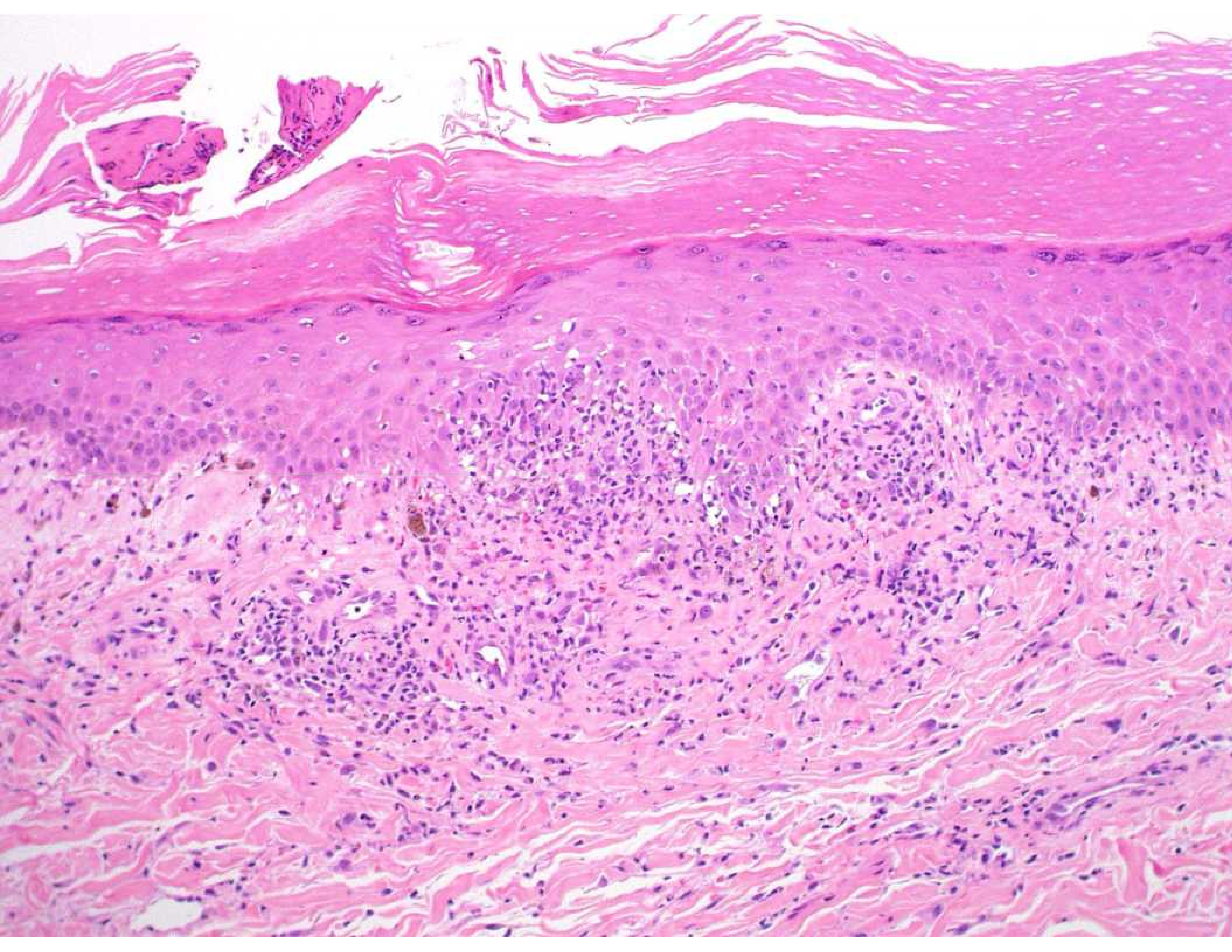
- Clinical
  - Acute
    - Associated with systemic lupus erythematosus
    - Erythematous lesions
    - Malar rash
    - Positive ANA and anti-DNA antibodies

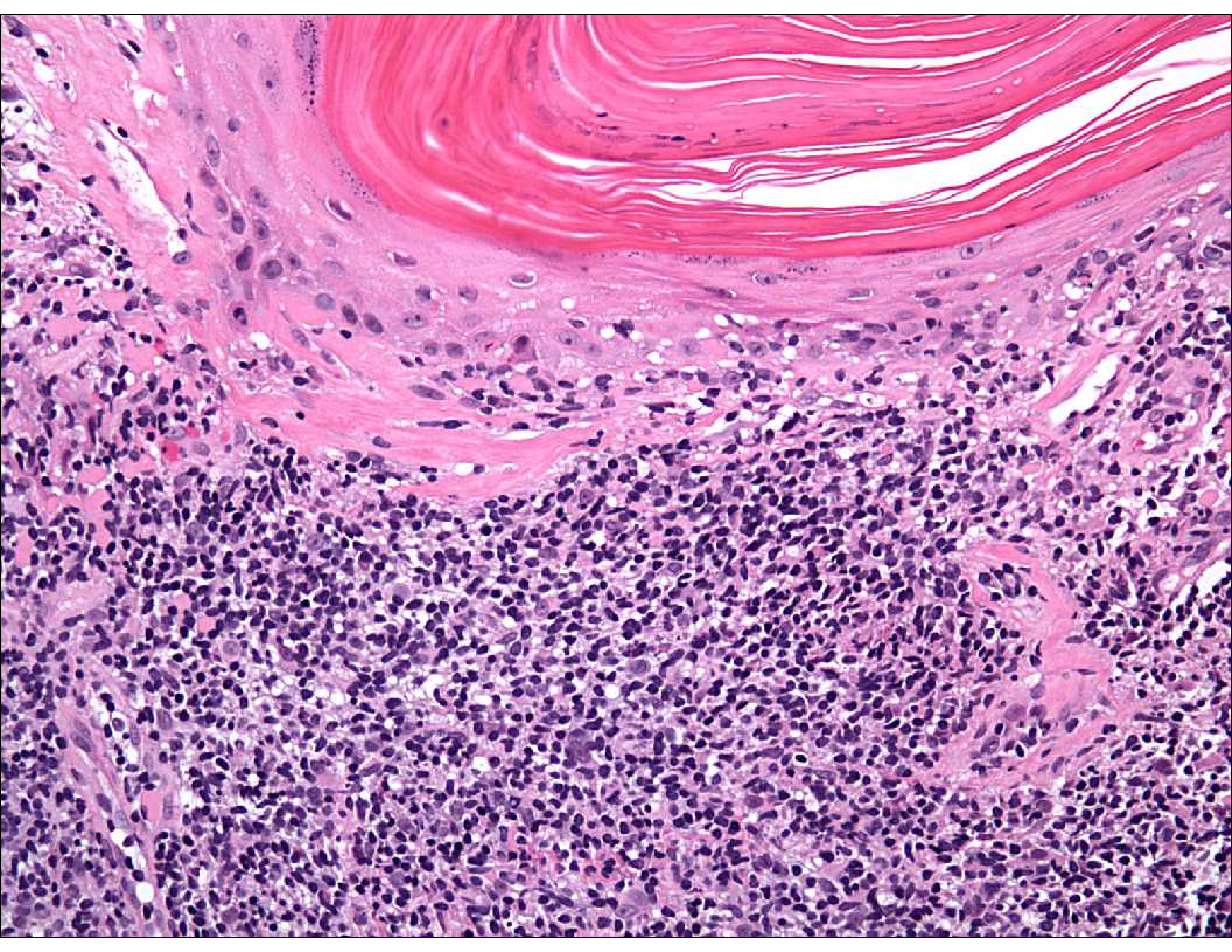




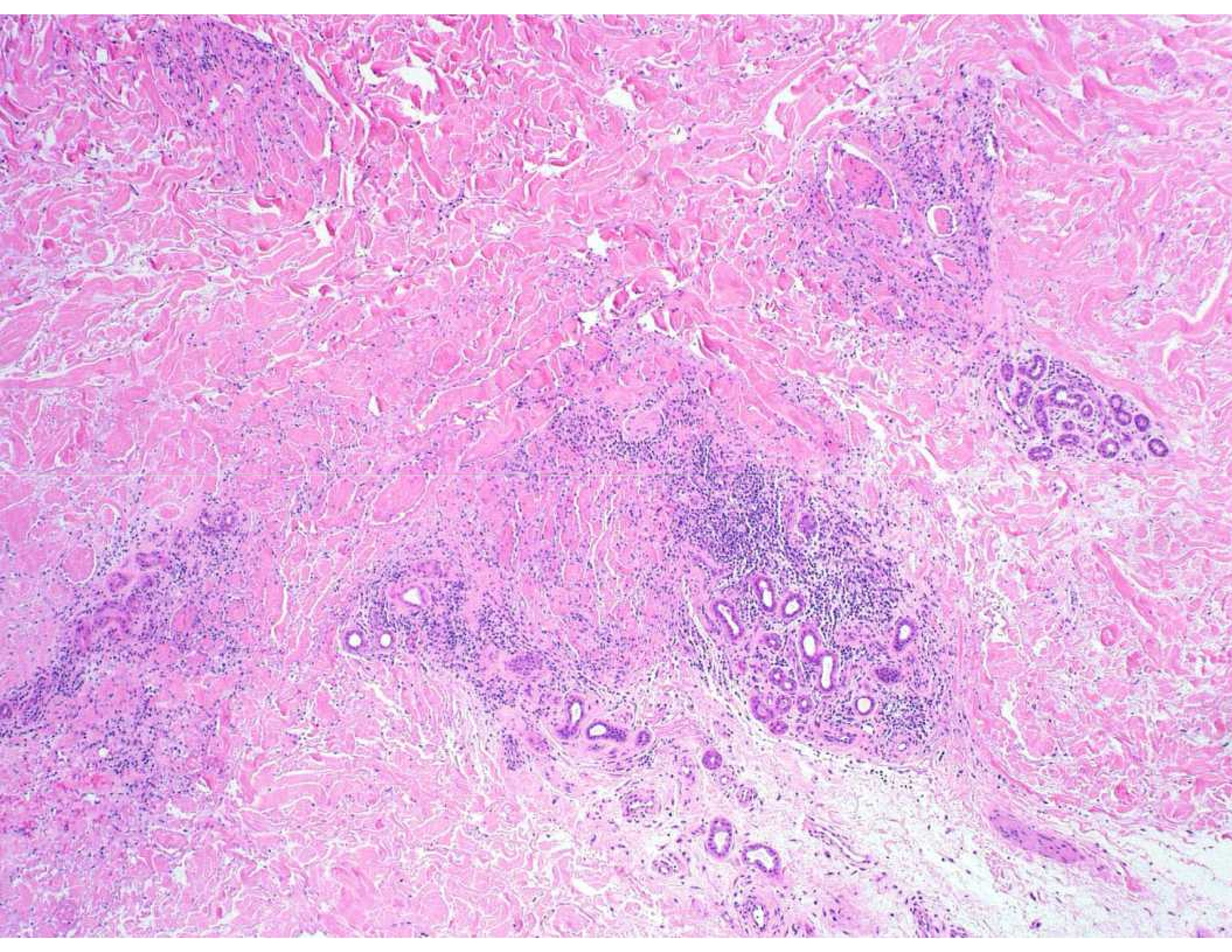
Lupus Erythematosus

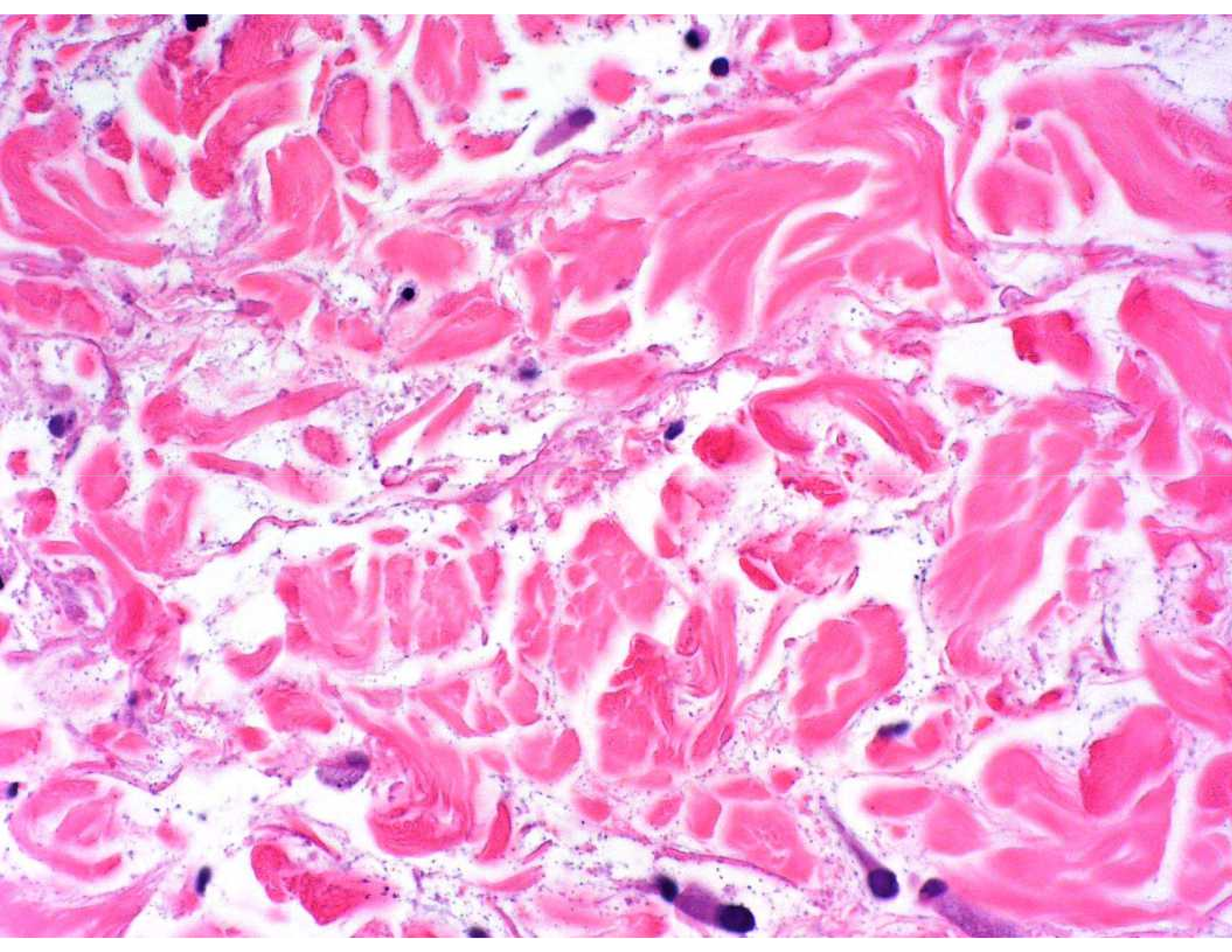
- Microscopic
  - Histologic overlap between subtypes
  - Basal vacuolization
  - Perivascular and periadnexal mononuclear cell infiltrate
  - Epidermal atrophy (often)
  - Thickened basement membrane (often)
  - Increased dermal mucin
  - Follicular plugging (often)
  - May have reactive squamous atypia (AK clue)

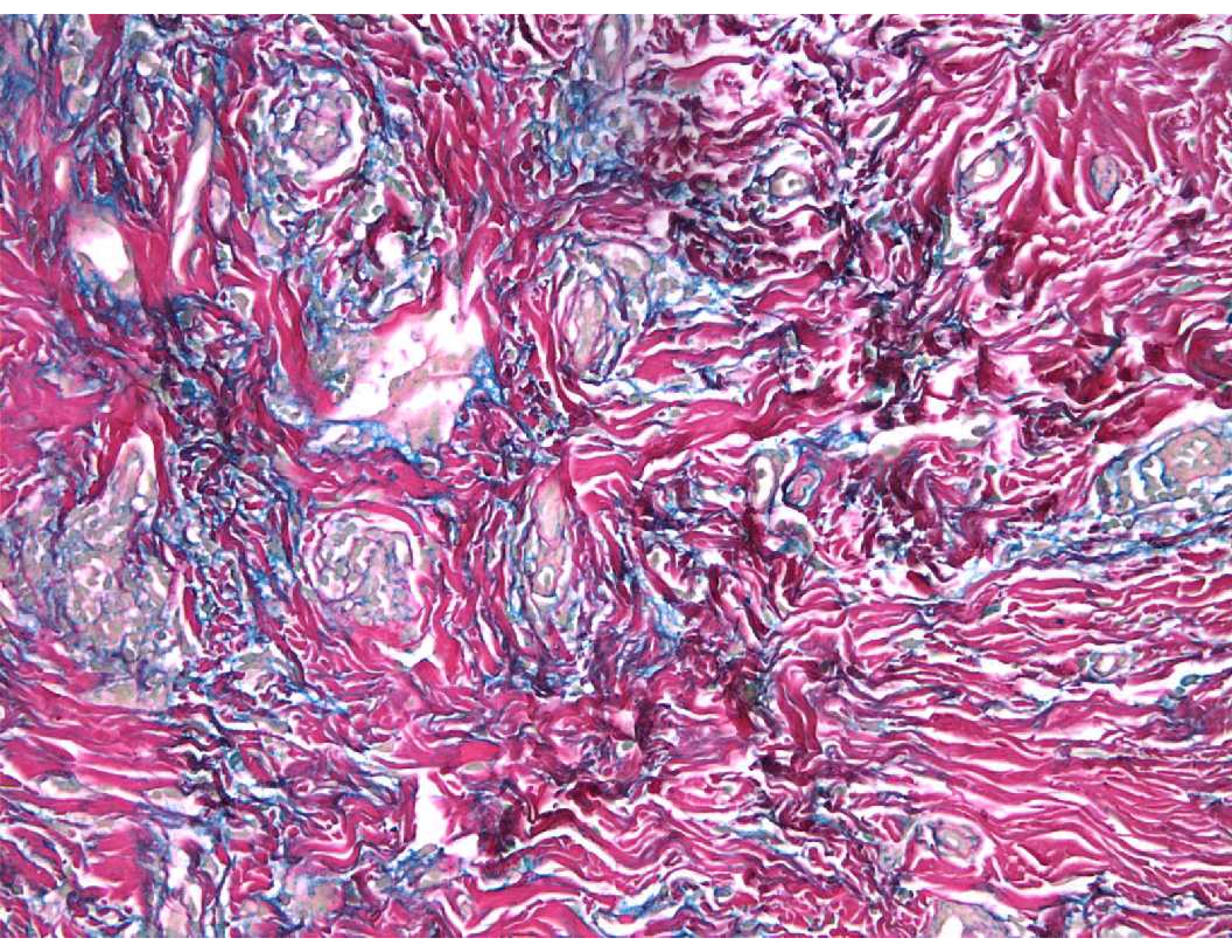










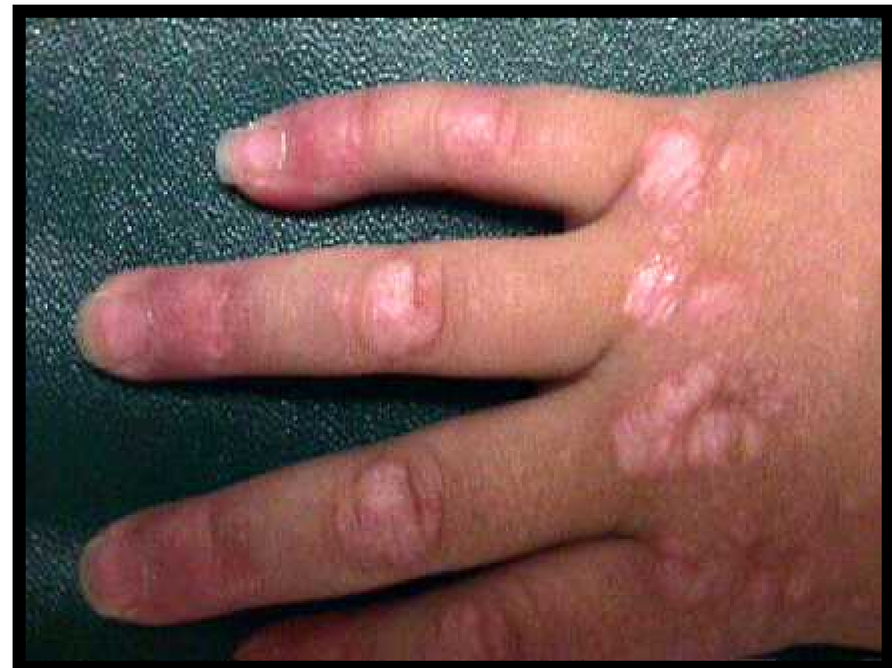


Lupus Erythematosus

- Differential diagnosis
  - Dermatomyositis
  - Lichen planus
  - Actinic keratosis
    - Reactive atypia versus dysplasia
    - Lacks dermal mucin, follicular plugging, deep inflammation

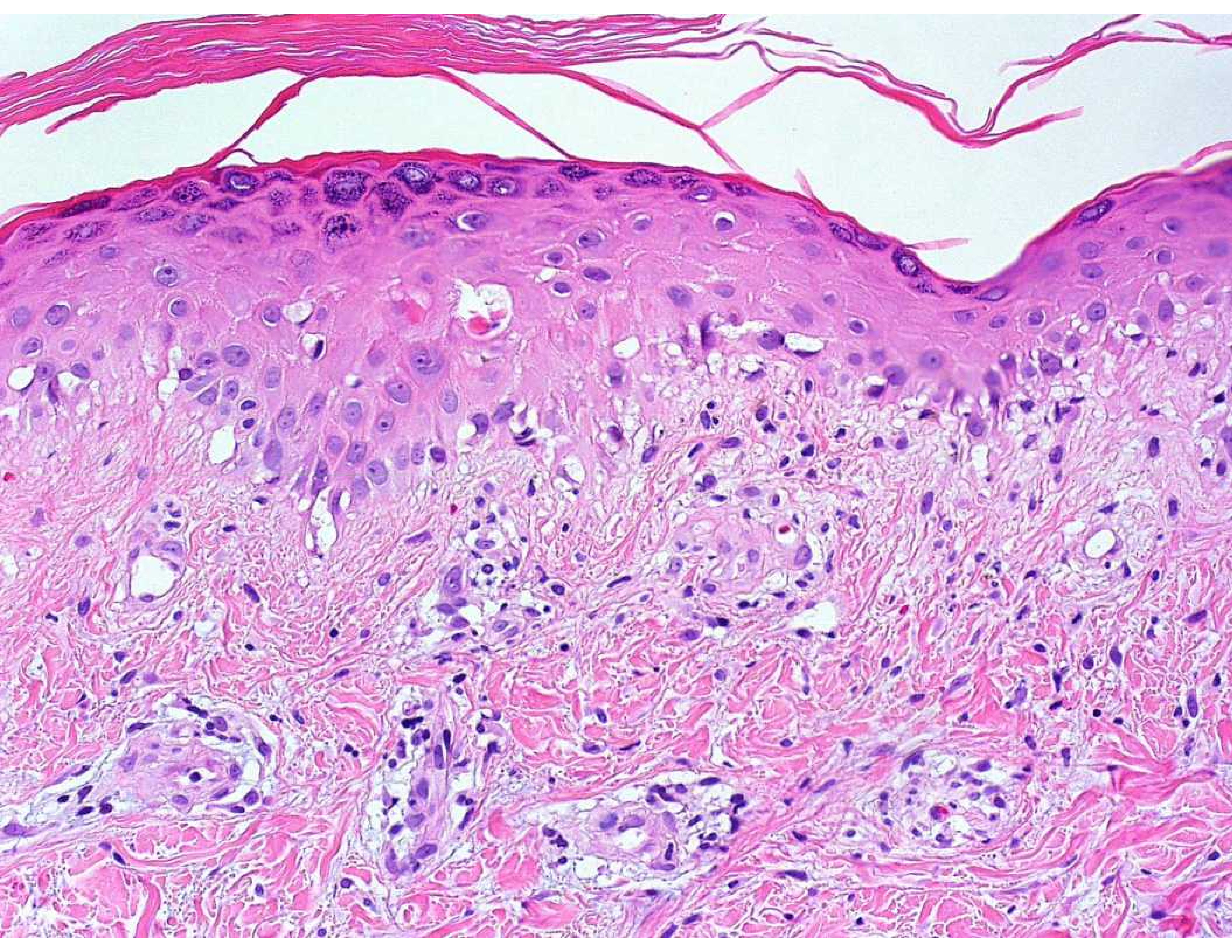
Dermatomyositis

- Clinical
  - Systemic disease with muscle weakness (some patients have only cutaneous disease)
  - Heliotrope periorbital discoloration
  - Violaceous rash on face and neck
  - Periungual erythema
  - Gottron's papules on hands



Dermatomyositis

- Microscopic
  - Basal vacuolization
  - Superficial perivascular mononuclear cell infiltrate, usually mild
  - Increased dermal mucin
- Differential diagnosis
  - Lupus erythematosus

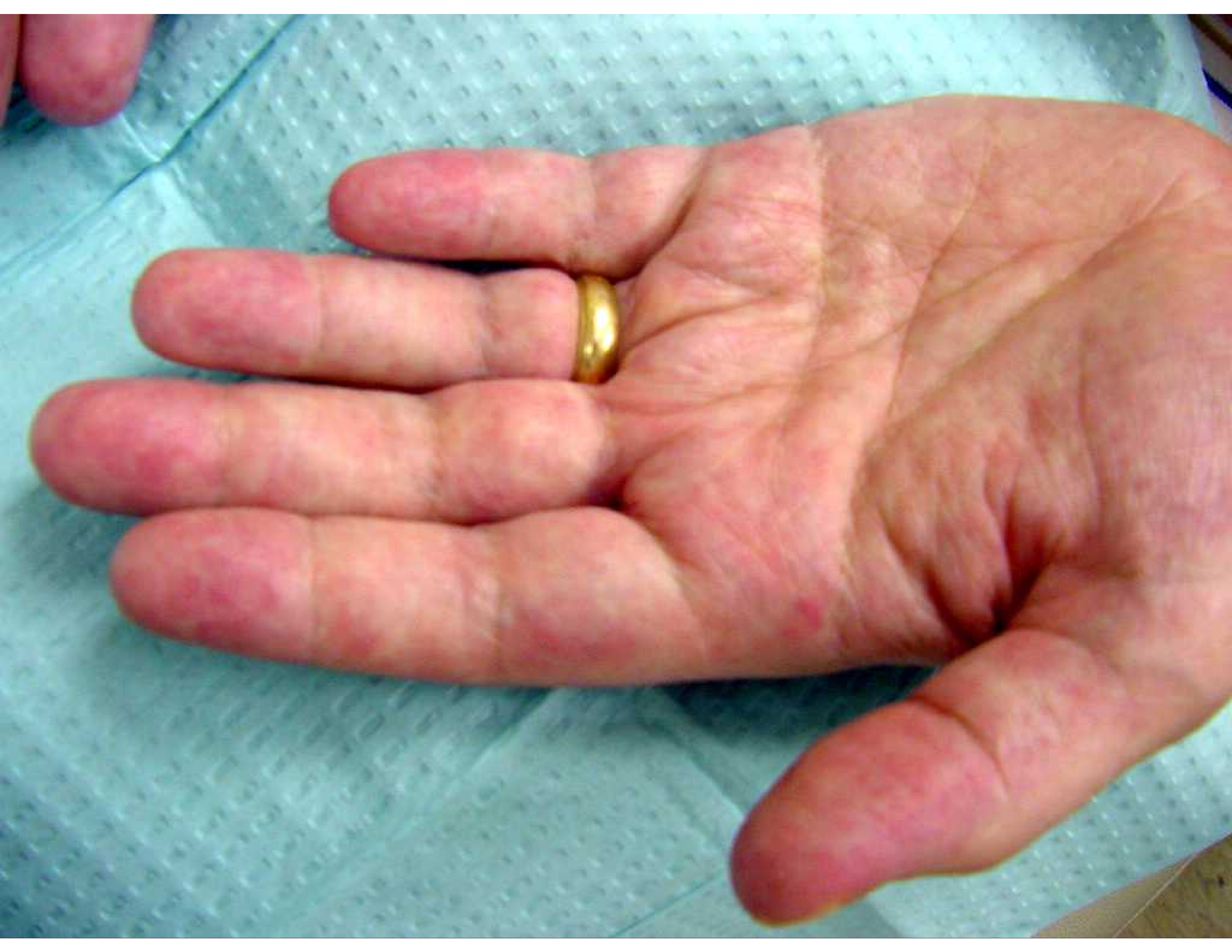


Practical Tips LE/DM

- Eosinophils absent
- Mucin helpful but non-specific
- LE may have superficial or superficial and deep perivascular patterns
- ‘AK’ clue: reactive atypia in keratinocytes
- DM generally does not have deep infiltrate
- DM cannot be distinguished from LE
- Descriptive Dx: interface dermatitis
  - Note: The ddx would include connective tissue disease such as lupus erythematosus.

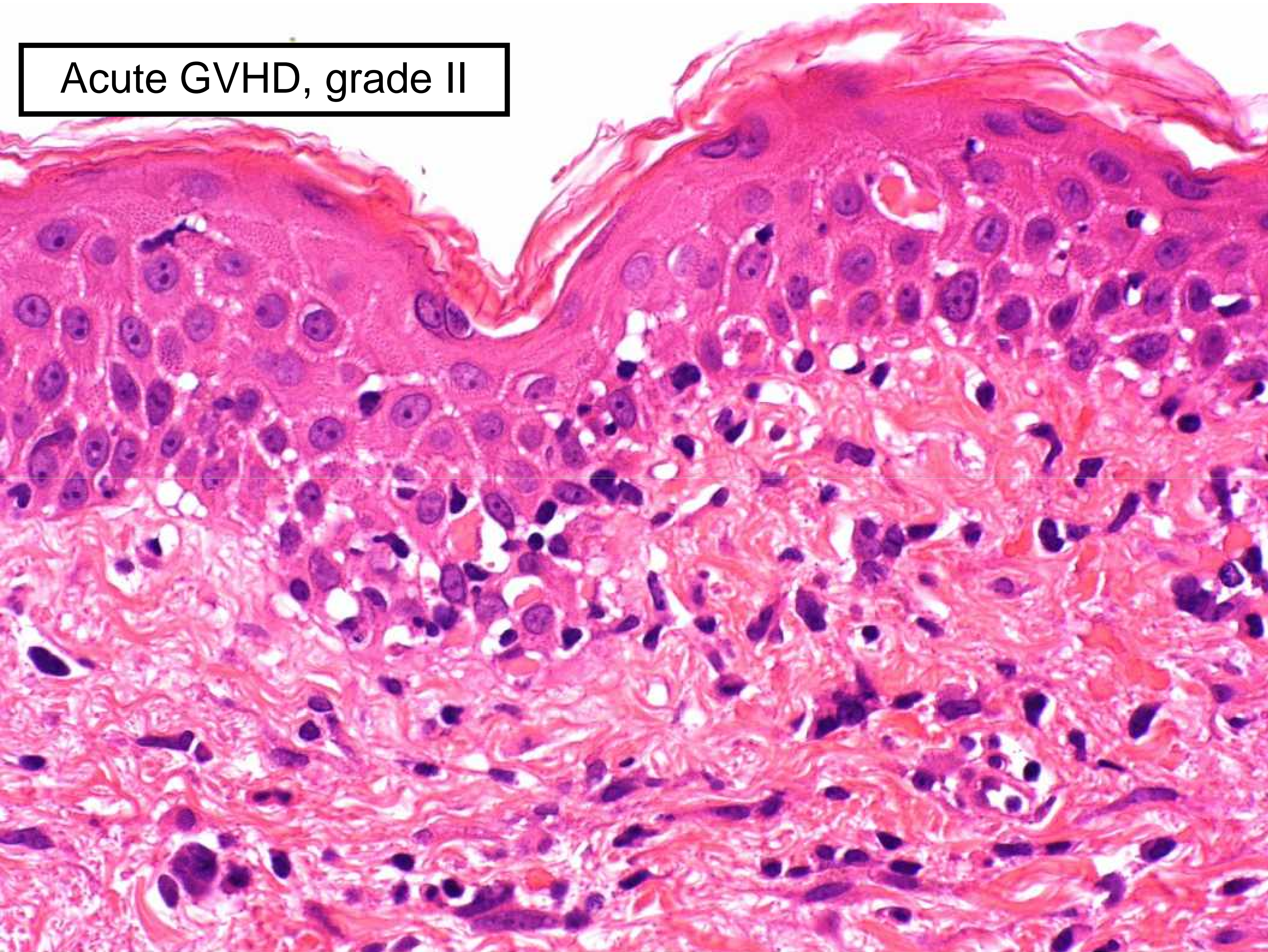
Graft vs. Host Disease

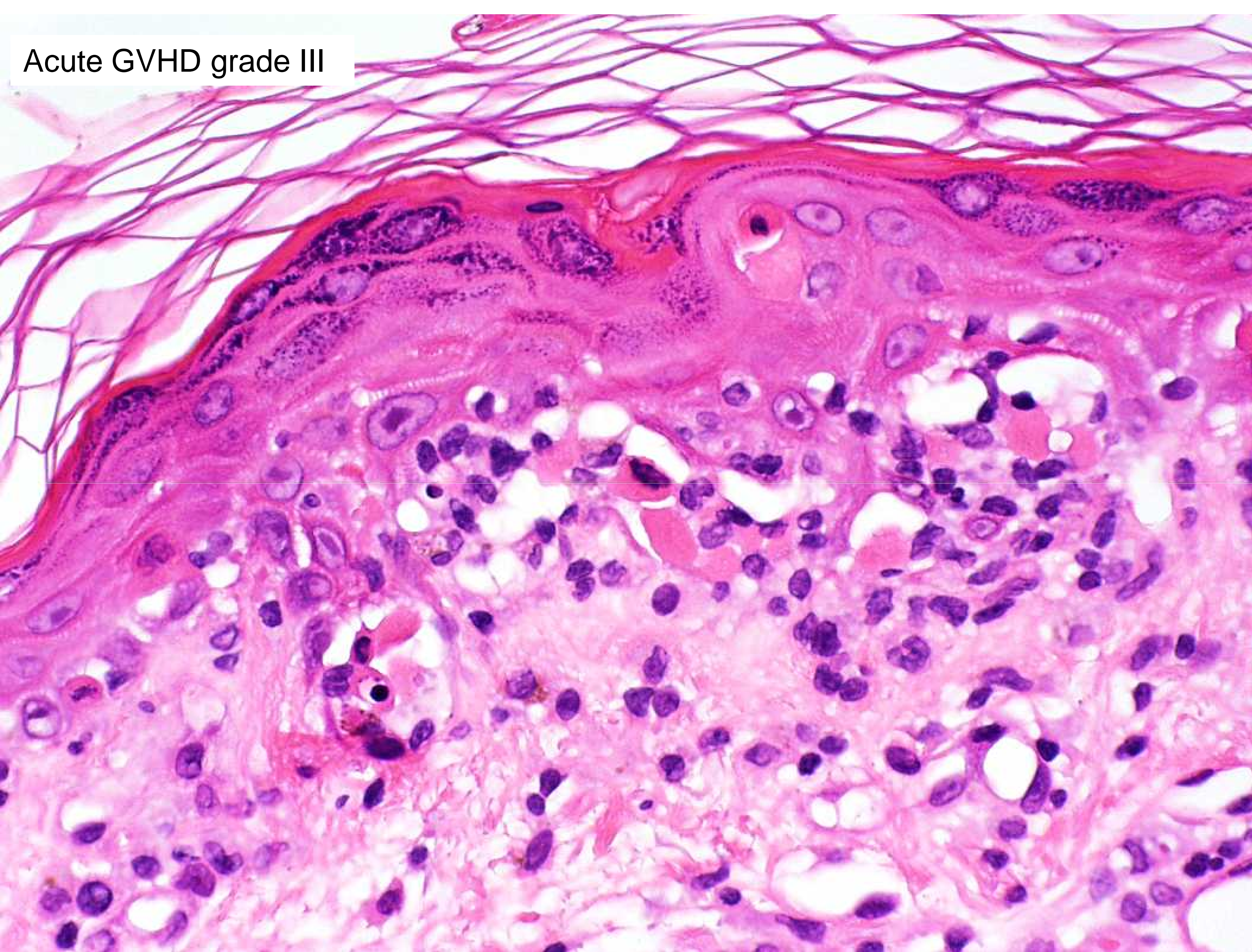
- Clinical
  - Acute GVHD
    - Usually 2-4 weeks after bone marrow transplant
    - Late onset with lymphocyte reinfusion
    - Rarely solid organ transplants
    - Macular erythema on trunk, neck, hands, and feet
    - May form blisters
    - Systemic symptoms (e.g. diarrhea)
  - Chronic GVHD
    - Months to years after bone marrow transplant
    - Lichenoid: violaceous papules on extremities, palms, and soles
    - Sclerodermoid: presents as dermal sclerosis

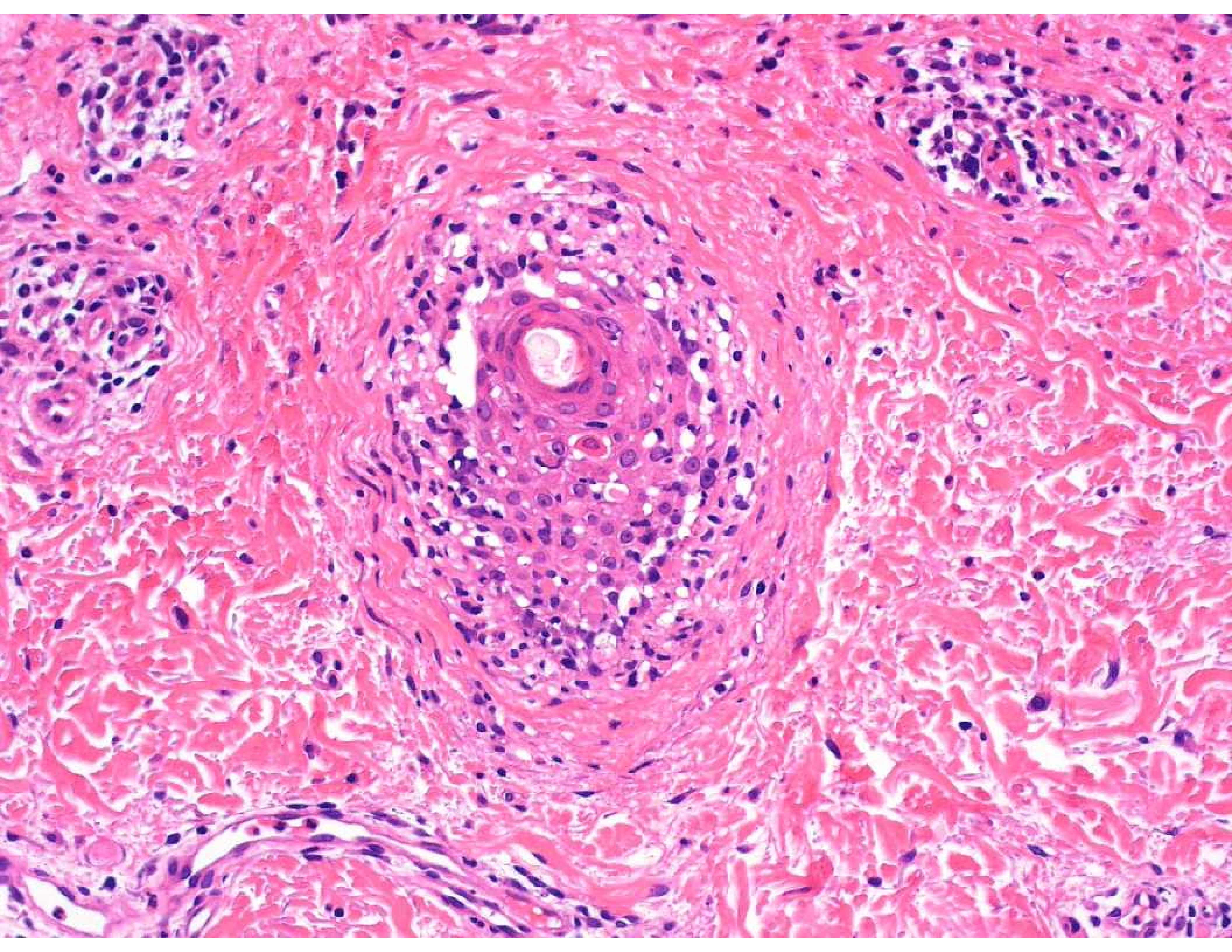


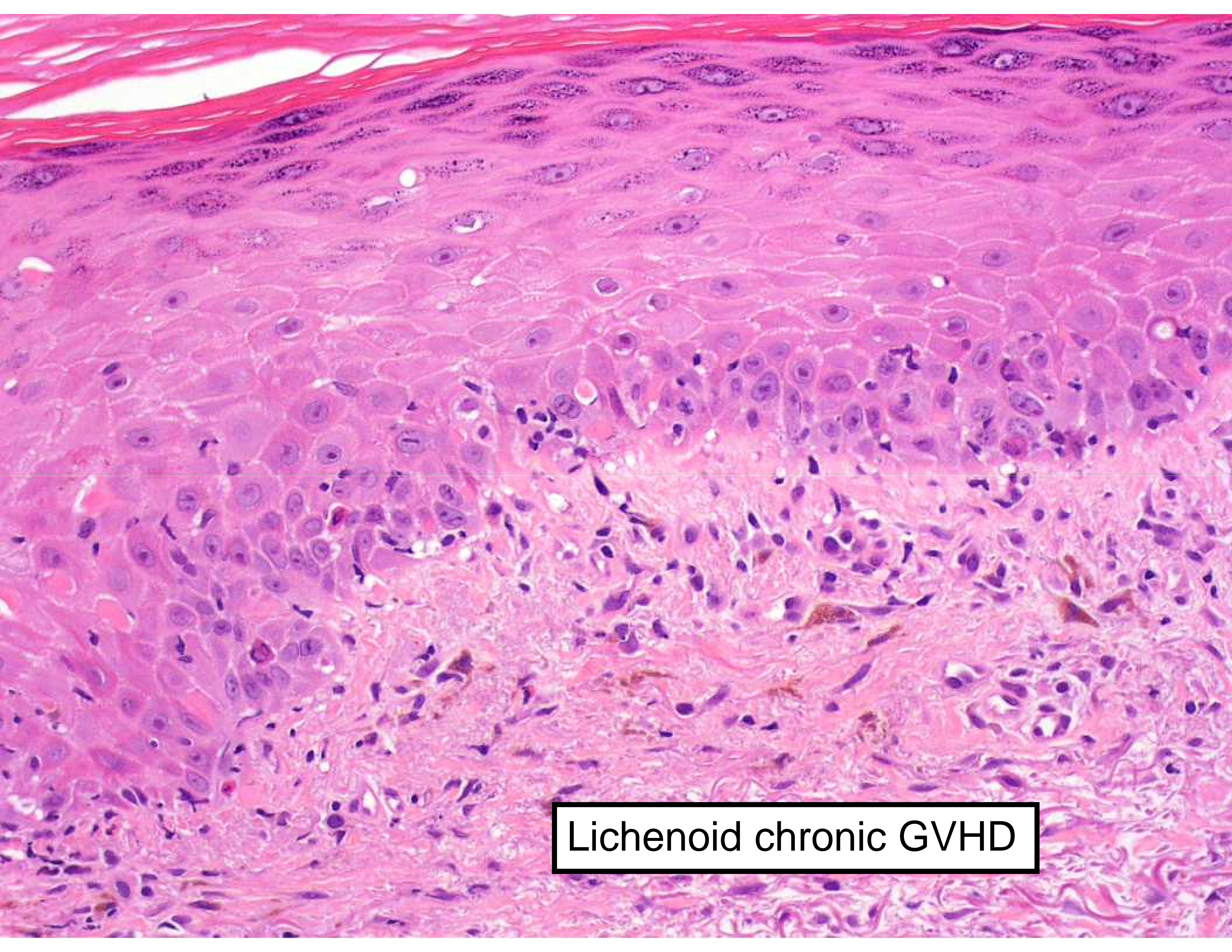
Graft vs. Host Disease

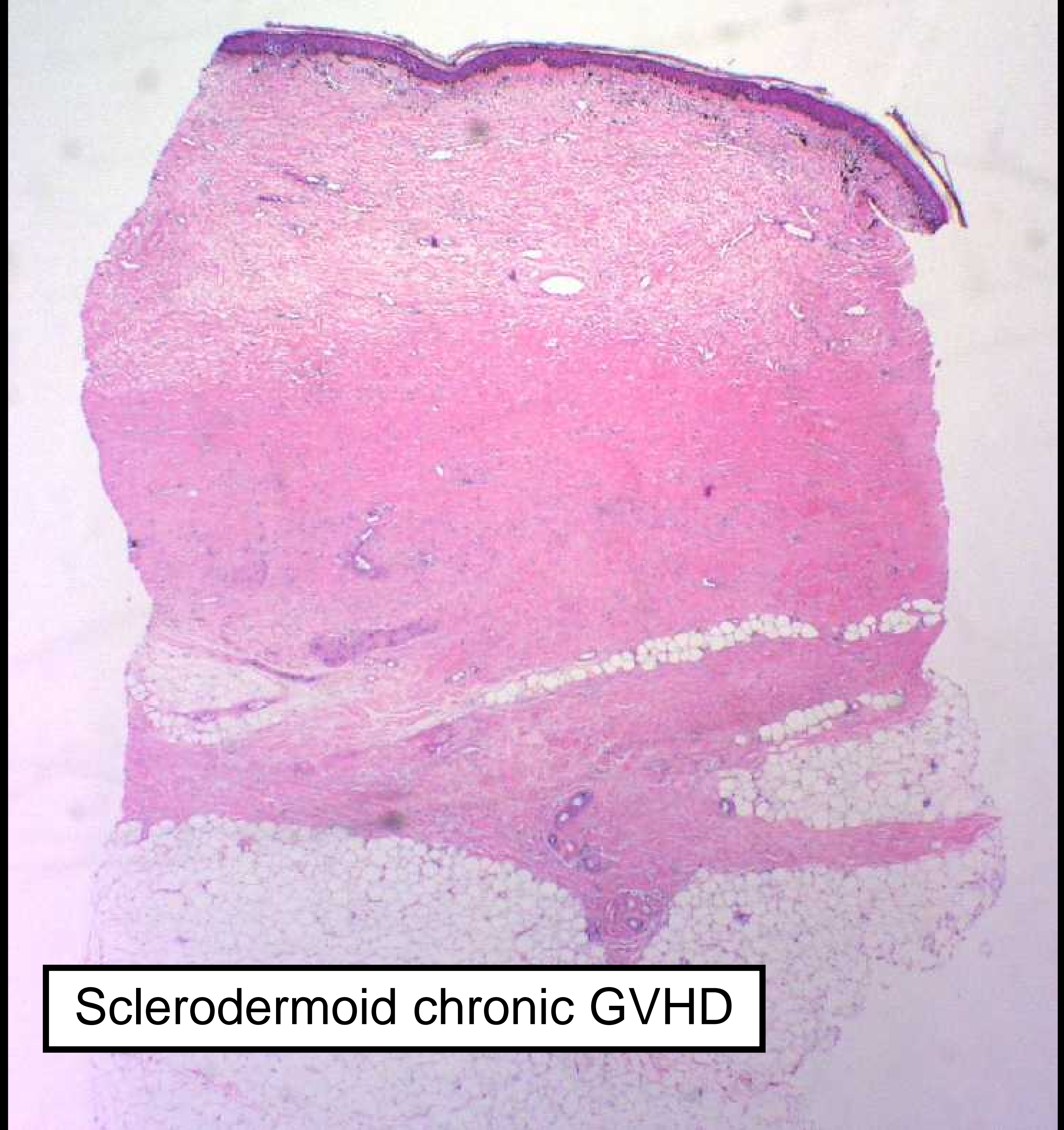
- Microscopic
  - Acute GVHD
    - Grade 0 : normal epidermis
    - Grade 1: Basal vacuolization, mild superficial perivascular lymphocytic infiltrate
    - Grade 2: Same as Grade 1 changes with dyskeratotic keratinocytes, satellite cell necrosis
    - Grade 3: Same as grade 2 but with cleft formation between dermis and epidermis
    - Grade 4: Same as Grade 3 but with complete separation of epidermis from dermis


Acute GVHD, grade II


Acute GVHD grade III




Lichenoid chronic GVHD


Sclerodermoid chronic GVHD

Practical Tips: Acute GVHD

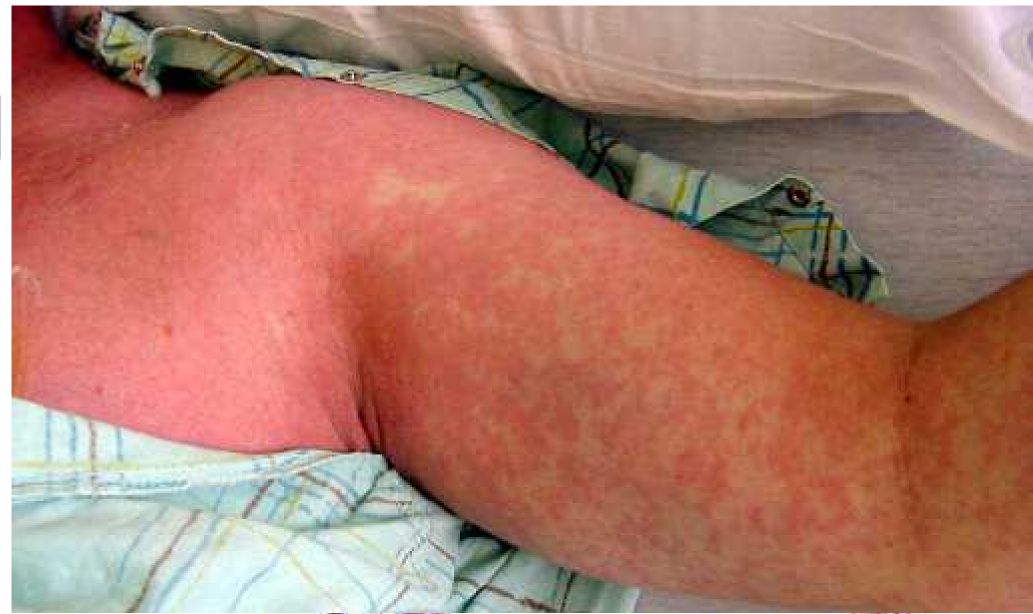
- Rare to see GVHD earlier than 14 days
- May see late onset acute GVHD in some settings
- Eosinophils may be seen in GVHD
- Dx of drug eruption should be approached with caution
- Multiple levels may be needed

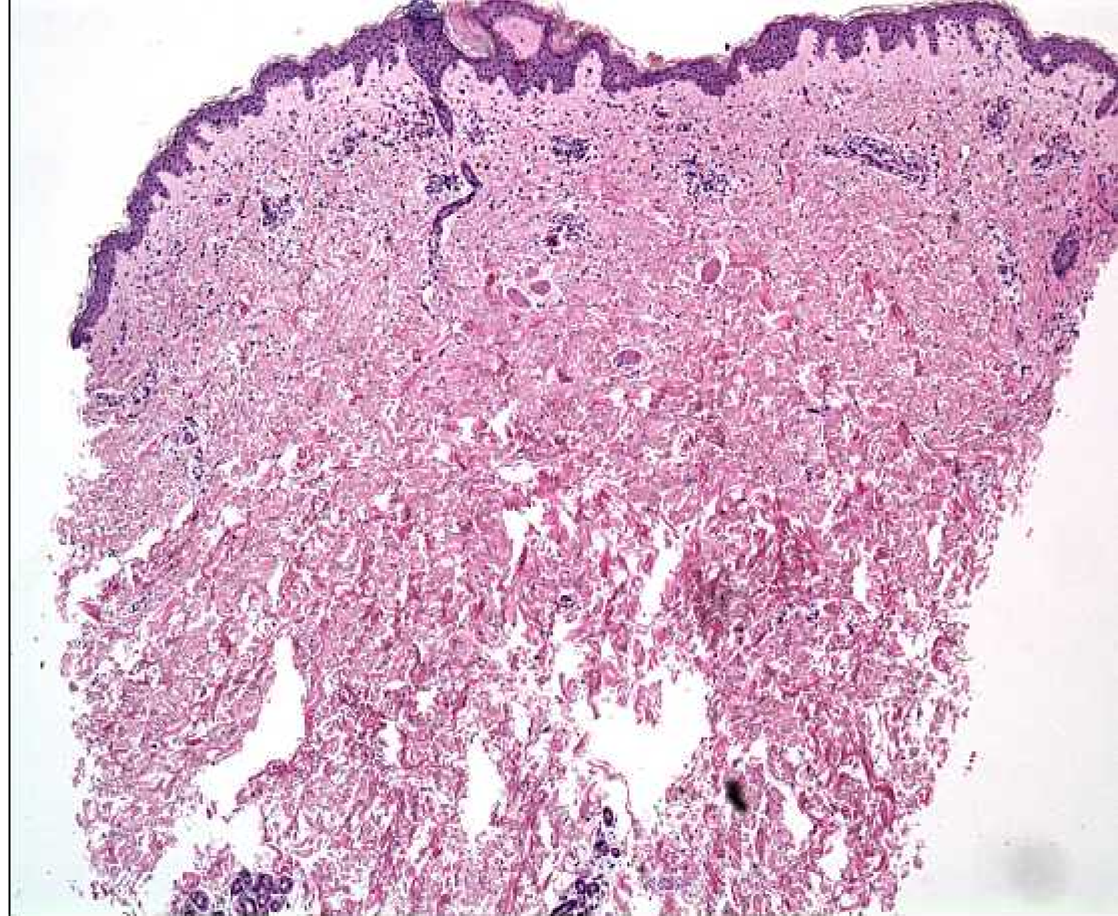
Dermal Hypersensitivity Reaction

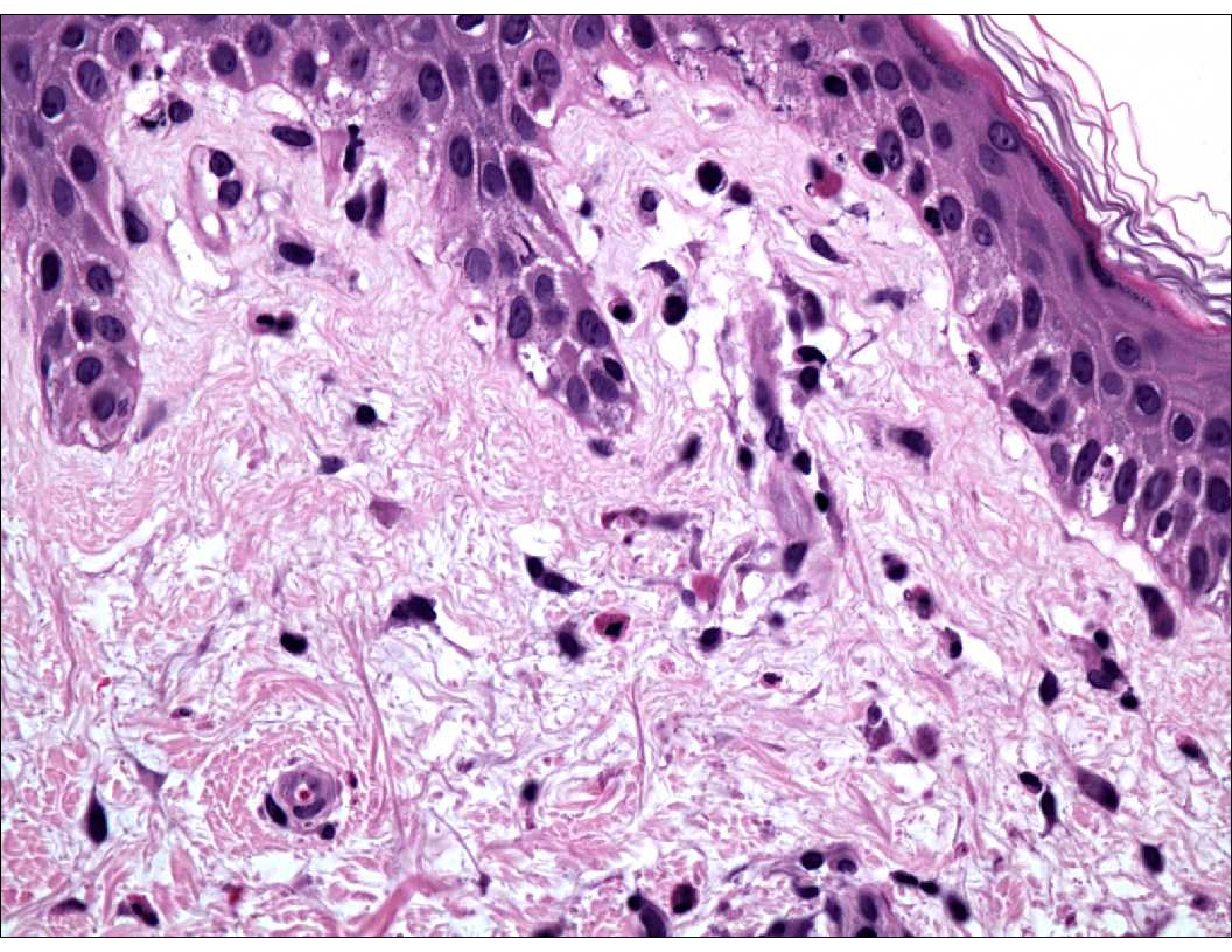
- Clinical: Variable
  - Drug eruption
  - Urticaria
  - Arthropod bite reaction
- Microscopic
  - Superficial or superficial and deep perivascular infiltrate
  - Lymphocytes and some eosinophils, variable neutrophils

Morbilliform drug eruption

- Clinical
  - Blanchable, Symmetric, widespread macular or papular eruption
- Microscopic
  - Superficial perivascular infiltrate of lymphocytes and eosinophils
  - Mild vacuolar interface change sometimes present

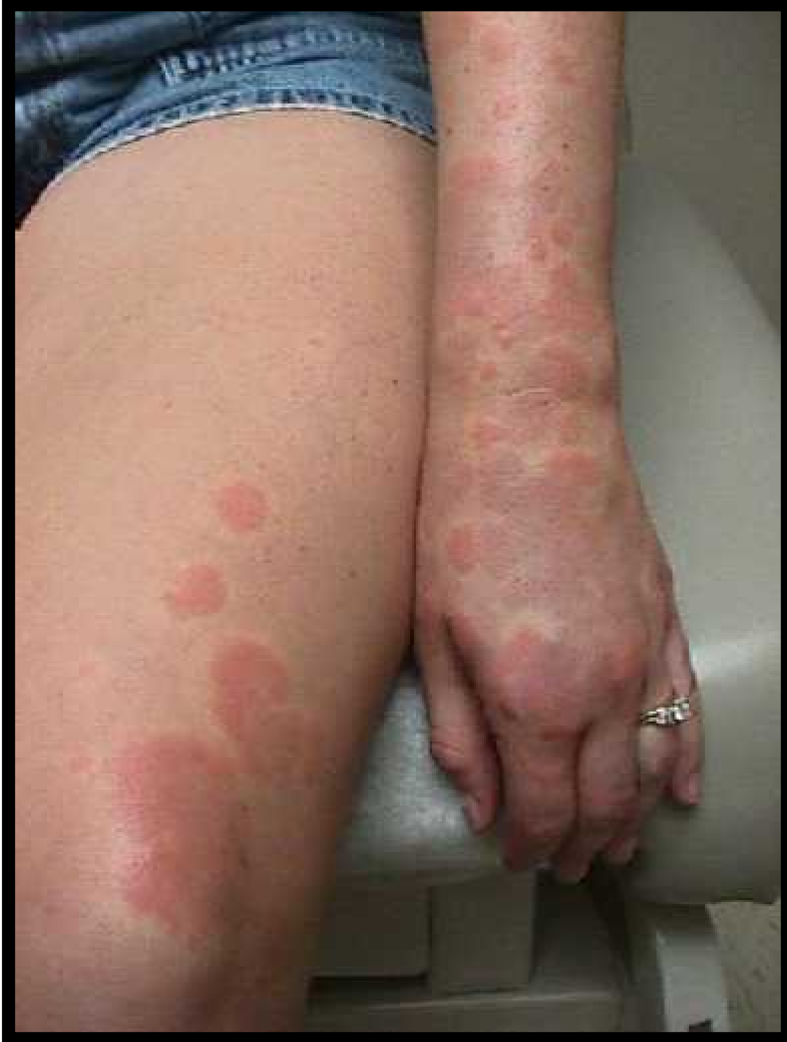


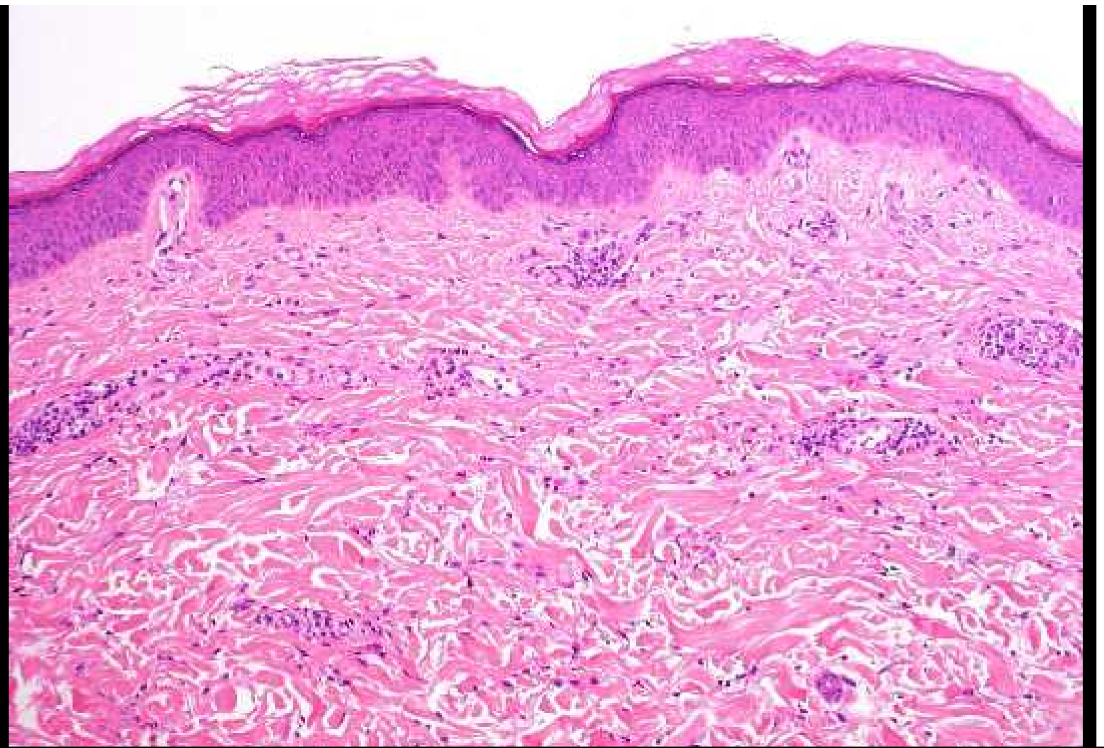


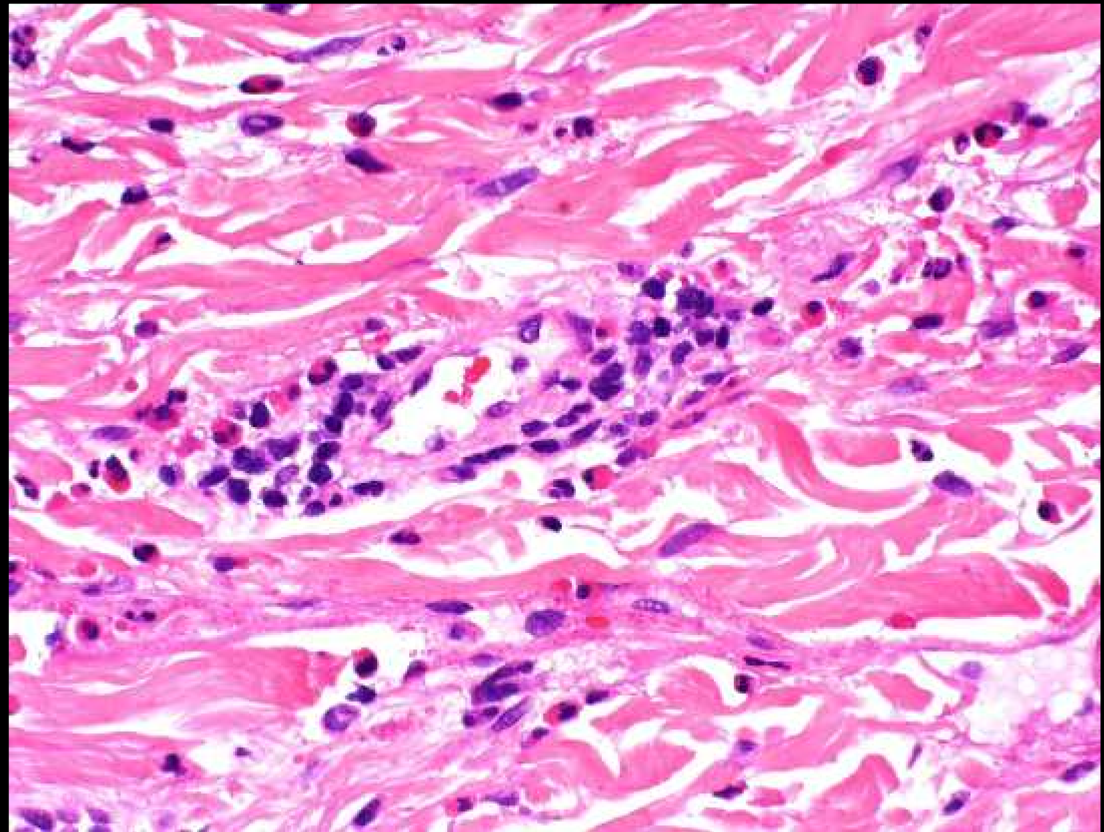


Urticaria

- Clinical
  - Transient edematous pruritic plaques (hives)
  - Typically resolve in 24 hours
- Microscopic
  - Normal epidermis
  - Dermal edema
  - Superficial perivascular infiltrate of lymphocytes and eosinophils and sometimes a few neutrophils
  - Sometimes a deeper component present

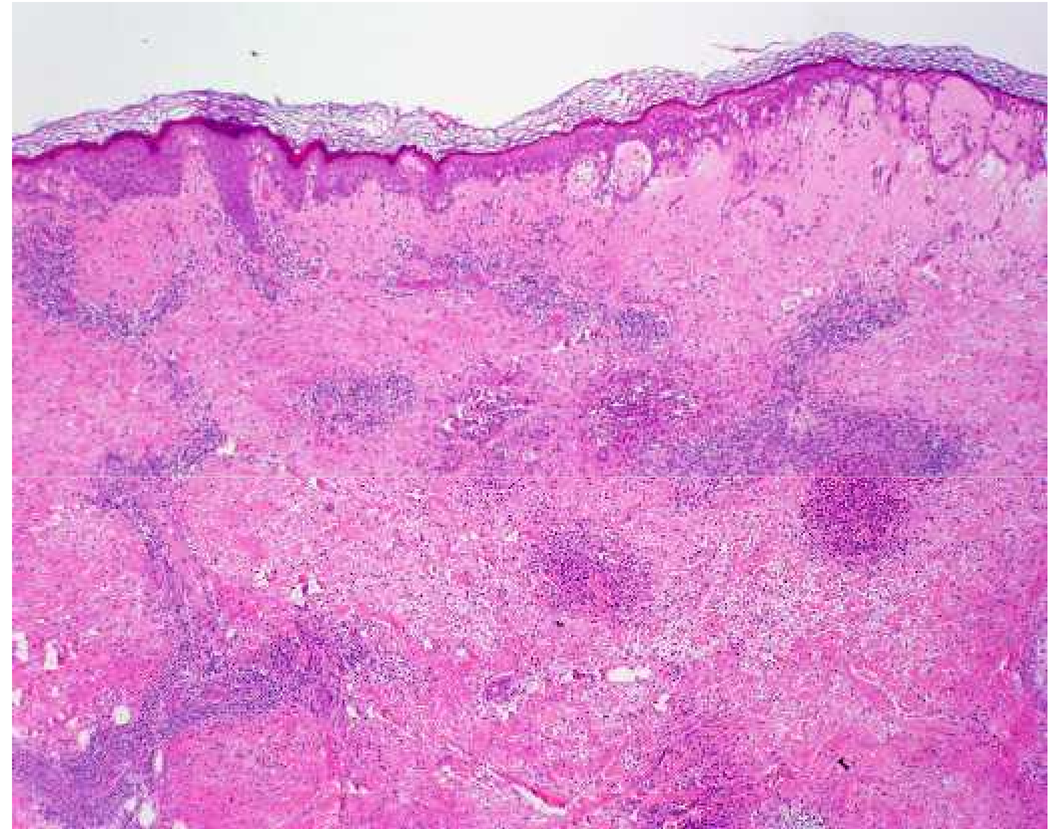






Arthropod bite reaction

- Clinical
  - Solitary or grouped papules
- Microscopic
  - Superficial and deep infiltrate
  - Usually dense infiltrate
  - Lymphocytes and eosinophils

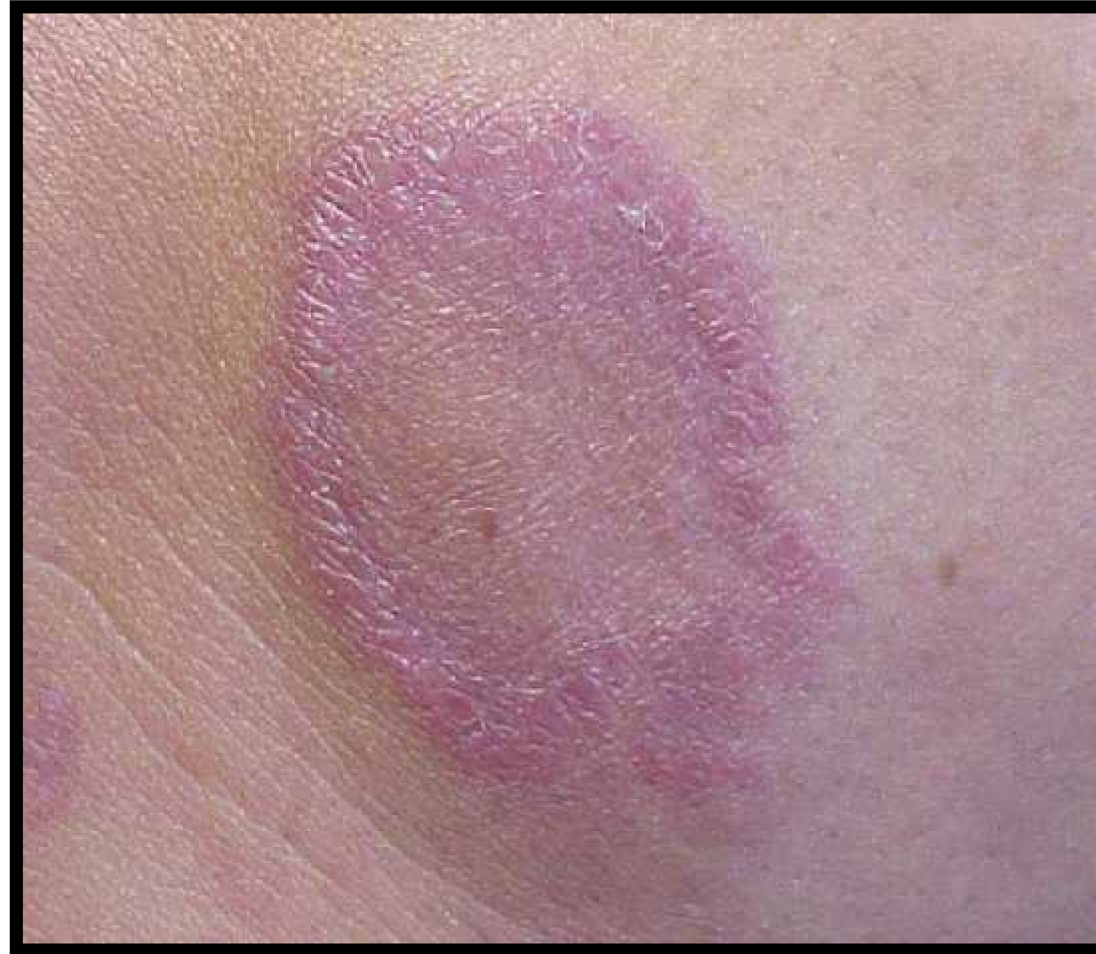


Dermal hypersensitivity reaction

- Practical Tips:
  - Descriptive dx: Dermal hypersensitivity reaction, see note
  - Note: The histologic features are consistent with a dermal hypersensitivity reaction such as a drug eruption. Clinicopathologic correlation is recommended.
  - Urticaria and drug eruption histologically indistinguishable but clinically different
  - If infiltrate is dense, consider arthropod bite reaction

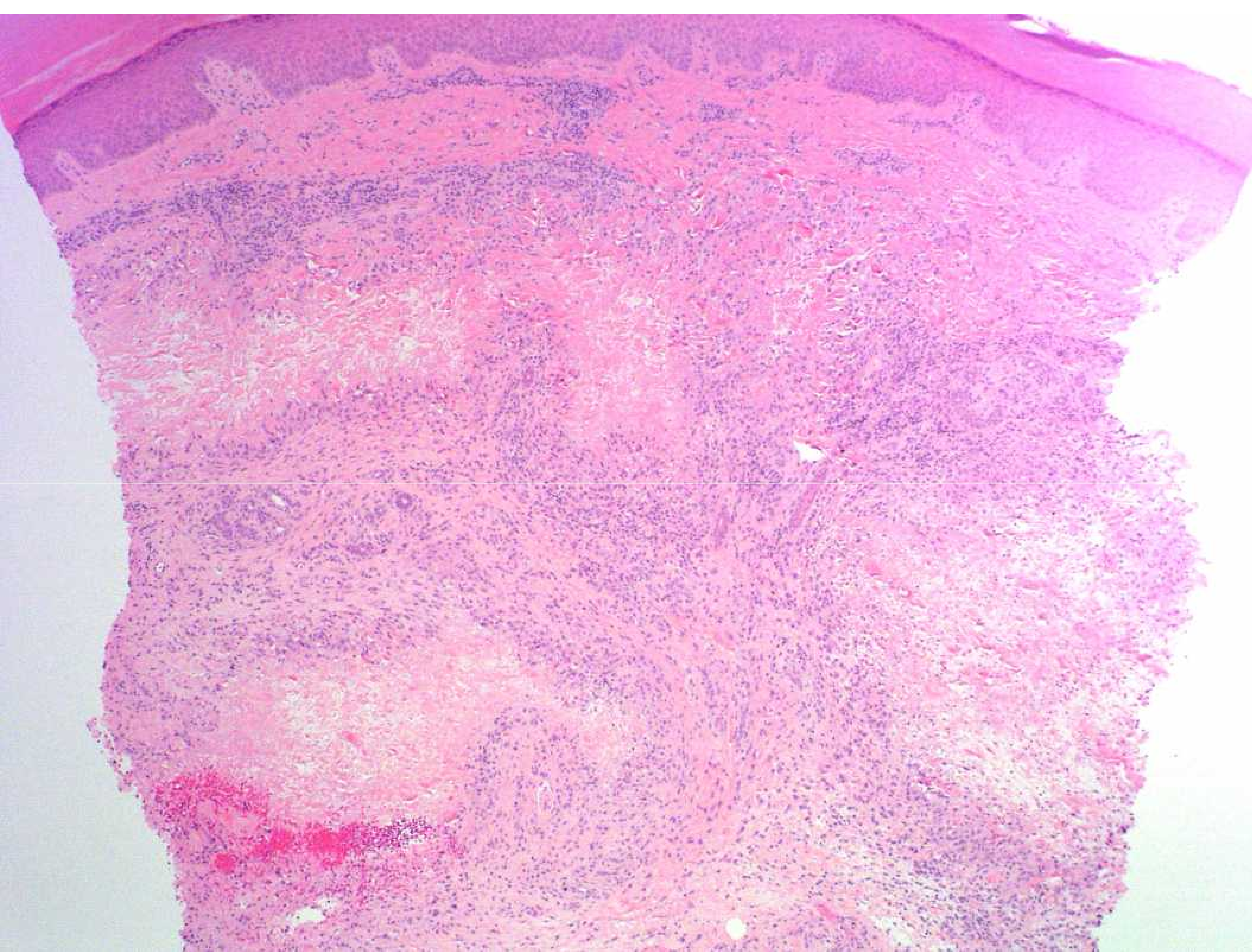
Granuloma Annulare

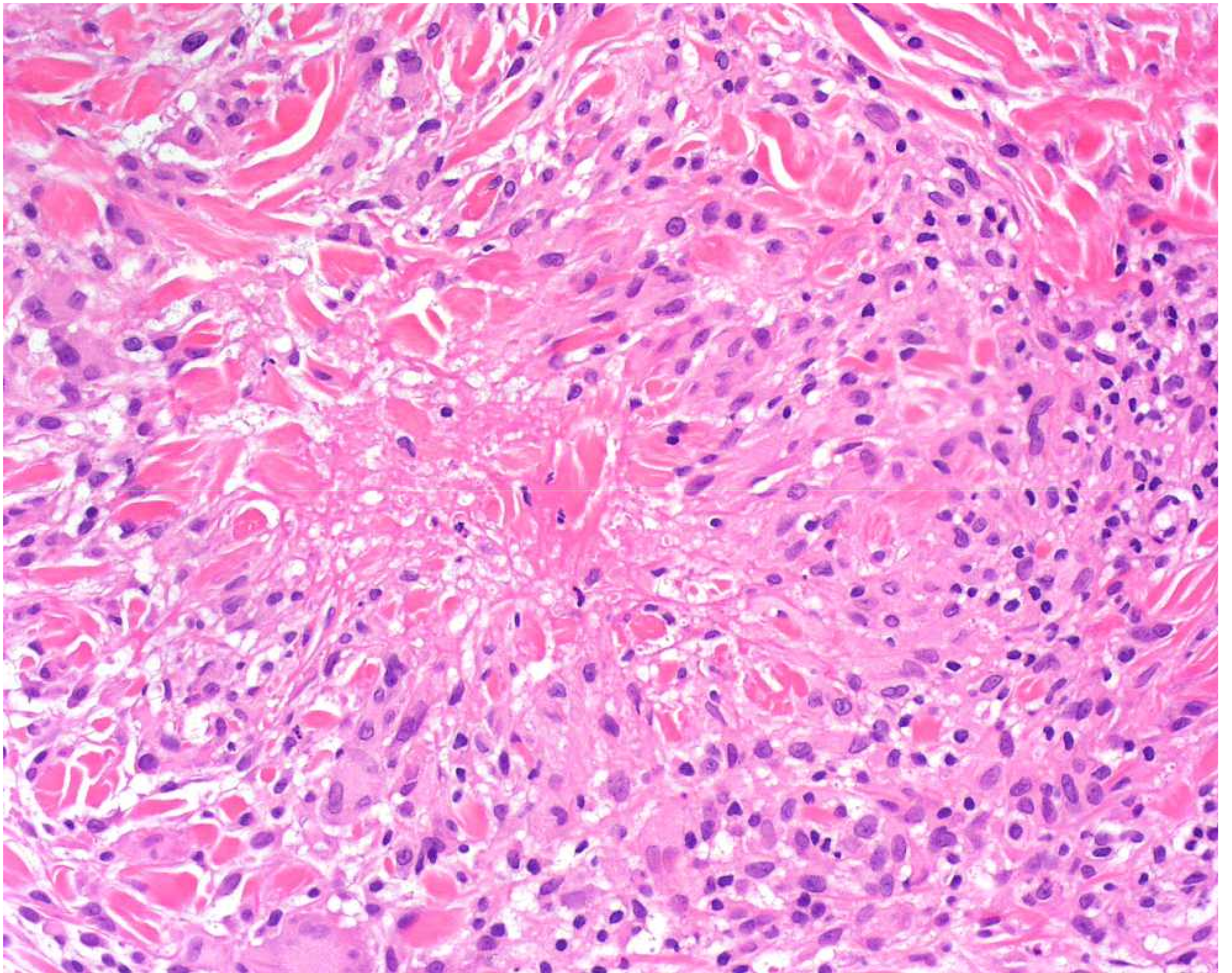
- Clinical
  - Asymptomatic papules with annular configuration
  - Usually on extremities

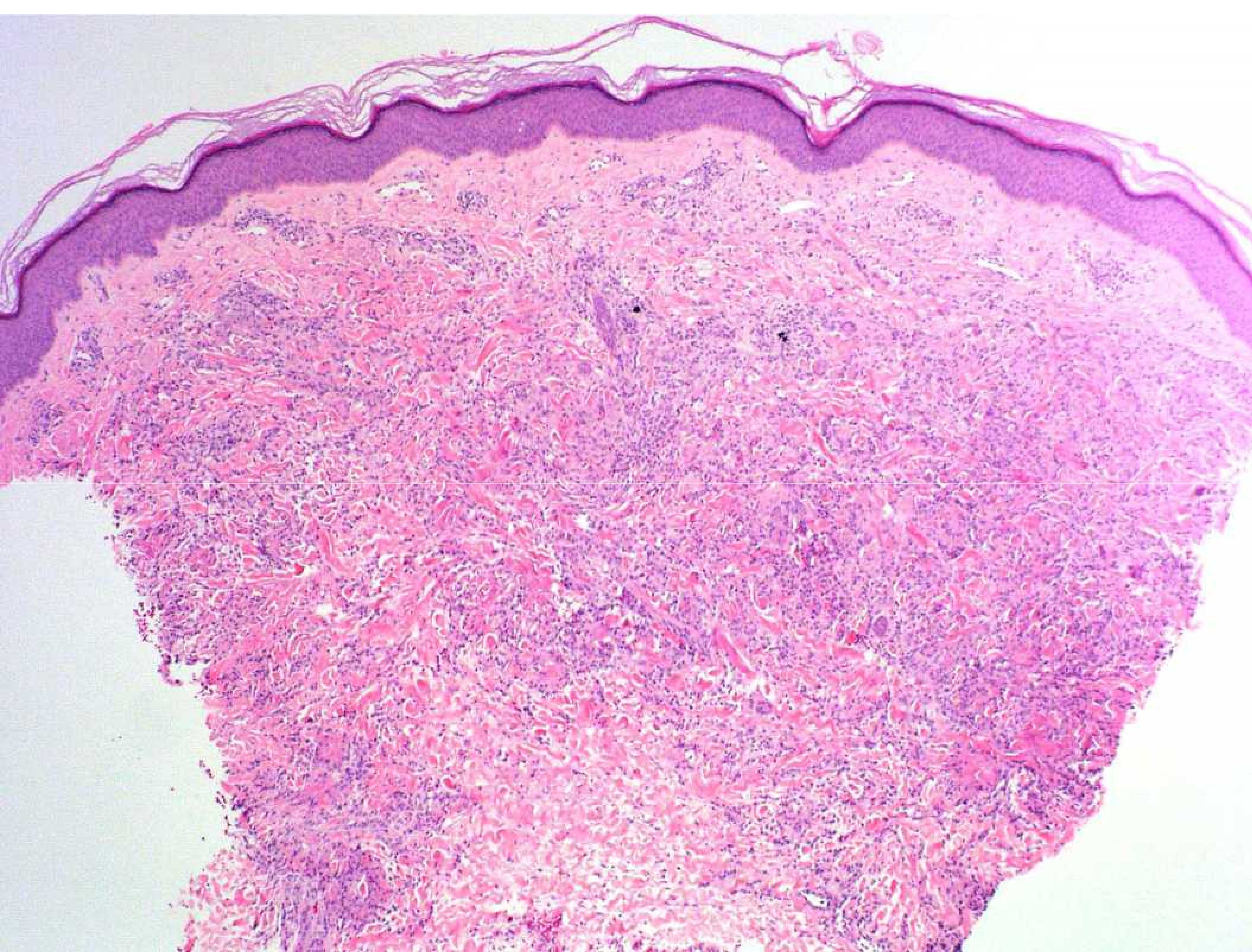


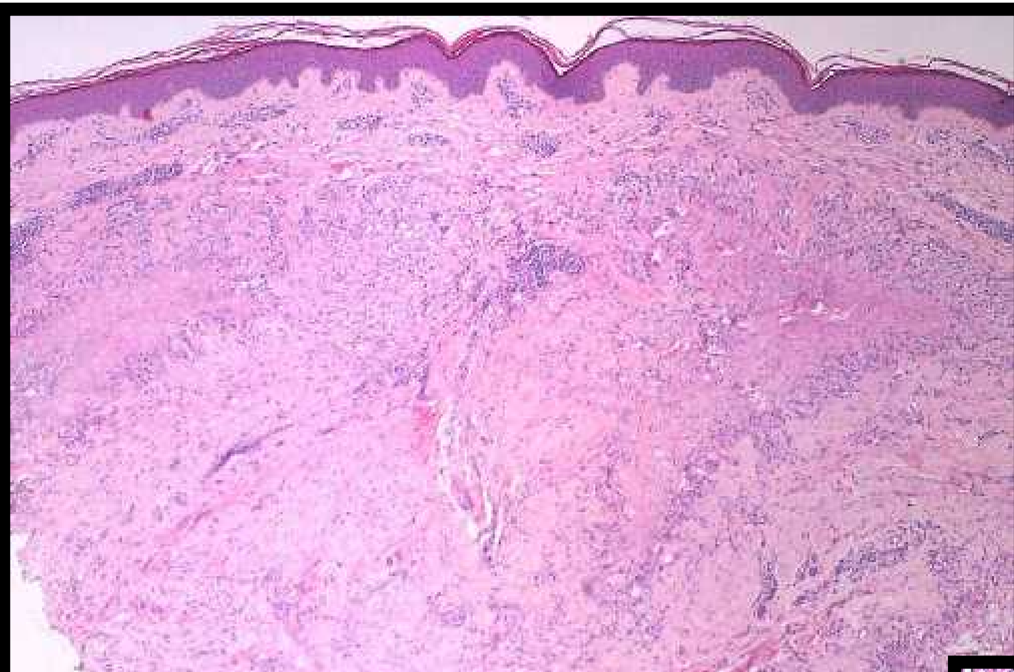
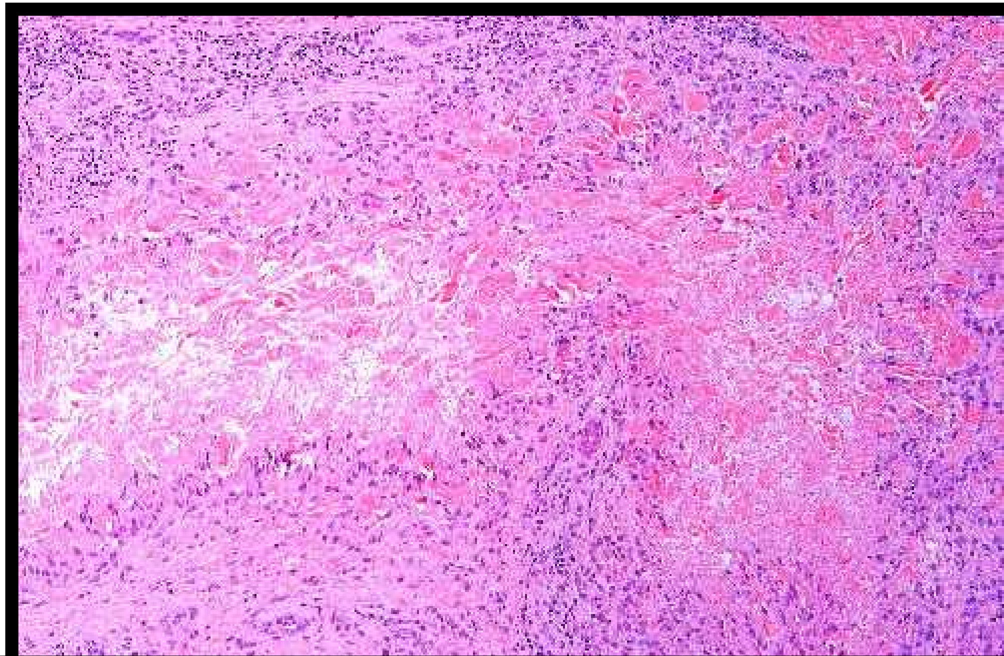
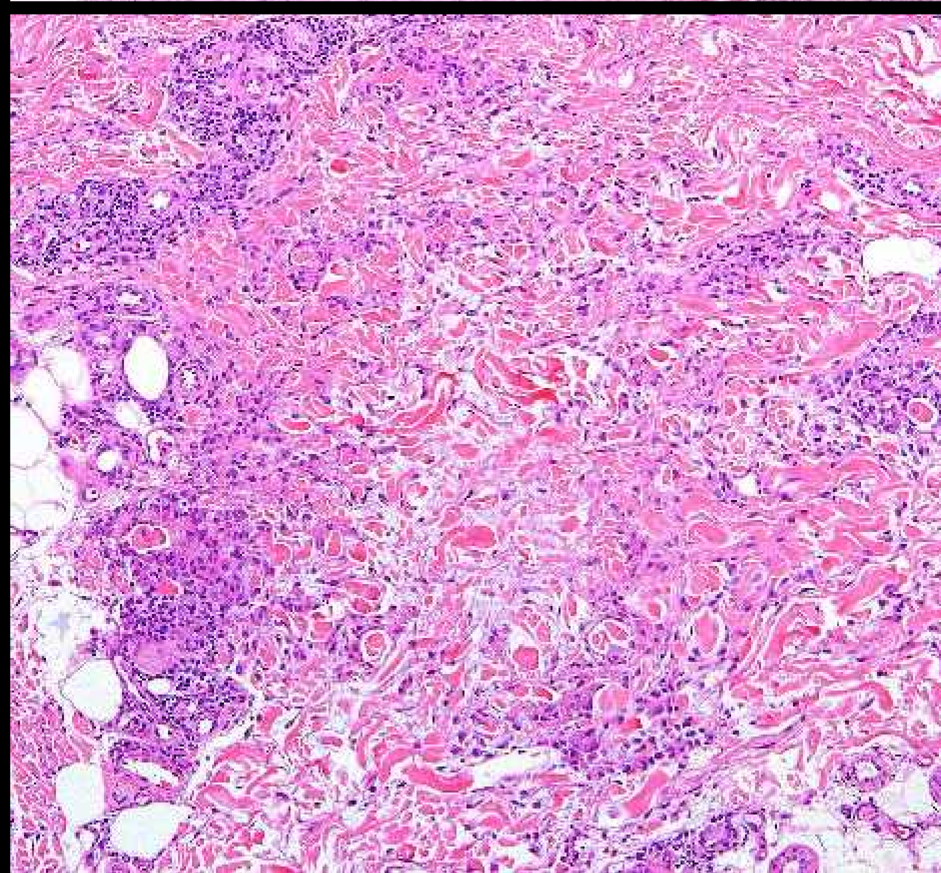
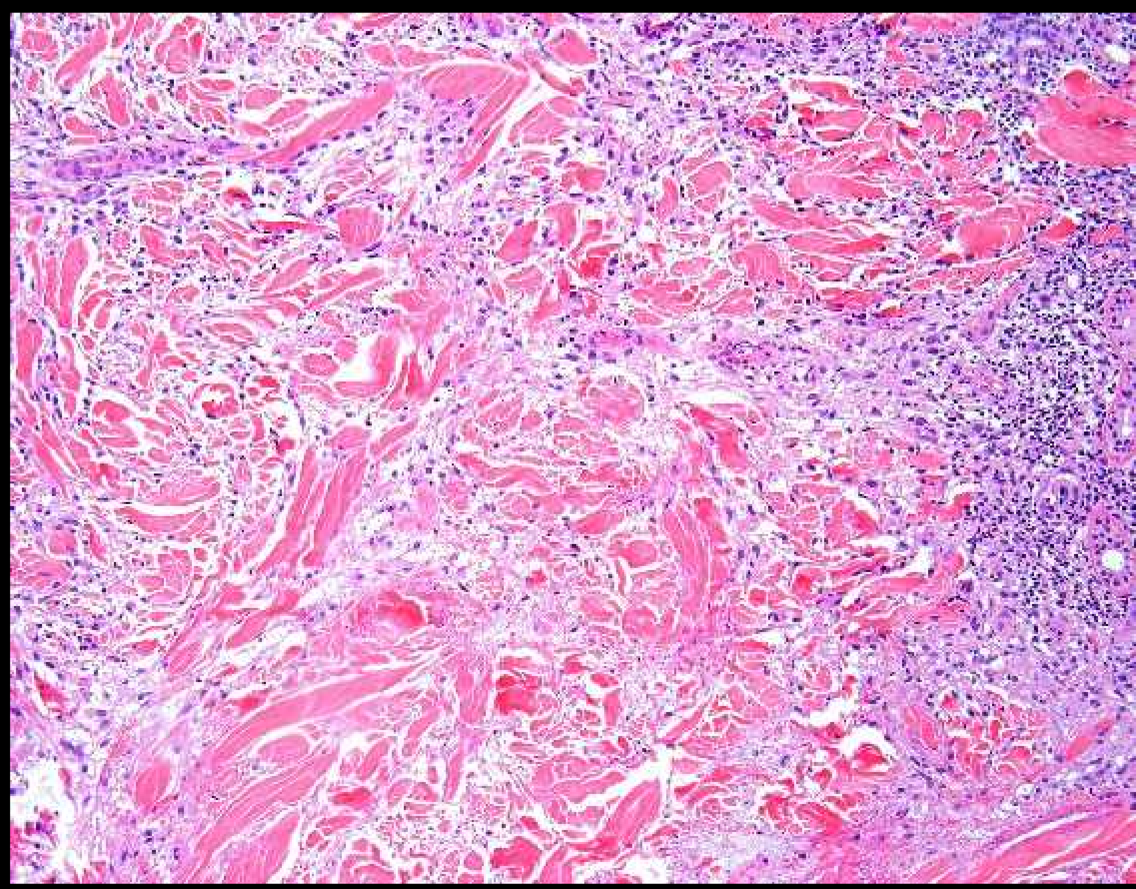
Granuloma Annulare

- Microscopic
  - Most commonly involves upper and mid reticular dermis
  - Central zone of altered collagen fibers with associated dermal mucin surrounded by a palisade of histiocytes with some giant cells
  - Interstitial pattern common
  - Perivascular lymphocytic infiltrate with variable numbers of eosinophils
  - Neutrophils may be prominent early
  - Rarely may resemble sarcoidal granulomas
  - Rarely may be confined to the subcutis







Granuloma Annulare

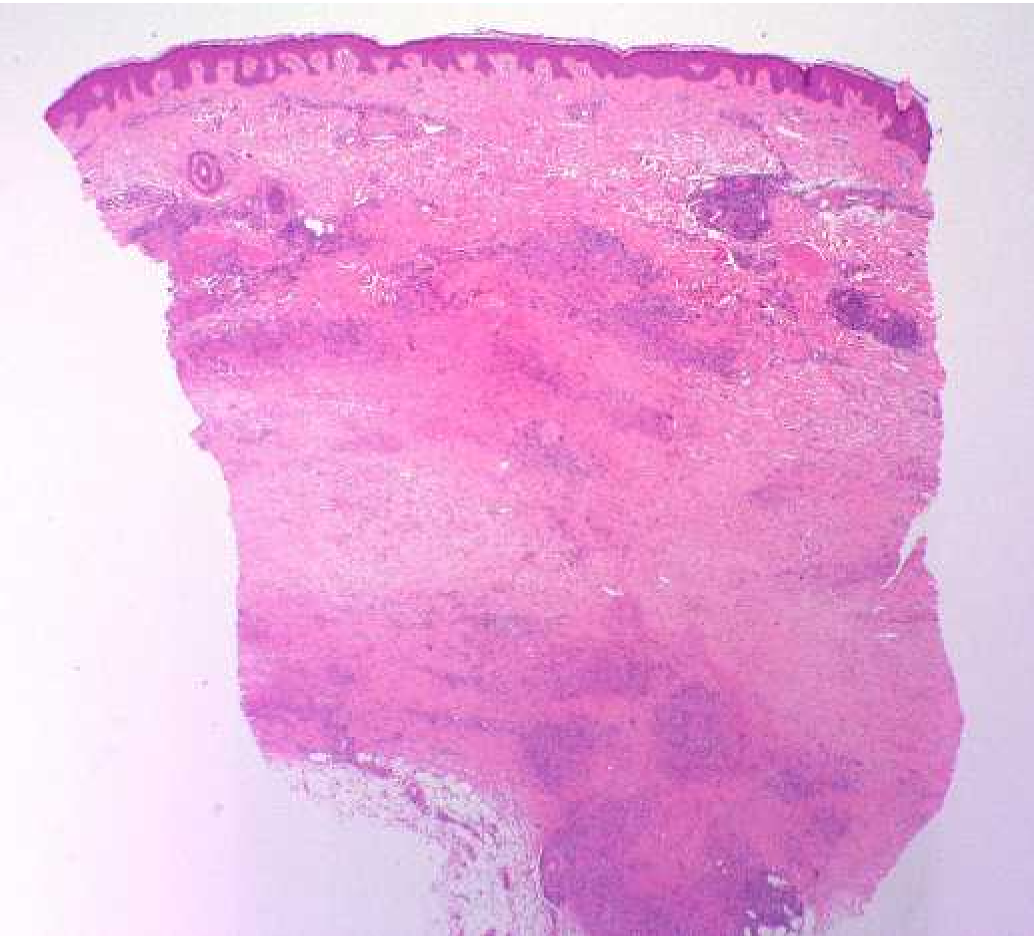
- Differential Diagnosis
  - *Necrobiosis lipoidica*
  - *Rheumatoid nodule*
  - Granulomatous drug reaction
  - Sarcoidosis
  - Dermatofibroma

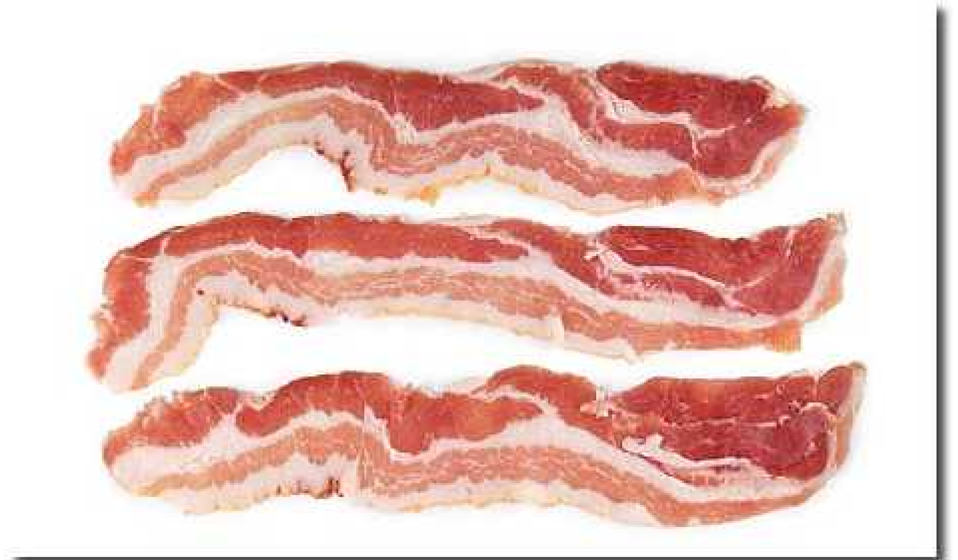
Practical Tips: Granuloma Annulare

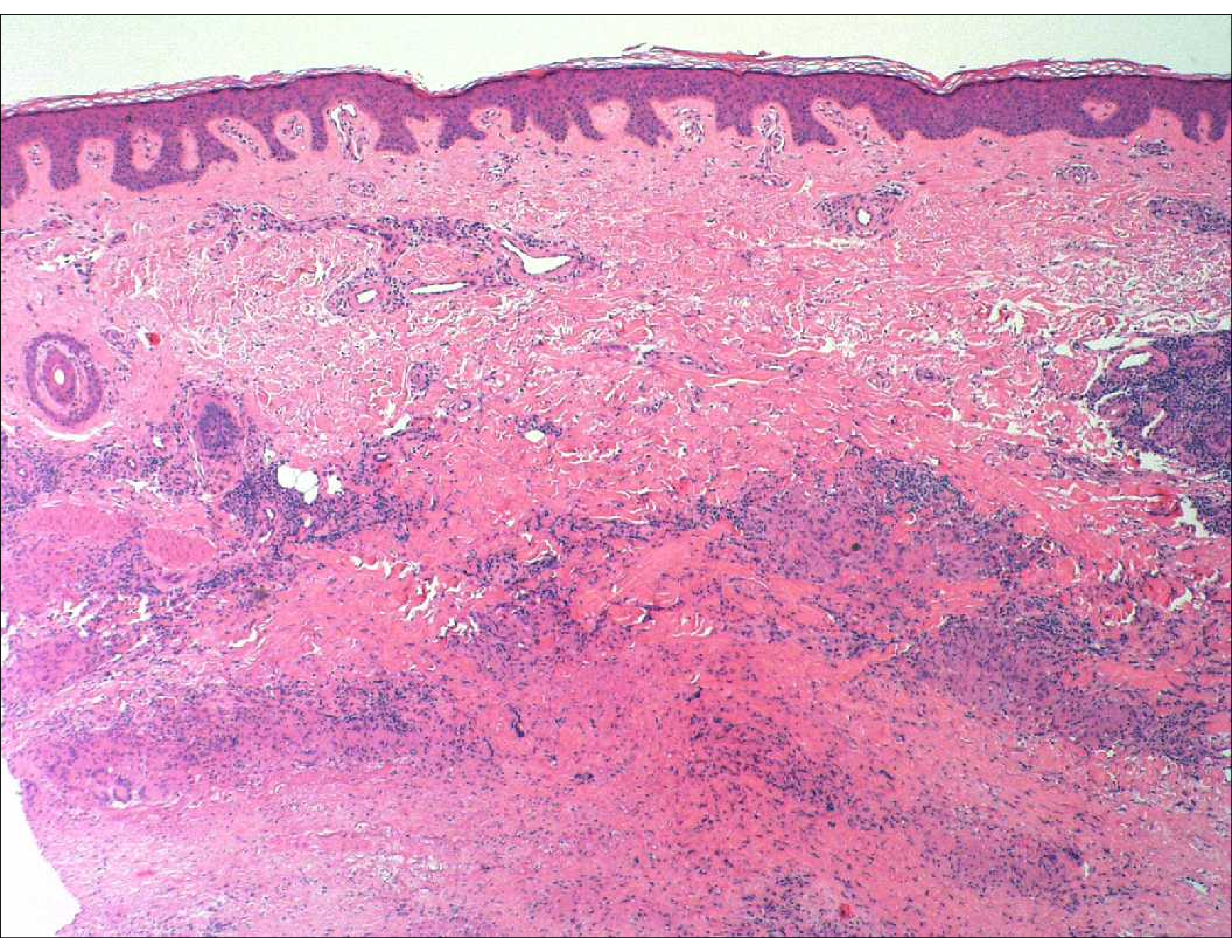
- Palisade not always well developed
- Low power examination
- Altered collagen looks more ‘red’
- Interstitial pattern common

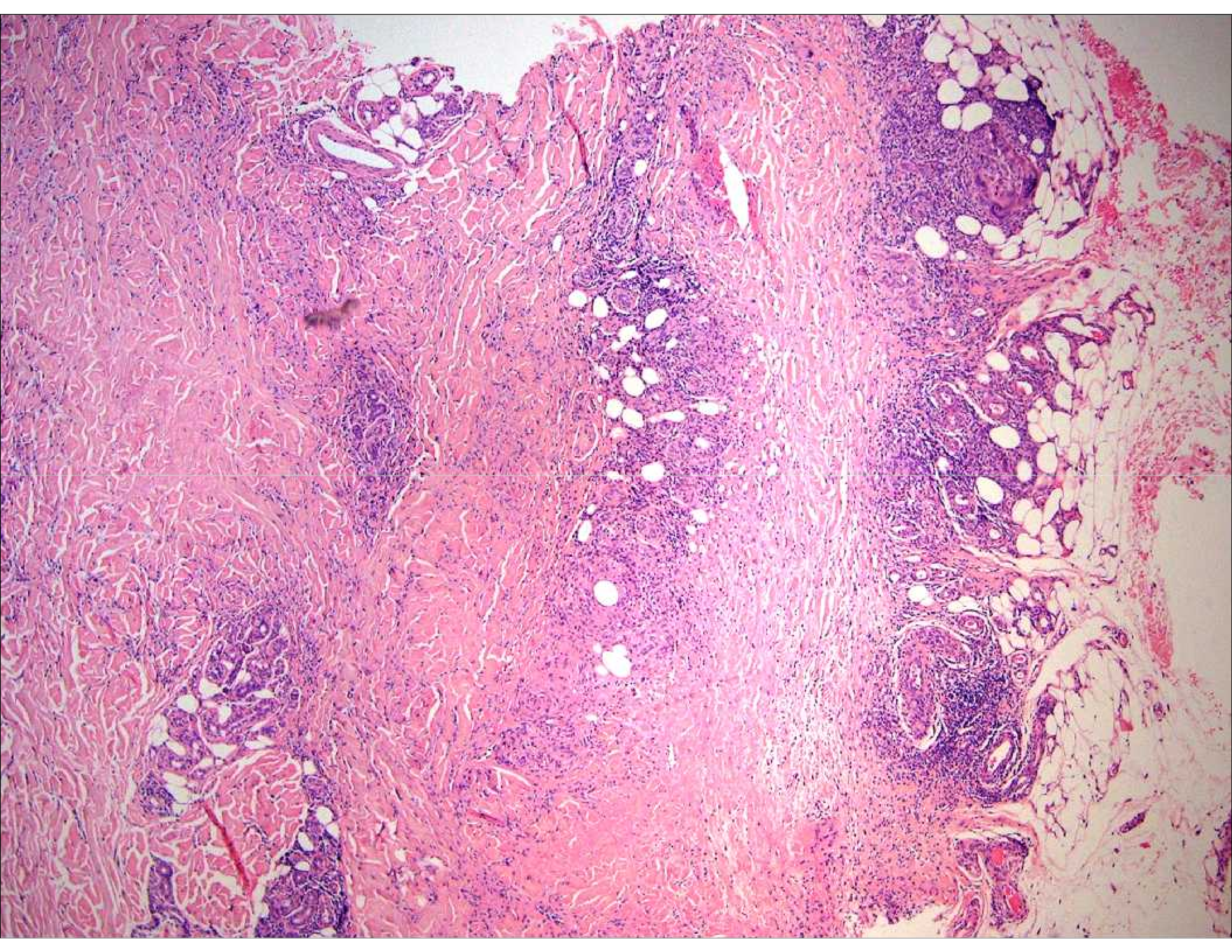
Necrobiosis Lipoidica

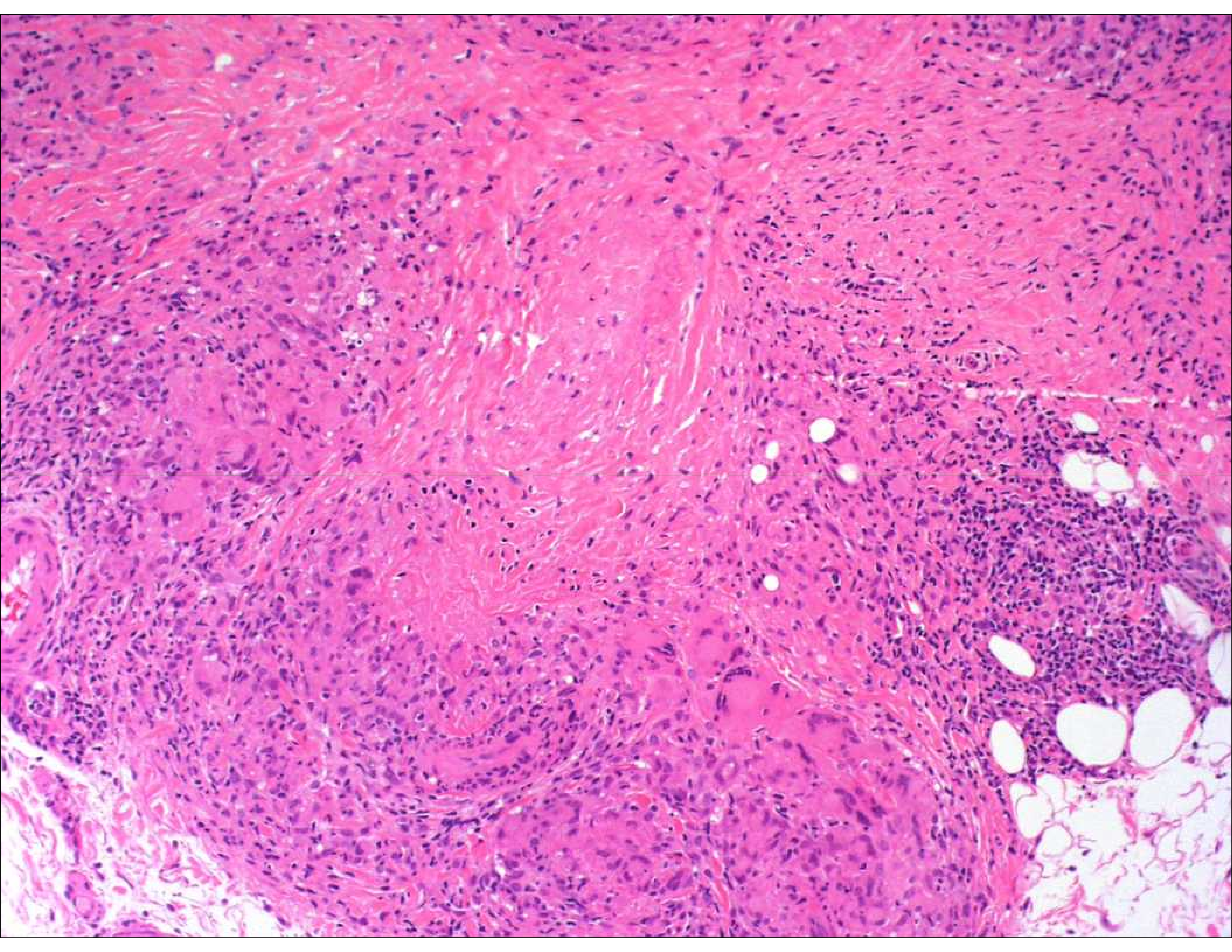
- Clinical
  - Yellow, indurated plaques on lower legs
  - Two-thirds of patients have underlying diabetes mellitus
- Microscopic
  - Affects entire dermis
  - Tiered arrangement of elongated zones of altered collagen (necrobiosis) separated by an interstitial infiltrate of histiocytes
  - Multinucleated histiocytes common
  - Aggregates of lymphocytes and plasma cells

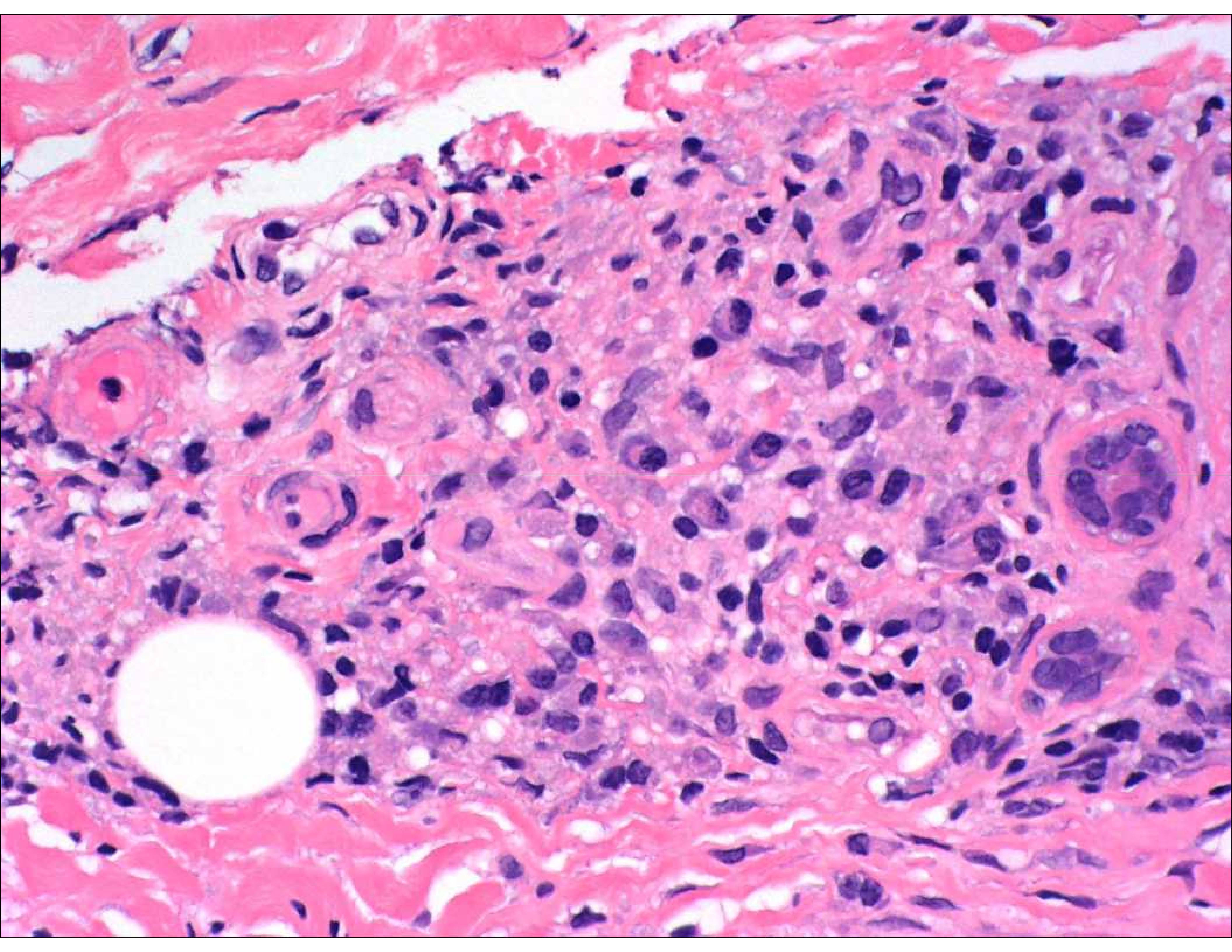








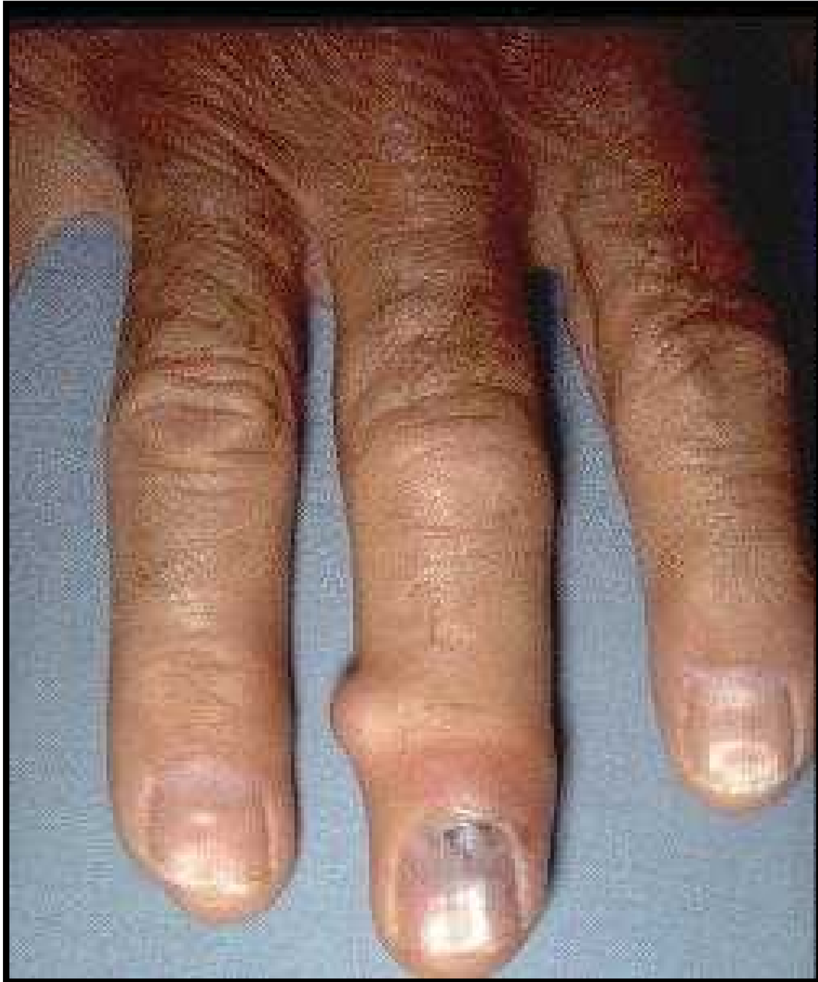


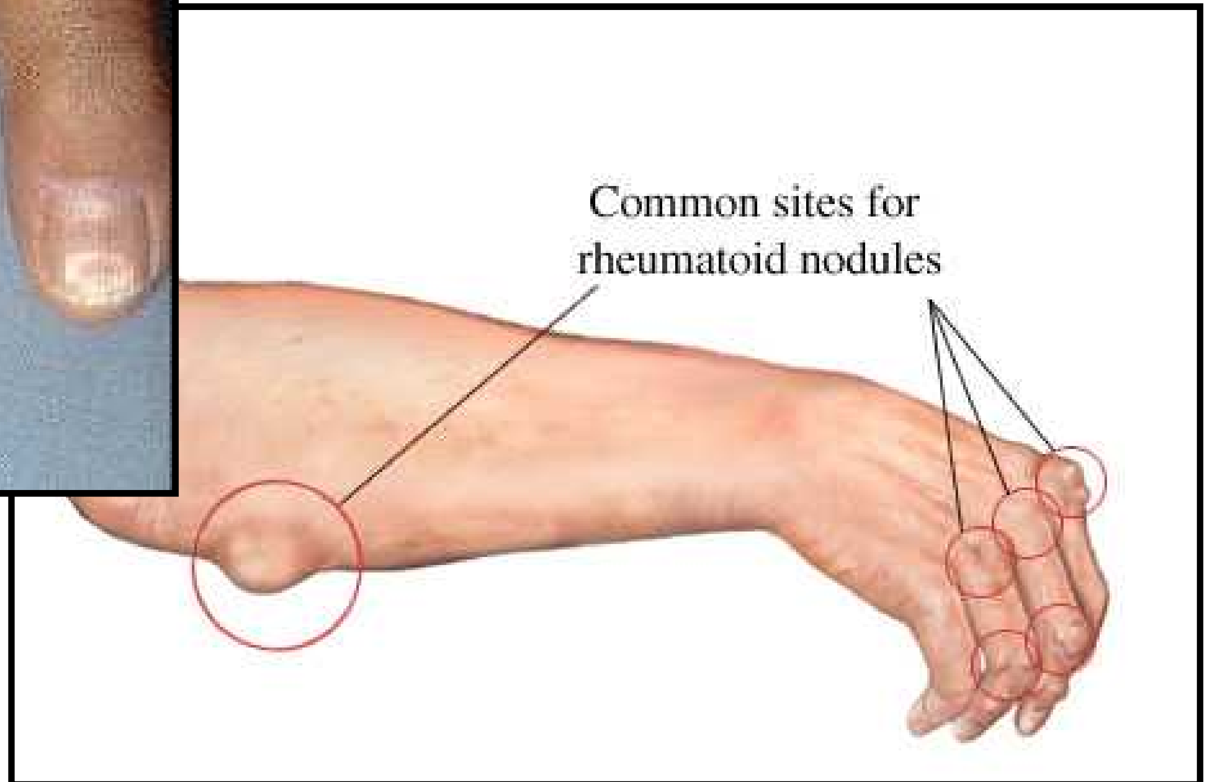


Practical Tips

- Low power examination
- Tiers of altered collagen and histiocytes create layer cake or bacon look
- Plasma cells favor necrobiosis lipoidica over GA
- Most cases on legs
- Ambiguous cases
  - Dx: palisading granulomatous dermatitis
  - Note: what you favor

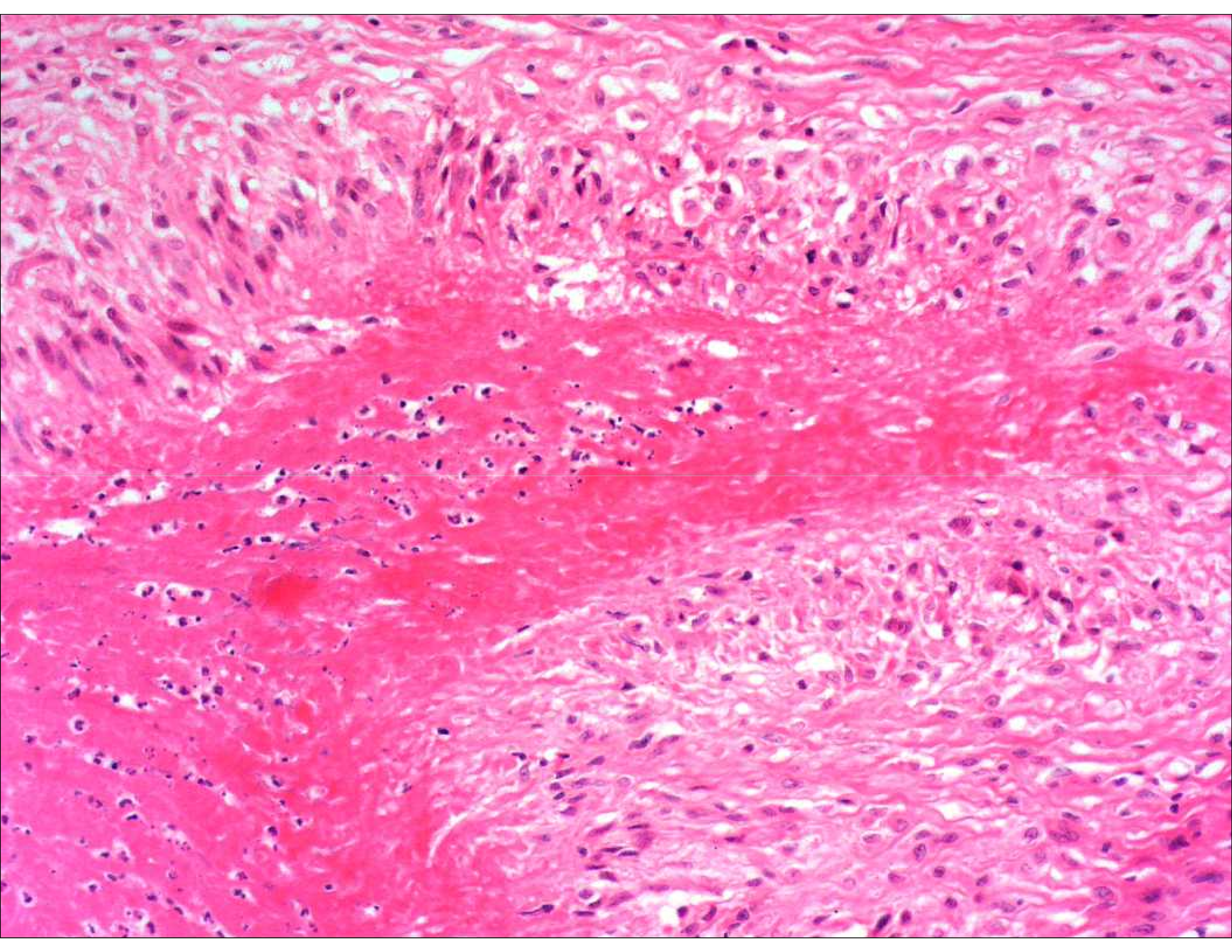
Rheumatoid Nodule





Rheumatoid Nodule

- Microscopic
  - Lesions are located in the deep dermis, subcutaneous fat or soft tissue
  - Central areas of acellular fibrin surrounded by histiocytes and giant cells in a palisaded pattern
  - Lymphocytes, plasma cells and eosinophils may be present

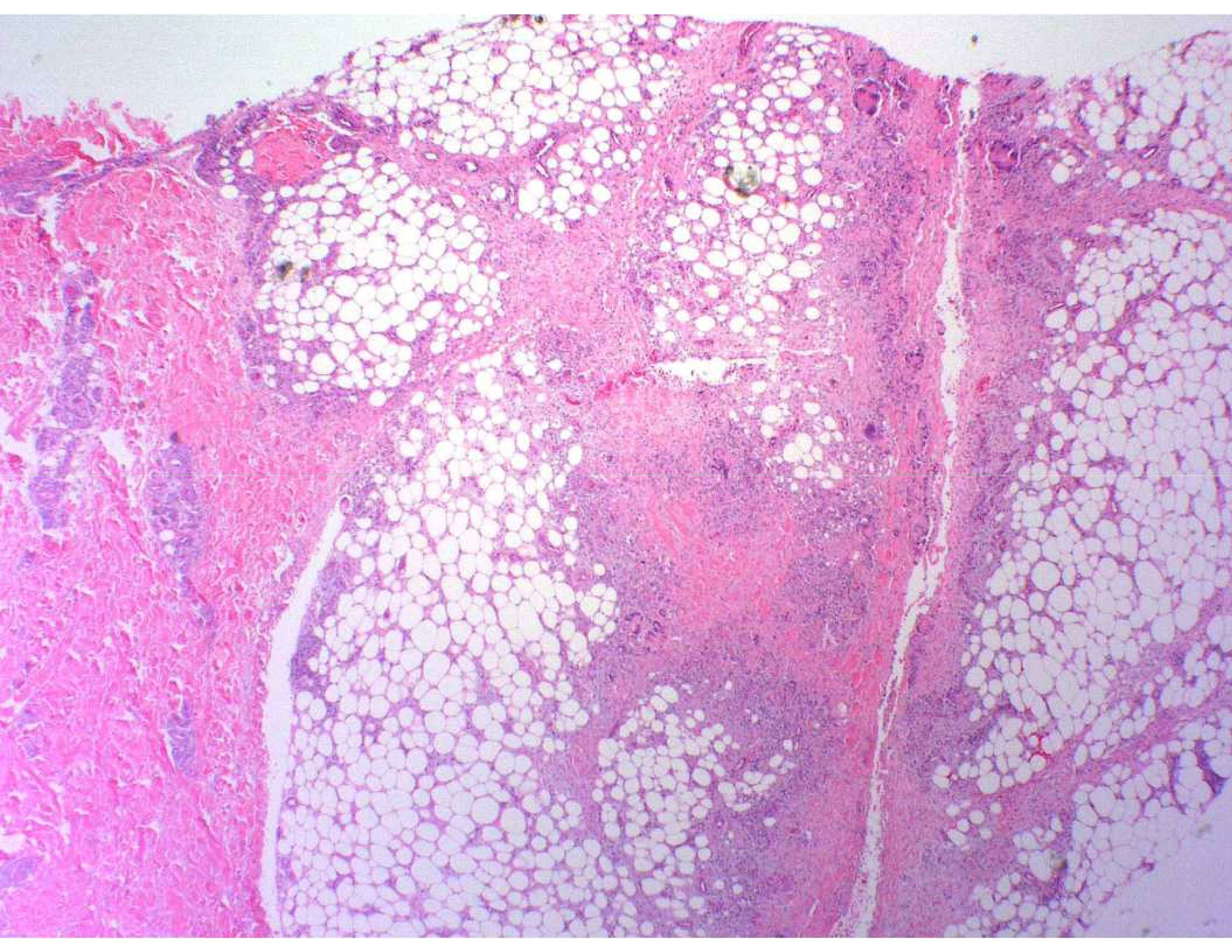


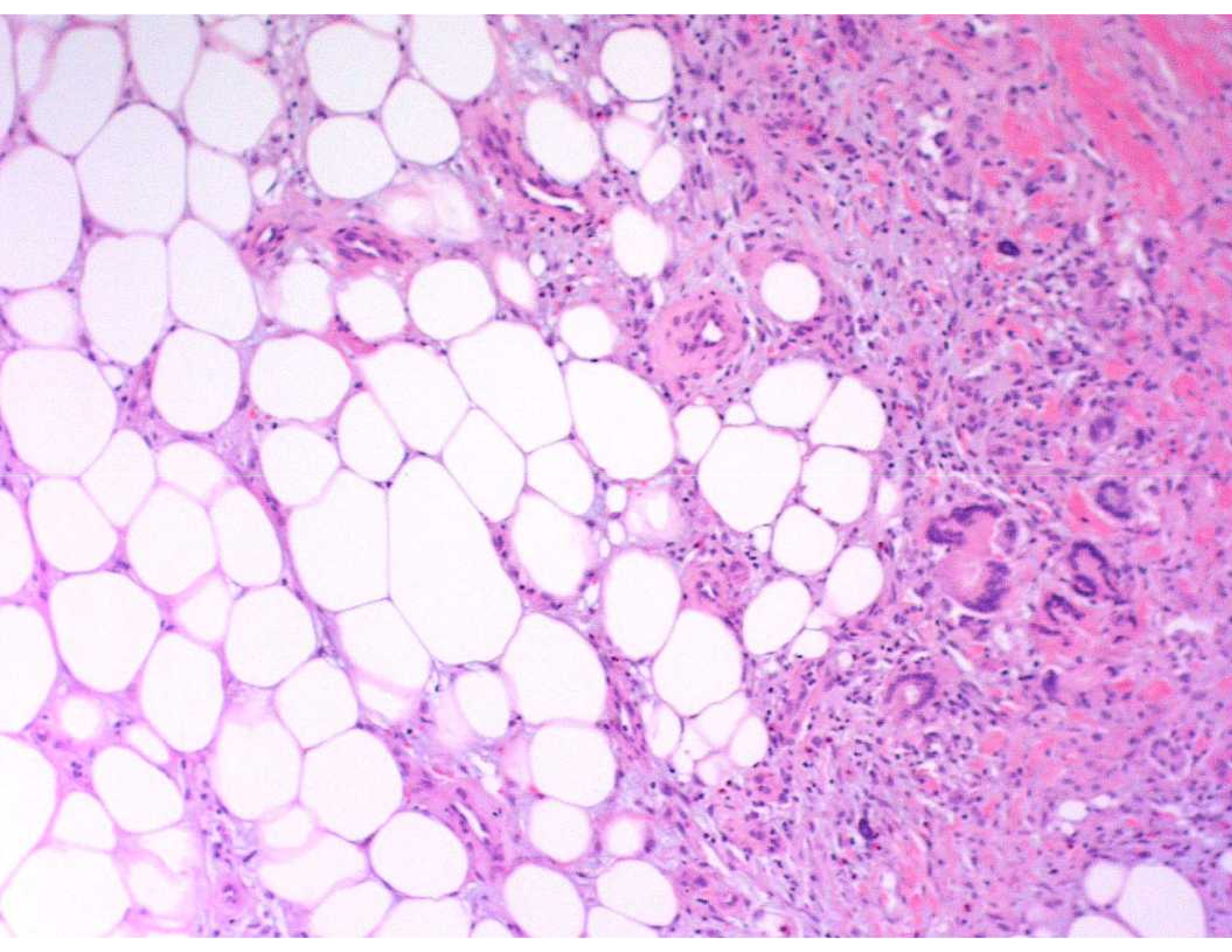
Erythema Nodosum

- Most common form of panniculitis (>80%)
- Acute onset of tender, erythematous nodules
- Shins most common site, often bilateral
- Subcutaneous hypersensitivity reaction
  - Idiopathic
  - Associated with infection (e.g. group A -hemolytic streptococcus)
  - Drugs (e.g. sulfa drugs, oral contraceptives)

Erythema Nodosum

- Microscopic
  - Widened septae with edema, inflammation, and later fibrosis
  - Lymphocytes, histiocytes, eosinophils and some neutrophils
  - Small granulomas
  - Lobular inflammation at periphery of subcutaneous fat lobule



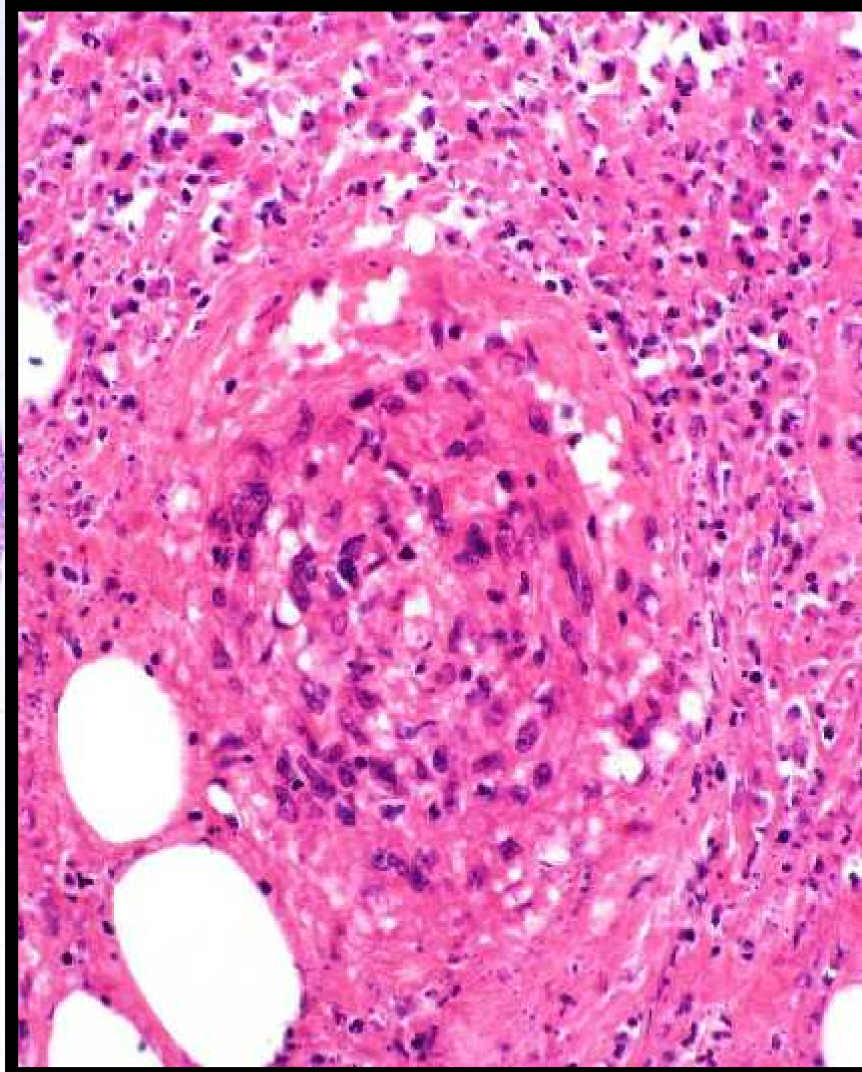


Erythema Nodosum

- Differential Diagnosis
  - Infection
  - Trauma
  - *Erythema induratum*
  - *Lipodermatosclerosis*

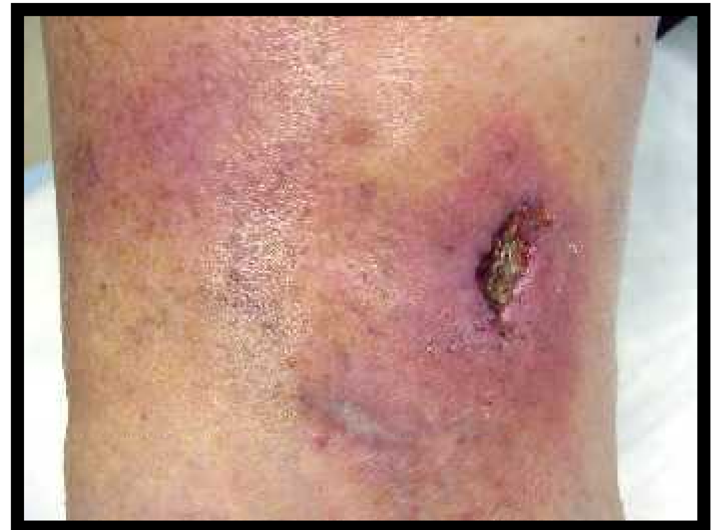
Nodular Vasculitis (Erythema Induratum)

- Clinical
  - Chronic, recurring tender nodules on lower legs, especially calves
  - Subcutaneous hypersensitivity
    - Subset: reaction to underlying infection with *M. tuberculosis*
- Microscopic
  - Acute vasculitis in septae affecting artery and/or veins
  - Adjacent lobular panniculitis with granulomas and fat necrosis
  - Septae may be widened in older lesions

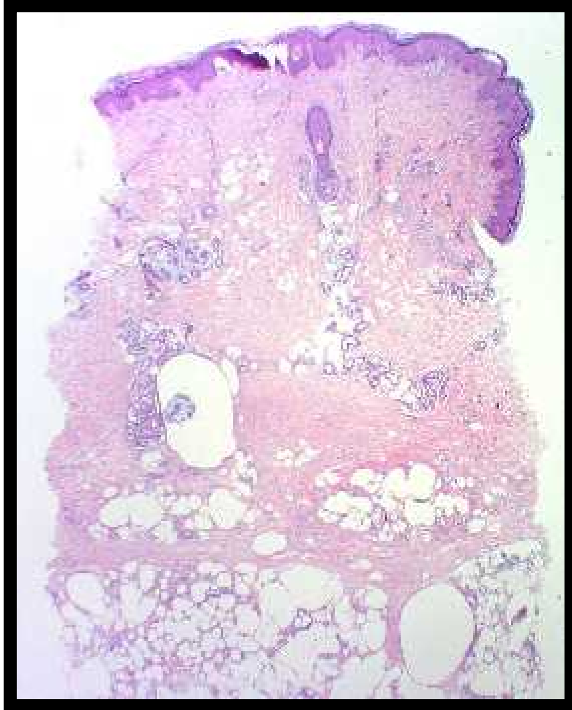


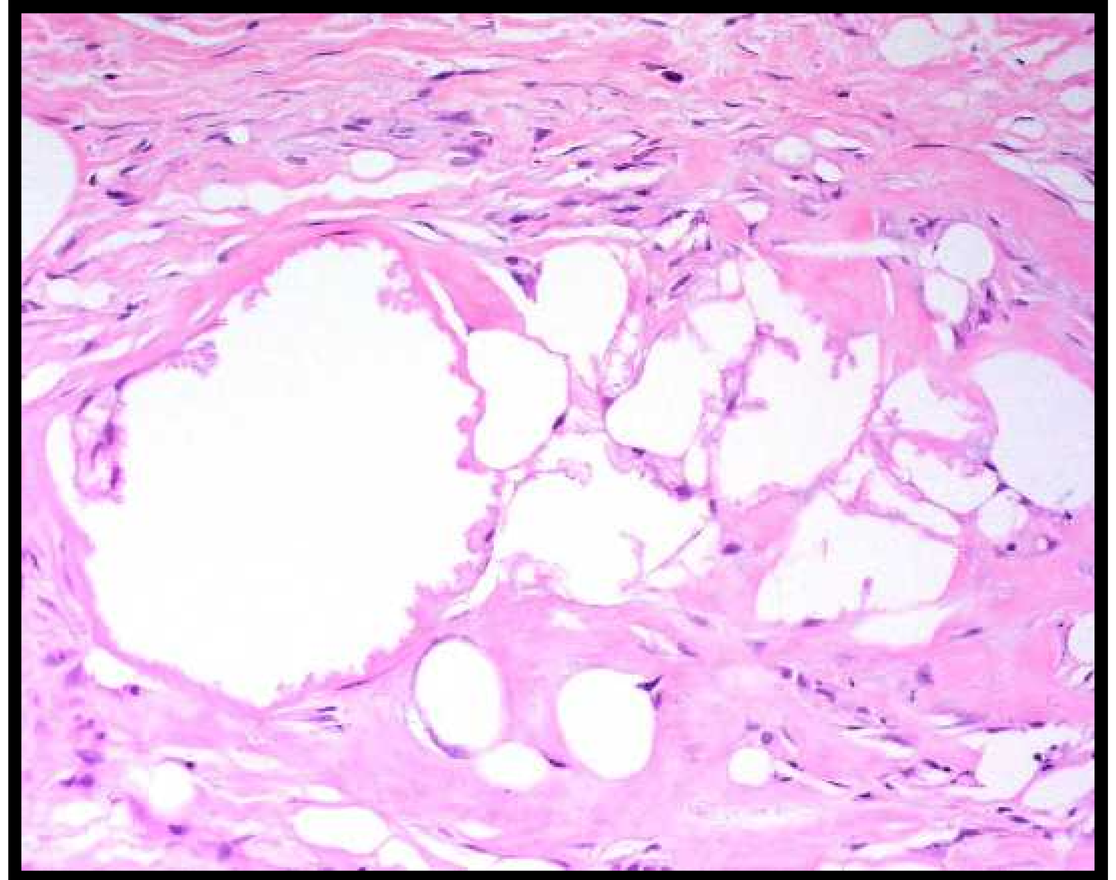
Lipodermatosclerosis

- Clinical
  - Usually bilateral indurated plaques on medial aspects of lower legs
  - Associated with stasis changes secondary to venous insufficiency and obesity



Lipodermatosclerosis





- Microscopic
  - Widened septae
  - Membranocystic fat necrosis
    - Cystic cavities lined by a crenulated, hyaline membrane
  - Mild perivascular lymphocytic infiltrate
  - Overlying features of stasis change in dermis and epidermis

Panniculitis practical tips

- Look for predominant pattern at low power
- Most cases are erythema nodosum
- Absence of inflammation: think lipodermatosclerosis

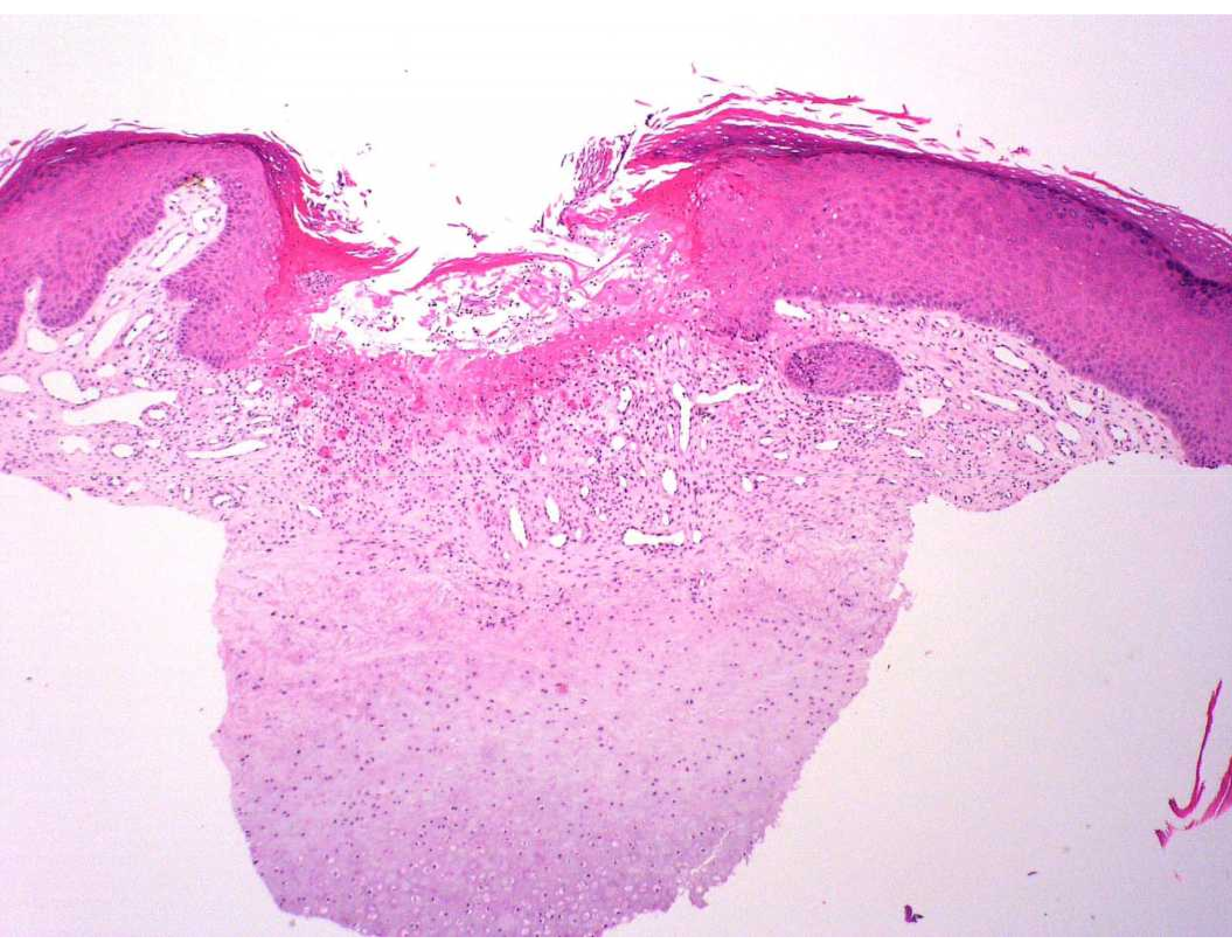
Bonus Diagnosis: Chondrodermatitis Nodularis Helicis

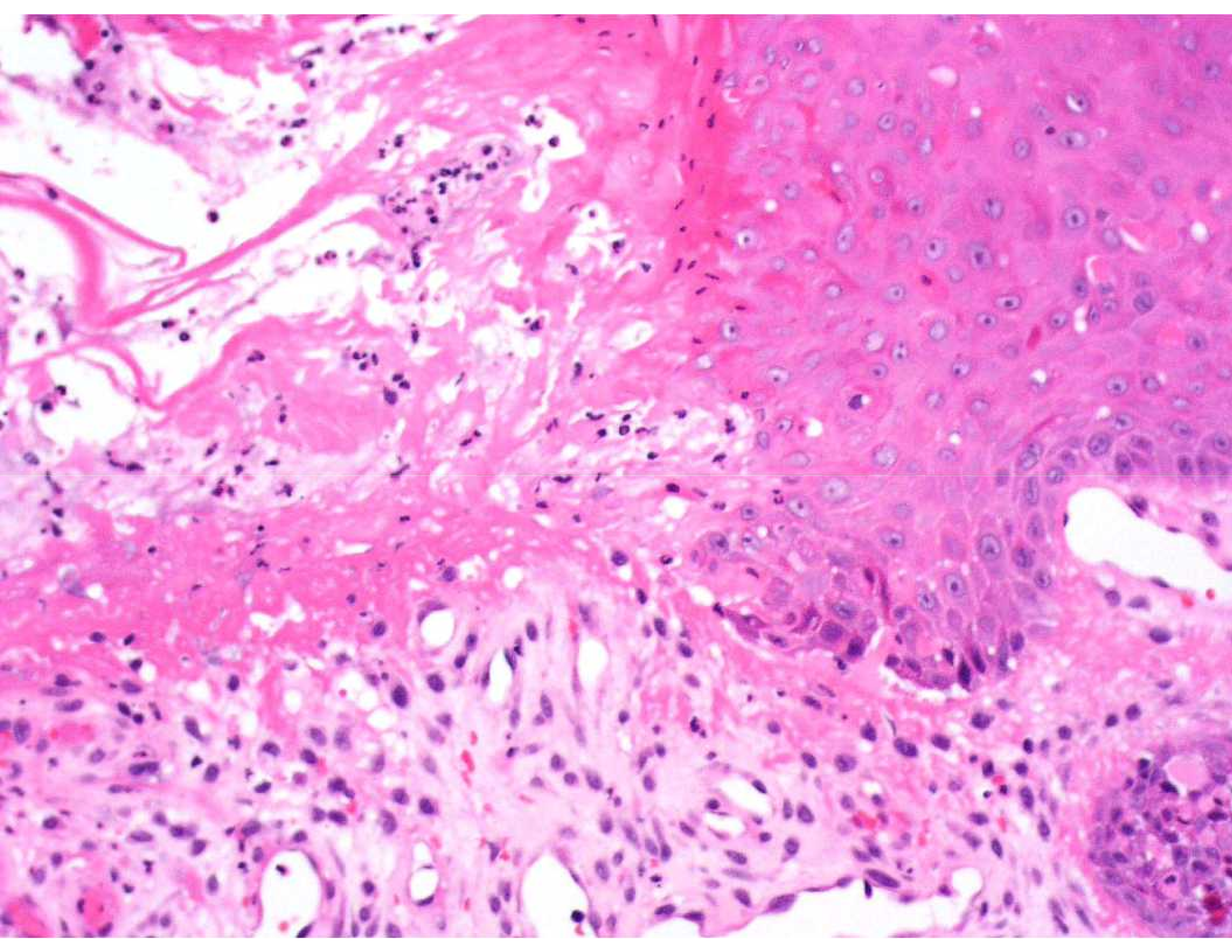
Chondrodermatitis Nodularis Helicis (CNCH)

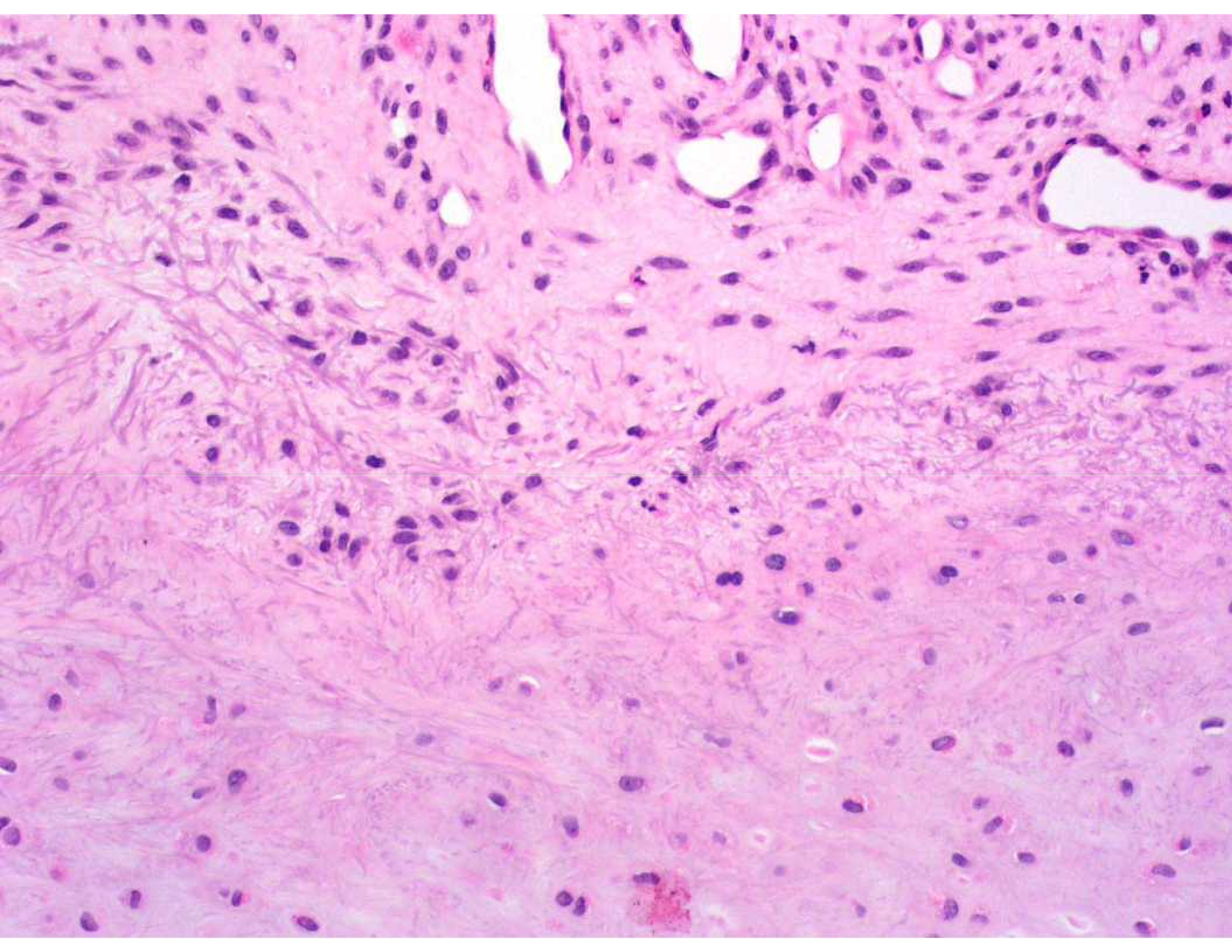
- Clinical
  - Older patients
  - Crusted to ulcerated lesion on helix
  - On “sleeping side”
  - Essentially a small pressure ulcer
  - Clinically mimics squamous cell carcinoma or basal cell carcinoma

CNCH

- Microscopic
  - Ulcer
  - Reactive epidermal hyperplasia
  - Fibrinoid degeneration of dermis
  - Proliferation of perichondrial fibroblasts





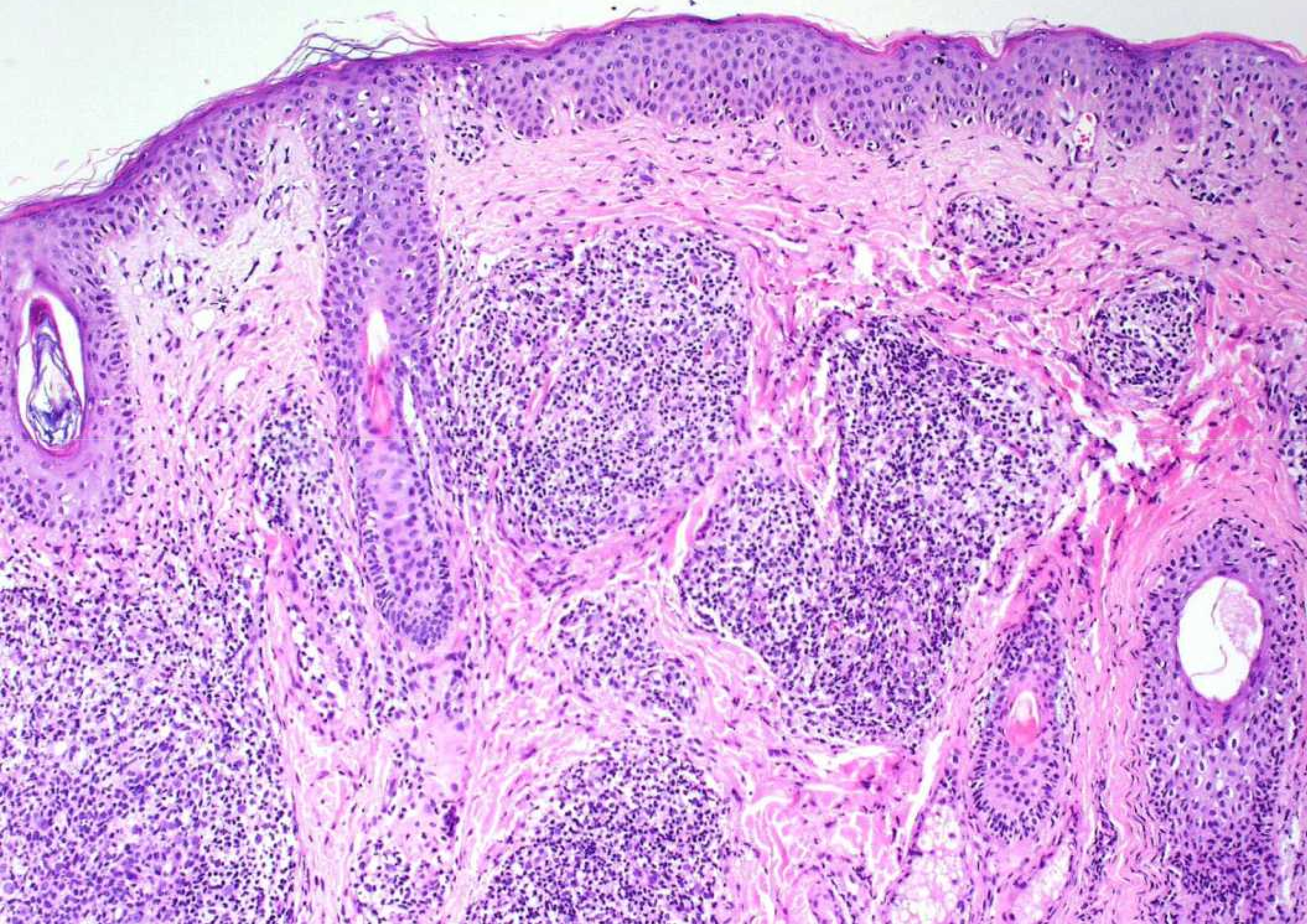


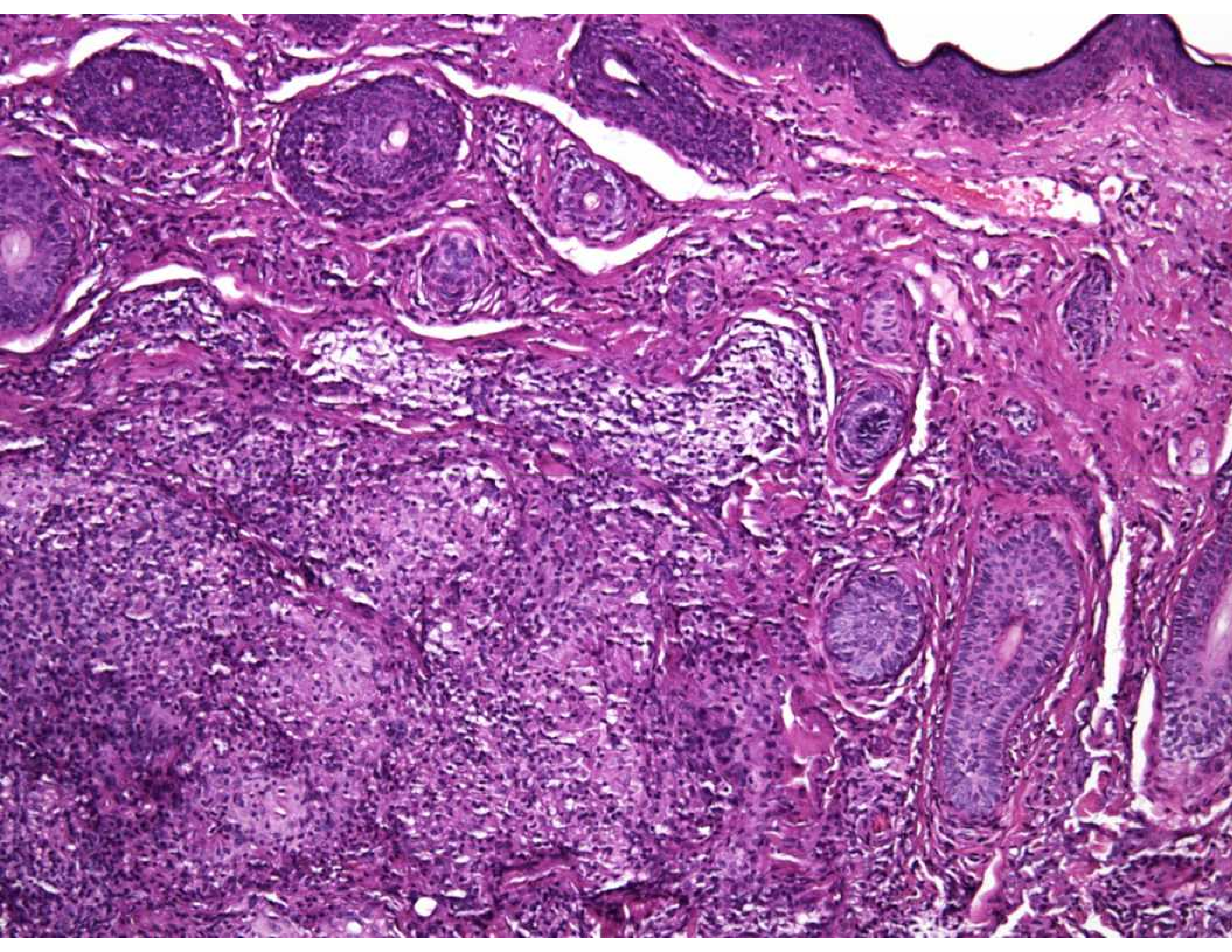
CNCH

- Tips
  - High index of suspicion from ear lesions
  - Fibrinoid change
  - Absence of atypia

Bonus Diagnosis: Rosacea

- Clinical features
  - Predominantly involves central face
  - Erythema, telangiectasia early
  - Acneiform lesions, pustules, papules later
  - Can mimic basal cell carcinoma
- Microscopic features
  - Perivascular and perifollicular infiltrate
  - Lymphocytes, histiocytes, sometimes granulomas





Rosacea Practical Tips

- If BCC suspected clinically, get deeper levels
- Diagnosis: Perivascular and perifollicular lymphohistiocytic infiltrate, see comment
- Comment: The histologic features are consistent with rosacea in the right clinical context. CPC recommended.