

Inflammatory dermatopathology: a practical approach

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Inflammatory dermatopathology

- Hard subject because:
 - the very broad and “non exhausting” terminology
 - a significant histologic overlap between the entities
 - inflammatory skin disease is dynamic: a particular entity may have a completely different appearance early in the course of the disease from what it looks like late in the disease process: “the life of lesions”

Too often, pathologists forget to use one of the most important tools: the telephone! **A good relationship with the dermatologist is a vital aspect of successful practice for any pathologist or dermatopathologist.**

Inflammatory dermatopathology

- What makes up an ideal report of an inflammatory diagnosis?
 - All reports from biopsies require 3 elements:
1/microscopic description, 2/ comment, 3/diagnosis
 - when possible, it is important to provide a specific histopathological diagnosis
 - unfortunately, a specific diagnosis is often not possible. In such cases is perfectly acceptable to provide a “descriptive diagnosis”.

Inflammatory skin pathology

- What is a descriptive diagnosis?
- A descriptive diagnosis is not synonymous of a non-specific chronic dermatitis!
- A descriptive diagnosis needs to be formulated in appropriate terms, in other words using the **reaction pattern that is present**
- what gives meaning to the descriptive diagnosis are the **accompanying microscopic description and the comment section of the report**

Inflammatory skin diseases : understanding the concept of the basic reaction patterns

- Predominant epidermal patterns (***spongiotic dermatitis, psoriasiform dermatitis, interface dermatitis***)
- Predominant dermal patterns (***perivascular dermatitis, nodular and diffuse dermatitis, sclerosing dermatitis***)
- ***Panniculitis (septal-lobular)***
- ***Infections***
- ***Vasculitis***
- ***Bullous dermatitis (intra-epidermal pattern, subepidermal pattern)***

Epidermal patterns: definition

- Spongiotic pattern : epidermal accumulation of edema fluid
 - Psoriasiform pattern: epidermal hyperplasia
 - Interface pattern: damage to basal layer of the epidermis by an inflammatory infiltrate.
- spongiotic and psoriasiform patterns frequently co-exist (overlap)

Dermal patterns: definition

- Perivascular dermatitis: an inflammatory infiltrate predominantly around blood vessels in a superficial or superficial and deep distribution
 - Nodular/diffuse dermatitis: the infiltrate is less vasculocentric
- there may be significant overlap between perivascular and nodular/diffuse patterns
- Sclerosing dermatitis: fibrosis of the dermis usually with relatively little inflammation

Inflammatory dermatopathology: reaction patterns

- Panniculitis: septal and lobular patterns
- Vasculitis (primary versus secondary vasculitis; small versus large vessel vasculitis; leucocytoclastic vasculitis versus “lymphocytic” vasculitis versus vasculopathic disease)
- Bullous pathology (intraepidermal and subepidermal bullous pathology)

Inflammatory dermatopathology: reaction patterns

- Alopecia pathology (inflammatory and non-inflammatory patterns)
- Infectious pathology: many of the infectious entities do not neatly fall into a reaction pattern! A very broad and heterogenic group (see lecture of Prof. Dr. E. Van Marck)

Spongiotic dermatitis

Spongiotic dermatitis

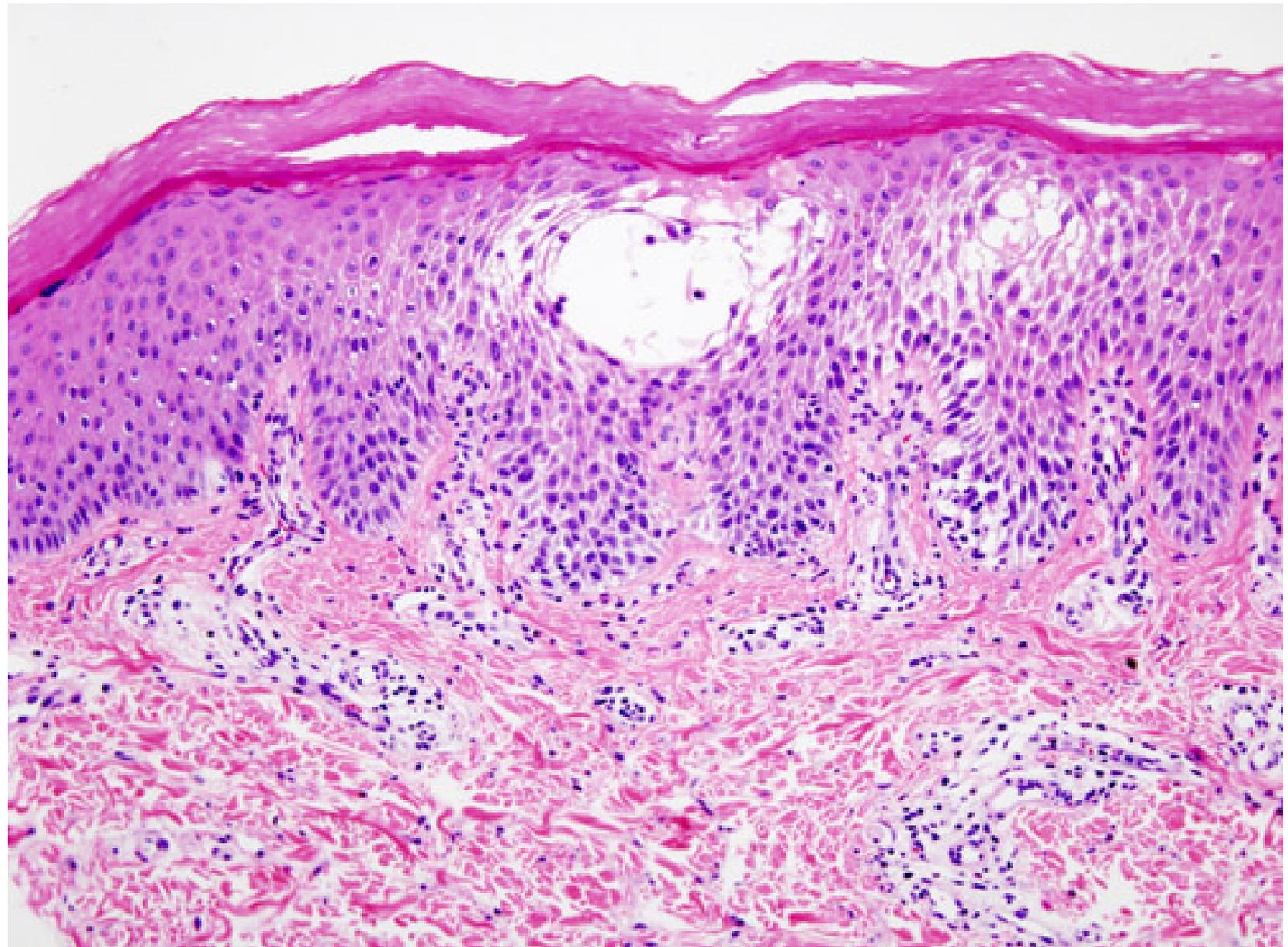
- **Eczematous dermatitis: histological prototype of spongiotic dermatitis**
- Stasis dermatitis
- Pityriasis rosea

Spongiotic dermatitis: histological classification

- Acute spongiotic dermatitis
- Subacute spongiotic dermatitis
- Chronic spongiotic dermatitis

Acute spongiotic dermatitis: key microscopic features

- Normal basket-weave stratum corneum
- Epidermal spongiosis with or without spongiotic microvesicles
- Variable papillary dermal edema
- Superficial perivascular inflammatory infiltrate of lymphocytes often (but not always) with admixed eosinophils



Subacute spongiotic dermatitis: key microscopic features

- Parakeratosis
- Spongiosis
- Acanthosis
- Little or no papillary dermal edema
- Superficial perivascular inflammatory infiltrate of lymphocytes often (but not always) with admixed eosinophils

Chronic spongiotic dermatitis: key microscopic features

- Compact hyperkeratosis and variable parakeratosis
- Acanthosis
- Minimal spongiosis
- Superficial perivascular inflammatory infiltrate of lymphocytes and often (but not always) with eosinophils. Usually mild in nature.
- Variable superficial dermal fibrosis

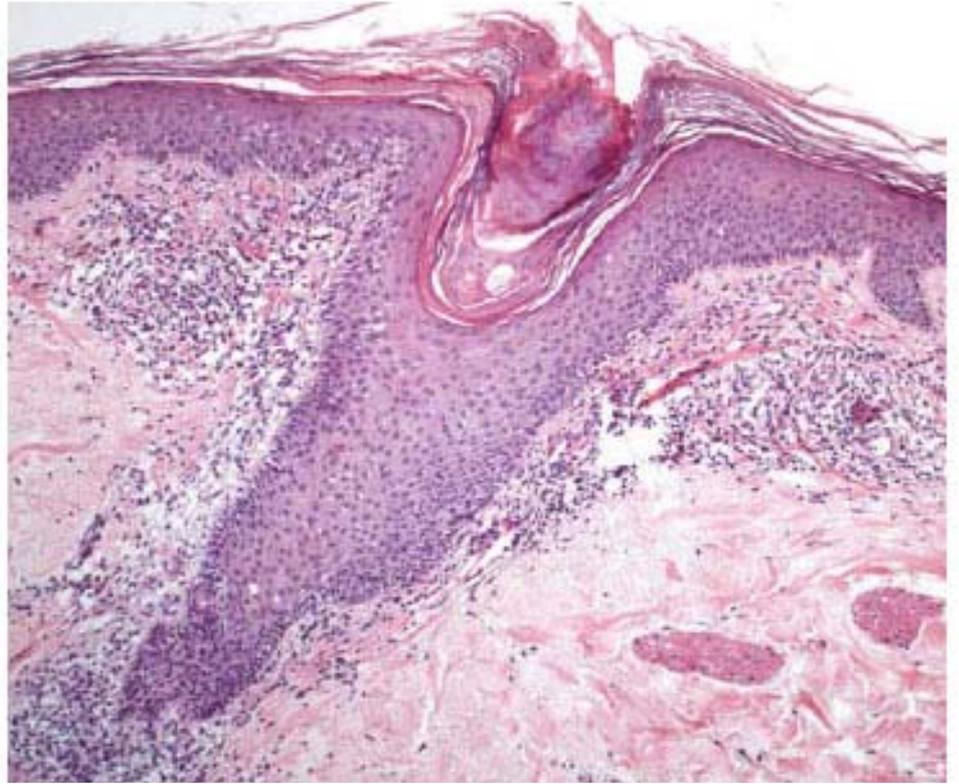
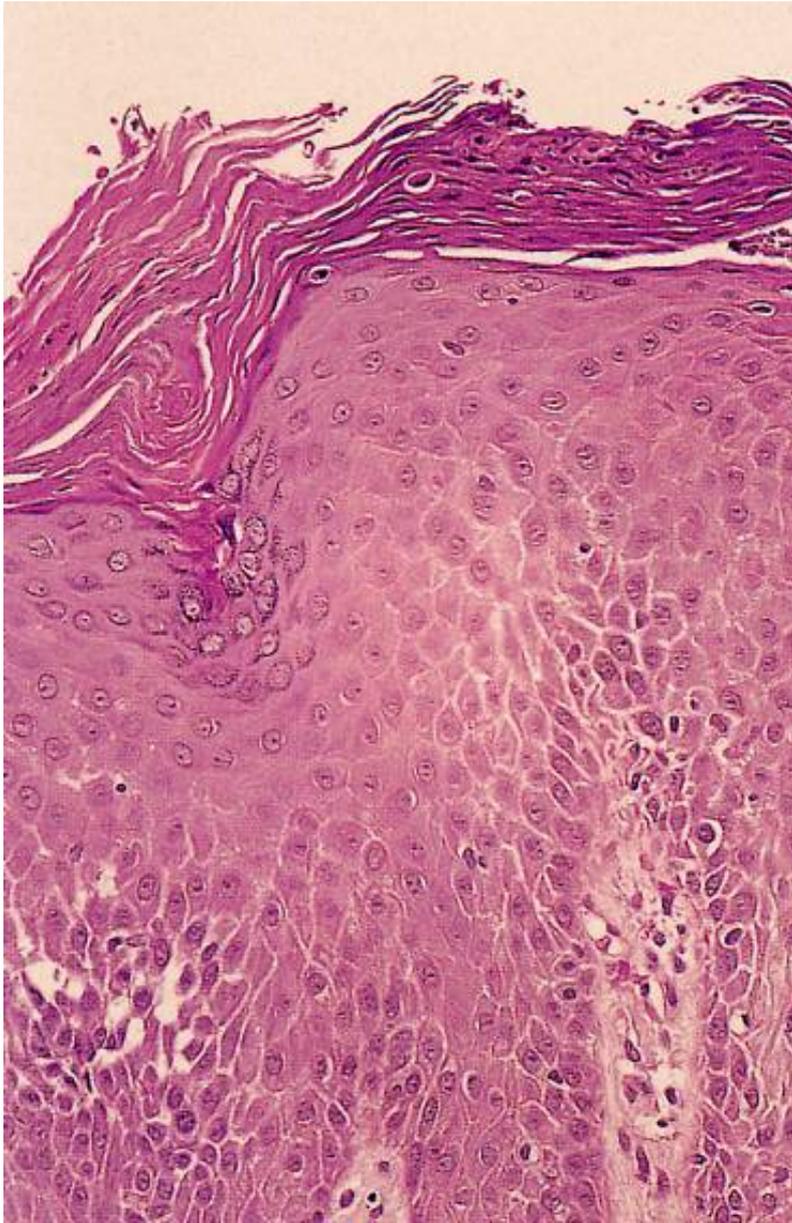


Spongiotic dermatitis

- Group of eczematous dermatitis (atopic dermatitis, nummular dermatitis, allergic contact dermatitis, irritant contact dermatitis, id reaction, papular dermatitis, seborrheic dermatitis, eczematous drug eruption)
 - all of these entities are essentially histologically identical.
 - they all can demonstrate the three patterns of spongiotic dermatitis depending on when the lesion is biopsied.

Eczematous dermatitis: some clues

- Eosinophilic spongiosis, Langerhans cell microabcesses in allergic contact dermatitis
- Necrotic keratinocytes in irritant contact dermatitis
- Spongiosis localized to the ostia or upper infundibula of hair follicles, neutrophilic crust, perifollicular parakeratosis in seborrheic dermatitis

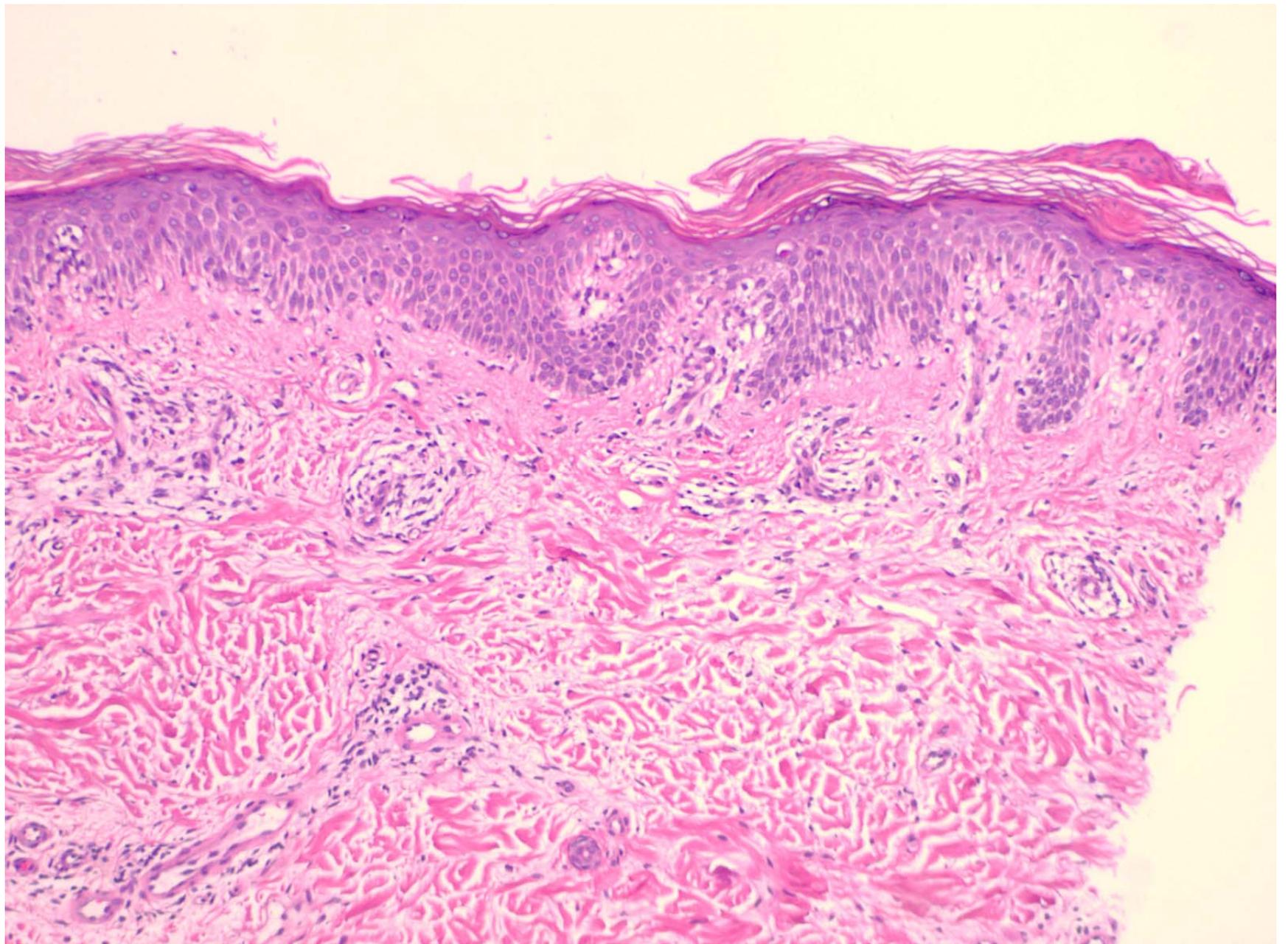


seborrheic dermatitis

Other forms of spongiotic dermatitis

Pityriasis rosea

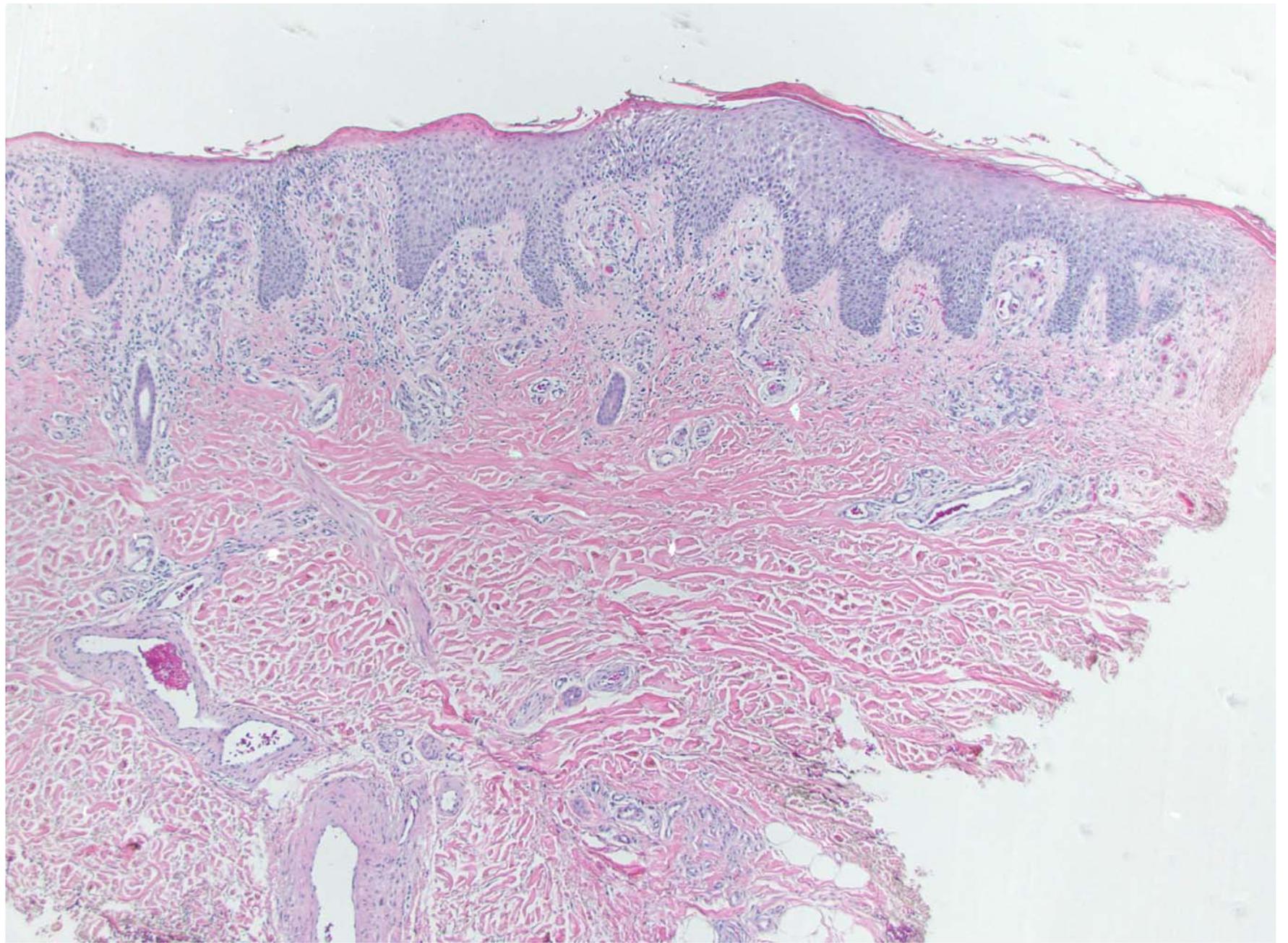
- focal discrete mounds of parakeratosis,
 - spongiosis and exocytosis
 - extravasation in papillary dermis
- clinicopathological correlation

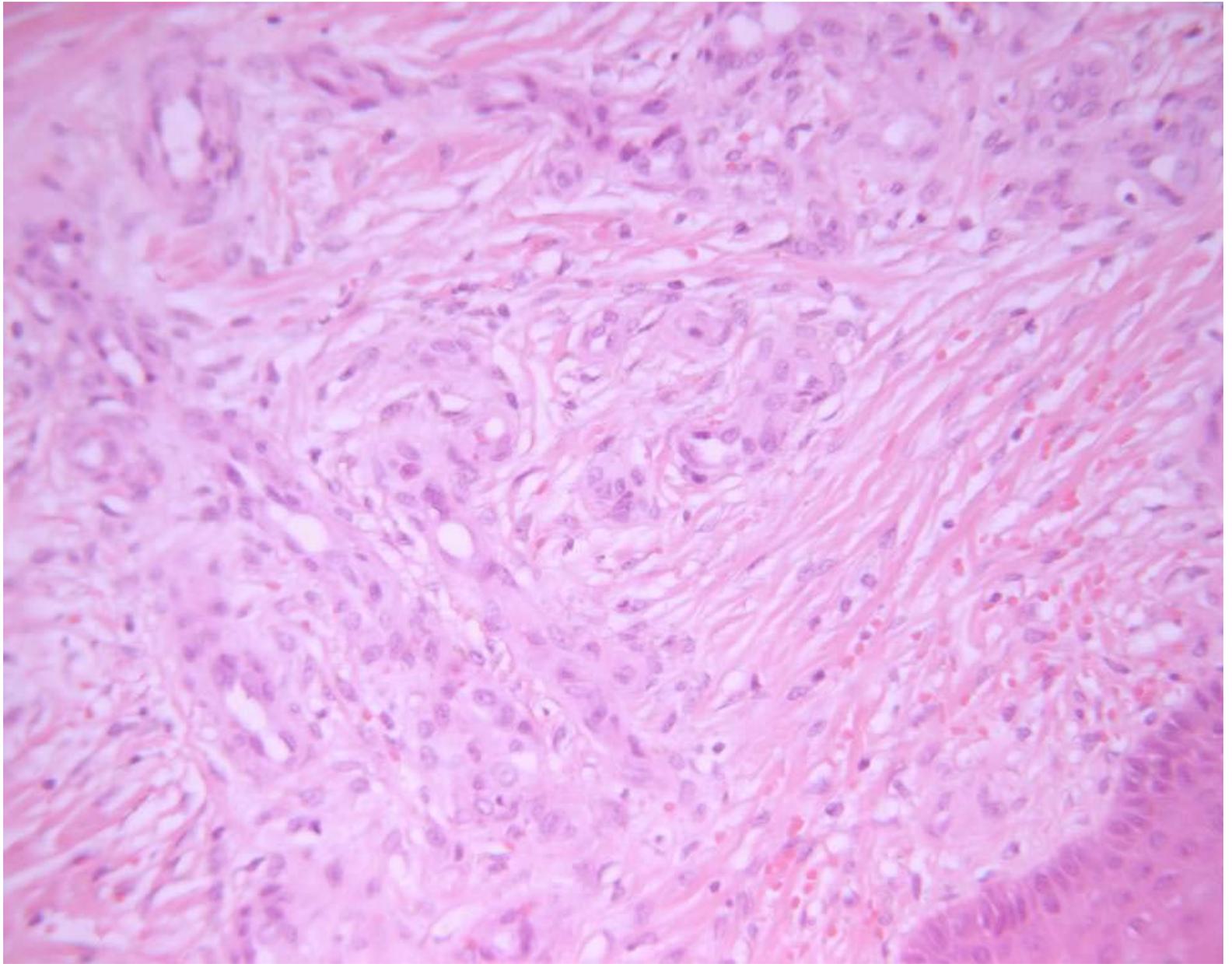


Other forms of spongiotic dermatitis

Stasis dermatitis

- variable acanthosis and spongiosis
- lobular proliferation of relatively thick-walled vessels in the superficial dermis
- extravasation of erythrocytes and siderophages common





Stasis dermatitis: practical tips

- Keep a high index of suspicion on biopsies from the lower legs
- The vascular changes are the most important feature
- Occasionally stasis dermatitis can clinically mimic a neoplasm and the clinician may submit a clinical diagnosis of squamous cell carcinoma

Eczematous dermatitis: differential diagnosis

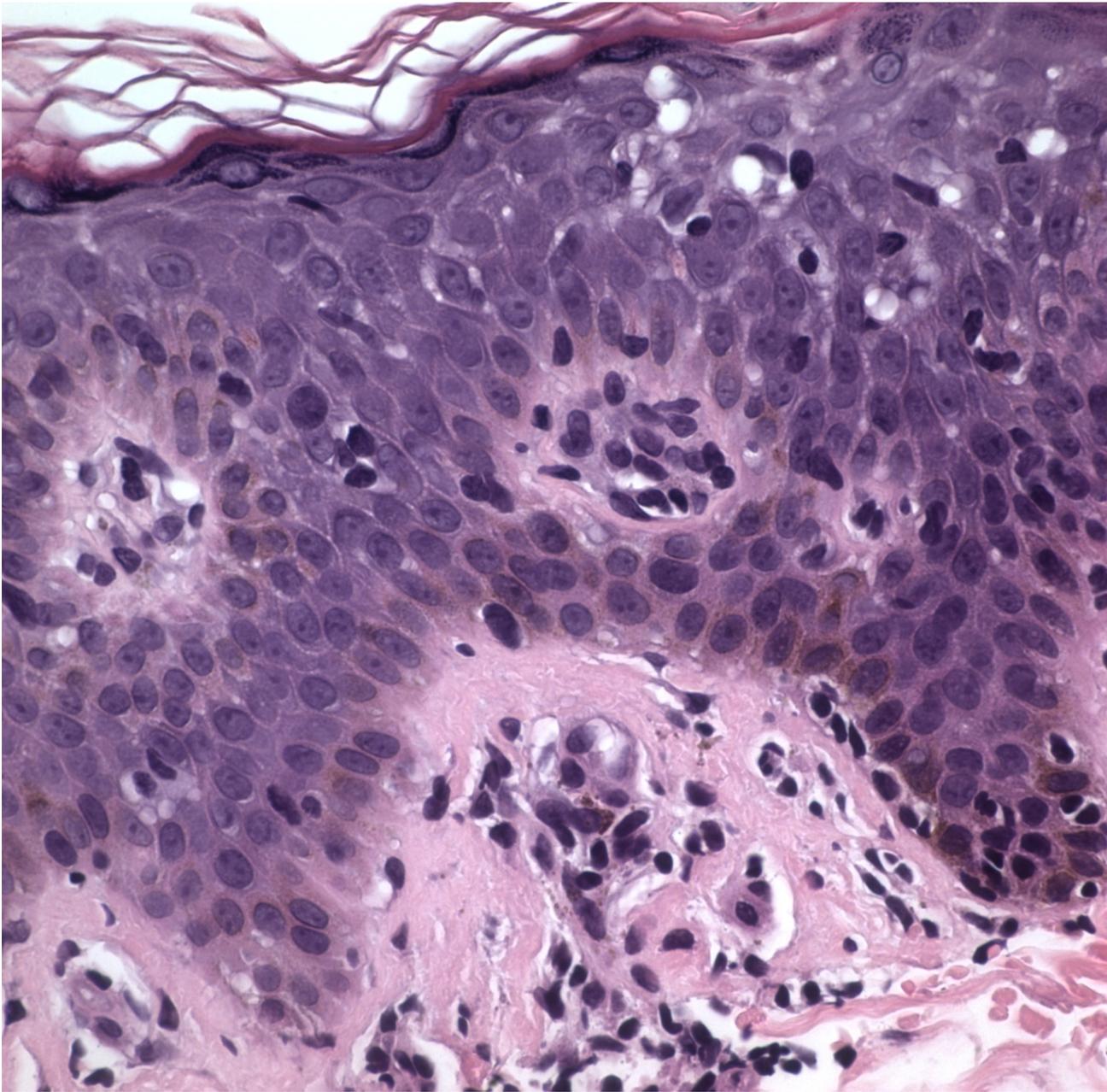
- *Dermatophytosis* (clue: crust formation with neutrophils in stratum corneum or epidermis), always do a PAS and/or Grocott staining
- *Drug eruption* (clue: deep dermal infiltrate with eosinophilic granulocytes, dyskeratotic/apoptotic keratinocytes)
- *Arthropode reaction especially in the early phase* (clue: deep dermal infiltrate of eosinophilic granulocytes)
- *Superficial variant of erythema annulare centrifugum* (predominant dermal perivascular pattern)

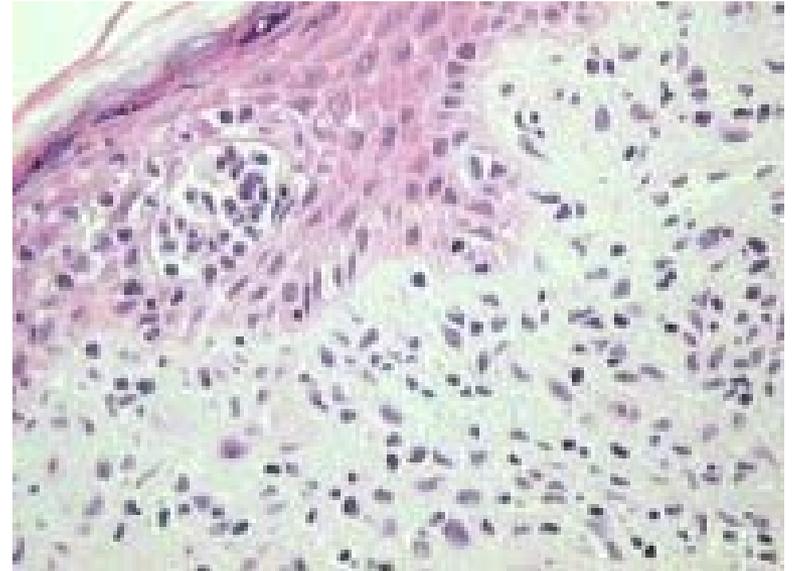
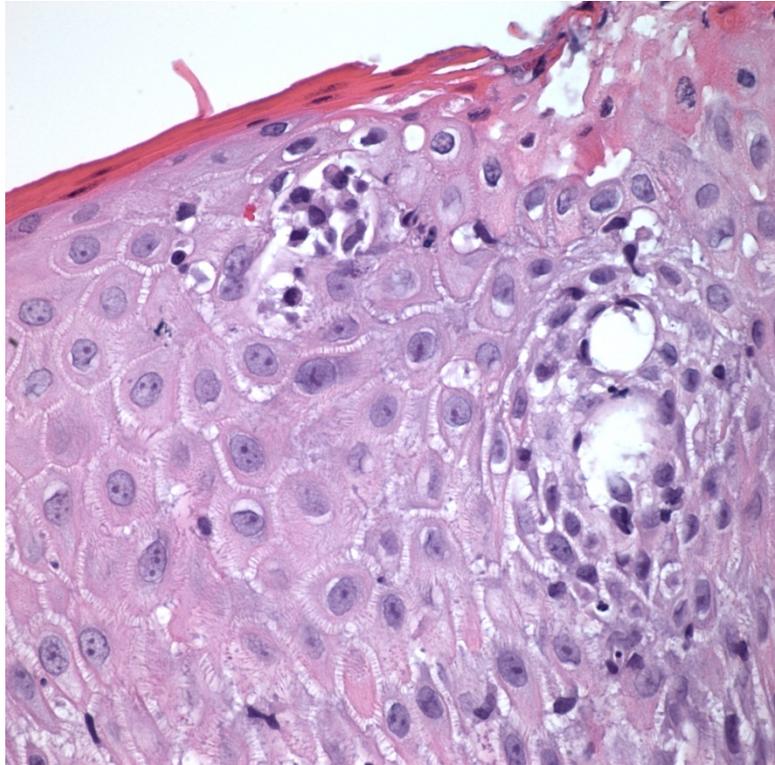
Eczematous dermatitis: differential diagnosis

- *Parapsoriasis small plaque*
- *Prebullous form of a vesiculobullous dermatitis, especially bullous pemphigoid*
(clue: aggregates of eosinophilic granulocytes at the dermo-epidermal junction and/or epiderm-eosinophilic spongiosis, immunofluorescence)

Eczematous dermatitis: differential diagnosis

- Early form of a mycosis fungoides (cave eczematous variant of mycosis fungoides)
 - epidermotropism
 - Pautrier microabscesses
 - atypical lymphocytes (hyperchromatic, irregular, “cerebriform” type of nuclei)
 - immunohistochemistry (CD3, CD2, CD4, CD8, CD7, CD5, CD20, CD30) can be useful
 - TCR rearrangement





Pautrier microabscesses different from Langerhanscell microabscesses (also CD4+)->do a CD1a staining in difficult cases!

Spongiosis is not synonymous for spongiotic dermatitis

- Spongiotic variant of m. Grover (acantholysis)
- Pityriasis lichenoides acuta (PLEVA) or chronica (interface dermatitis)
- Lichen striatus (interface dermatitis, deep infiltrates around eccrine ducts)
- Psoriasis (psoriasiform dermatitis, neutrophilic microabscesses, diminished or absent granular layer)

Eczematous dermatitis: practical tips

- The clinical variants of eczematous dermatitis have essentially the same histologic features
- Acute, subacute and chronic dermatitis represent a continuum. It is not important to sub-classify spongiotic dermatitis in the line diagnosis
- Use a descriptive diagnosis of “spongiotic dermatitis”

Eczematous dermatitis: practical tips

- Langerhans cell microabscesses are suggestive of allergic contact dermatitis
- Eliminate where possible more specific entities
- If neutrophils are in the stratum corneum or epidermis, exclude dermatophytosis or psoriasis
- Eczematous dermatitis is more spongiotic than mycosis fungoides

Psoriasiform dermatitis

Psoriasiform dermatitis

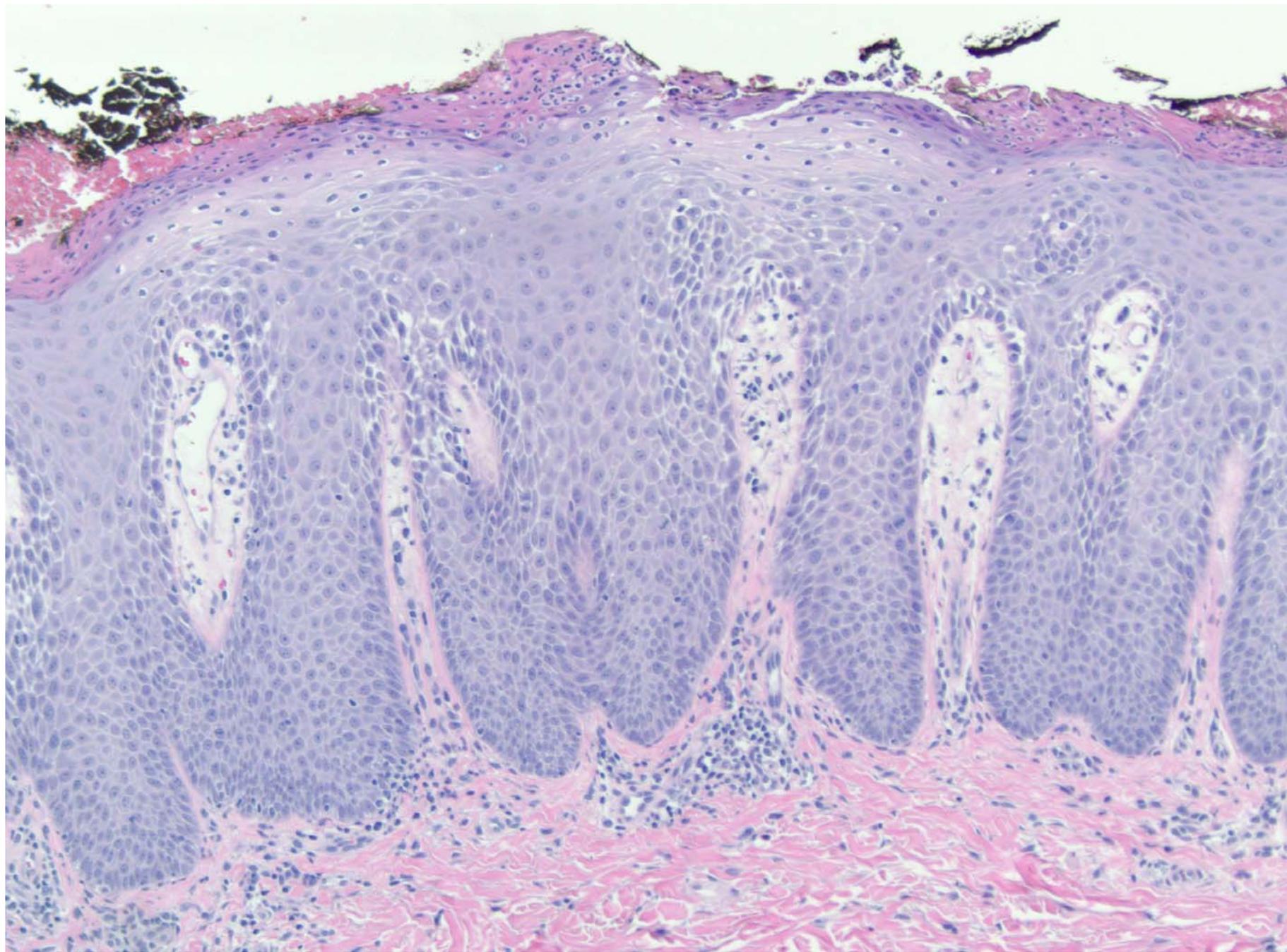
- Characterized by acanthosis (epidermal hyperplasia)
 - Overlap with the spongiotic dermatitis: acanthosis and spongiosis often coexist (chronic spongiotic dermatitis), classification of a dermatitis as spongiotic or psoriasiform can be somewhat arbitrary)
- I will focus on entities in which spongiosis is not typically a prominent feature

Psoriasiform dermatitis

- **Psoriasis** (psoriasis vulgaris, guttate psoriasis, pustular psoriasis): **histological prototype of psoriasiform dermatitis**
- Pityriasis rubra pilaris
- Lichen simplex chronicus/ Prurigo nodularis

Psoriasis vulgaris: key microscopic features

- Parakeratosis
- Neutrophils in stratum corneum and/or epidermis
- Diminished or absent granular layer
- Uniform epidermal hyperplasia
- Suprapapillary plate thinning
- Dilated and tortuous papillary dermal blood vessels



Psoriasis vulgaris: differential diagnosis

- **Eczematous dermatitis** (subacute and especially chronic eczema)
 - clues: eosinophils, Langerhans cell microabscesses, more irregular acanthosis, lacking of the suprapapillary plate thinning, retained granular layer, “wet” nature of parakeratosis with serous fluid and bacterial organisms: secondary bacterial impetiginization)

Psoriasis vulgaris: differential diagnosis

- *Dermatophyte infection of the skin* (more irregular acanthosis and usually eosinophils): do always a PAS and/or Grocott staining!
- *Seborrheic dermatitis* (clue: parakeratosis most conspicuous at follicular ostia; clinically a more restricted presentation on the scalp, central face and central chest)

Psoriasis vulgaris: differential diagnosis

- *Pityriasis rubra pilaris* (clues: lacks neutrophils and has alternating patterns of parakeratosis and orthokeratosis) (see also further)
- *Psoriasiform keratosis*: **solitary** benign cutaneous neoplasm usually presenting on the lower extremity of middle aged to older patients; significant histological overlap with psoriasis! Clinicopathological correlation is essential
- *Drug eruption* (especially TNF-alpha inhibitors) can mimick psoriasis: clinical information and eosinophils

Psoriasis vulgaris: practical tips

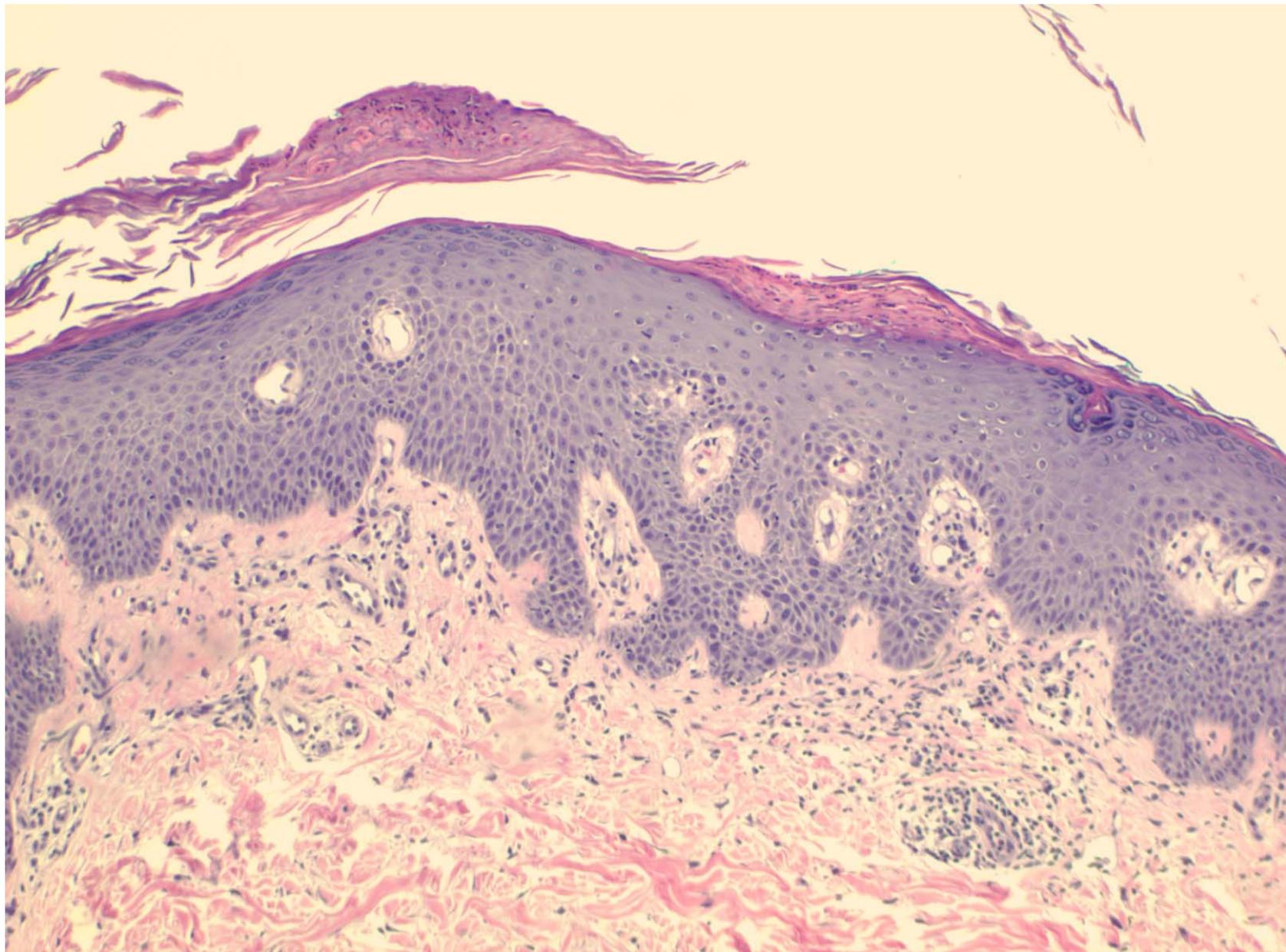
- Confluent parakeratosis is an important clue to diagnosis of psoriasis vulgaris
- The “dry” nature of the parakeratotic scale is a clue to psoriasis
- Neutrophils in the stratum corneum should always prompt consideration of psoriasis or a dermatophyte infection
- Psoriasis does not have eosinophils in the dermal infiltrate
- In excoriated/partially treated psoriasis vulgaris, the granular layer may be retained

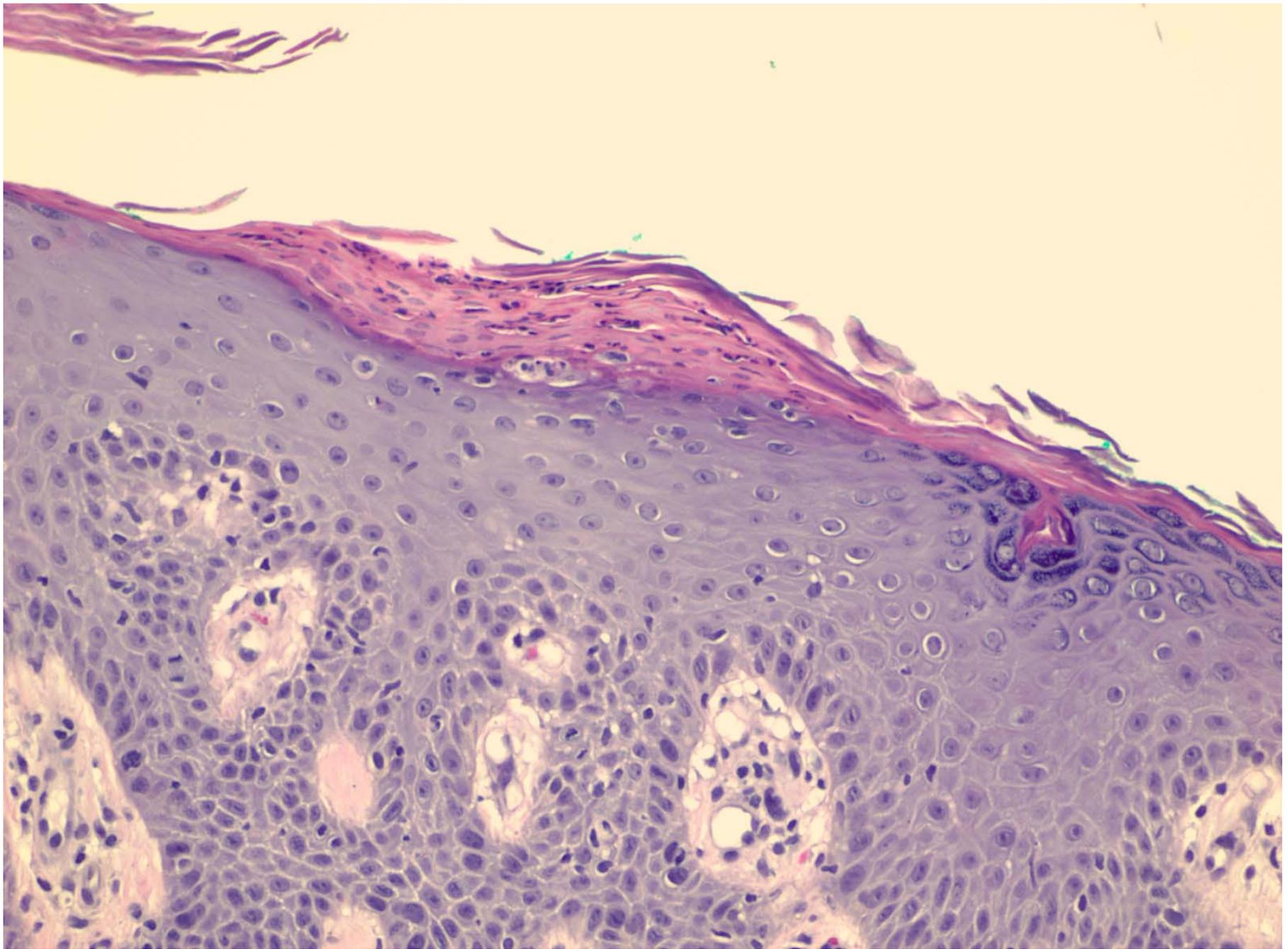
Psoriasis variants

- Guttate psoriasis
- Pustular psoriasis

Guttate psoriasis

- Clinical correlation: rapid onset of numerous small plaques. There is often a history of antecedent (streptococcal) pharyngitis.
- discrete mounds of parakeratosis with collection of neutrophils
- Epidermal changes less pronounced than psoriasis vulgaris



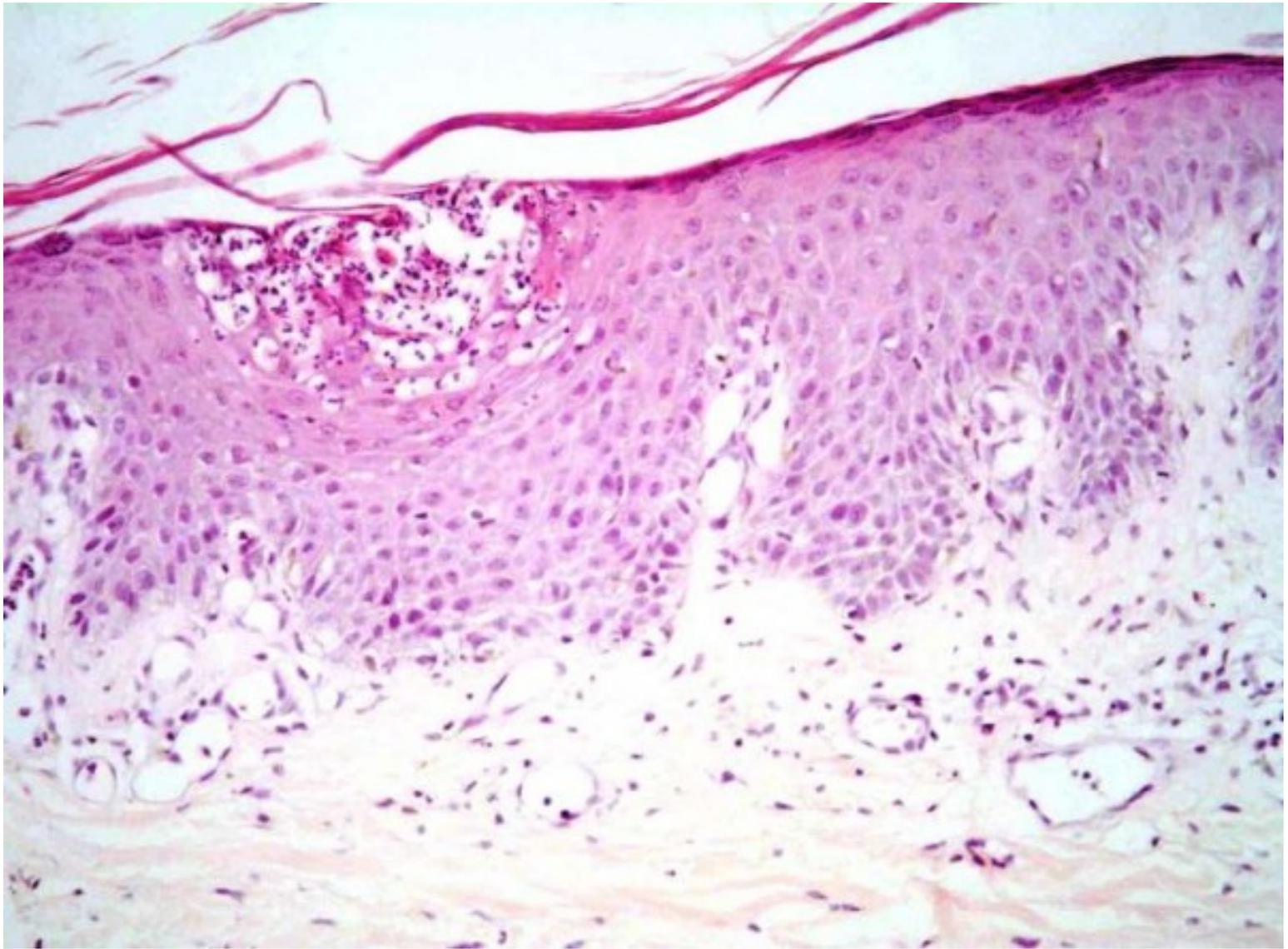


Guttate psoriasis: practical tips

- Mounds of parakeratosis with neutrophils should prompt consideration of guttate psoriasis
- Neutrophils are not always present, when absent also consider pityriasis rosea
- Clinical history of antecedent pharyngitis

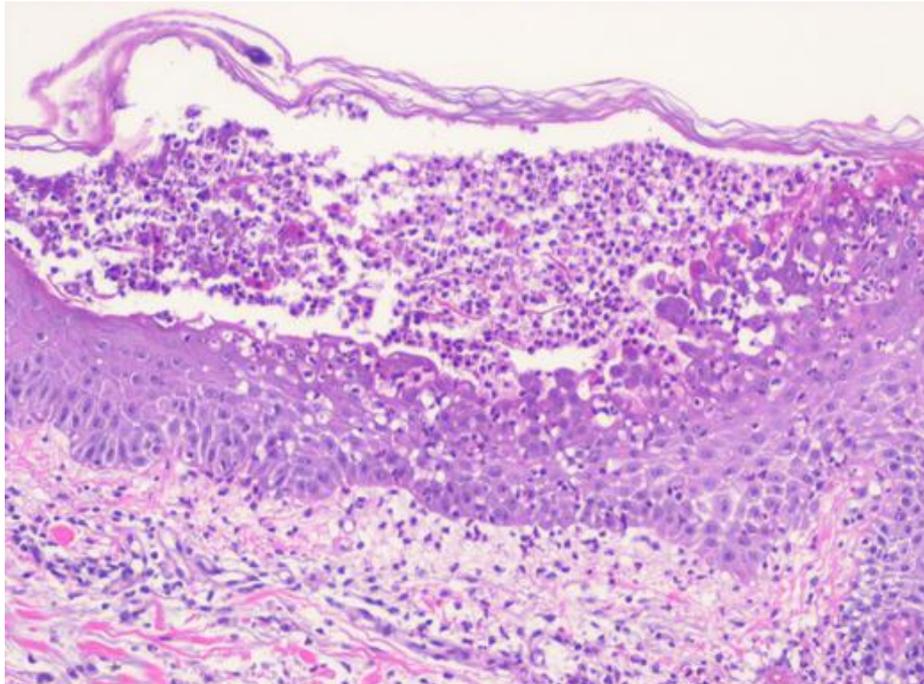
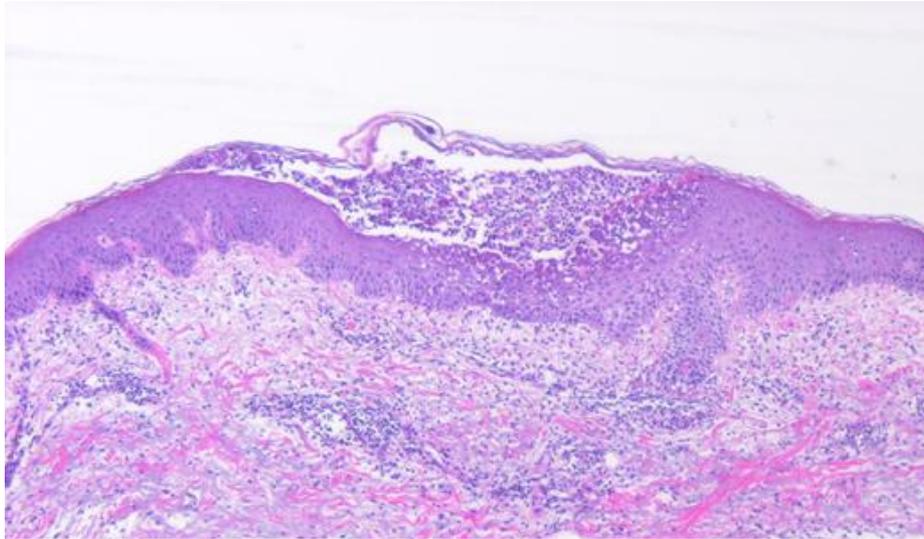
Pustular psoriasis

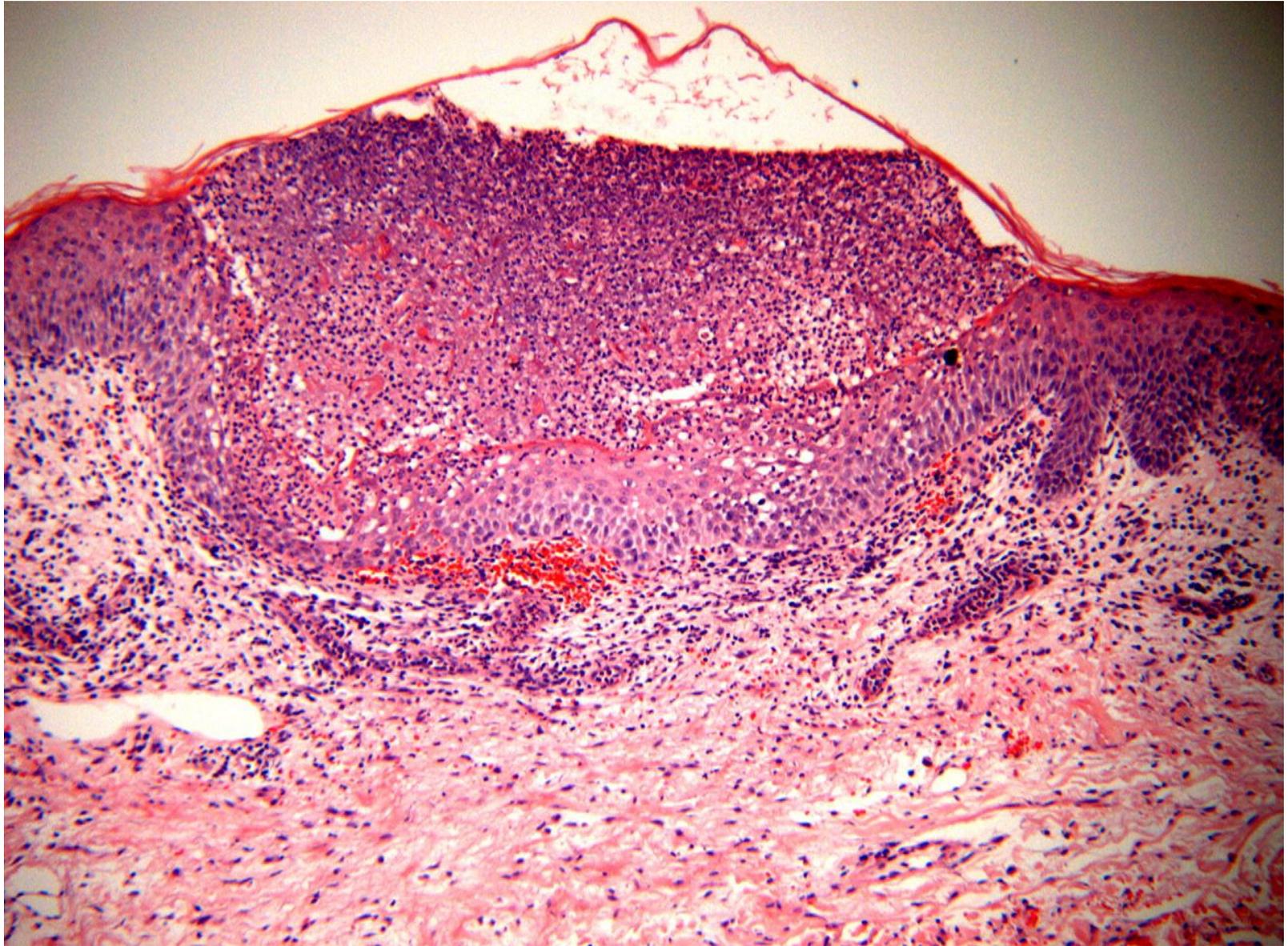
- Clinical correlation: widespread rapid onset of numerous pustules. It can be associated with pregnancy or discontinuation of systemic steroids in patients with psoriasis
- Large collections of neutrophils in stratum corneum or epidermis
- Less epidermal change than psoriasis vulgaris
- No eosinophils!



Pustular psoriasis: differential diagnosis

- **Infections (dermatophytosis and candidiasis):** both dermatophyte and yeast infections usually have some eosinophils! PAS or Grocott stains can help!
- **acute generalized exanthematous pustulosis (AGEP):** a peculiar form of drug eruption, can show striking resemblance to pustular psoriasis. Look to presence of eosinophils, history of new medications e.g. vancomycin)





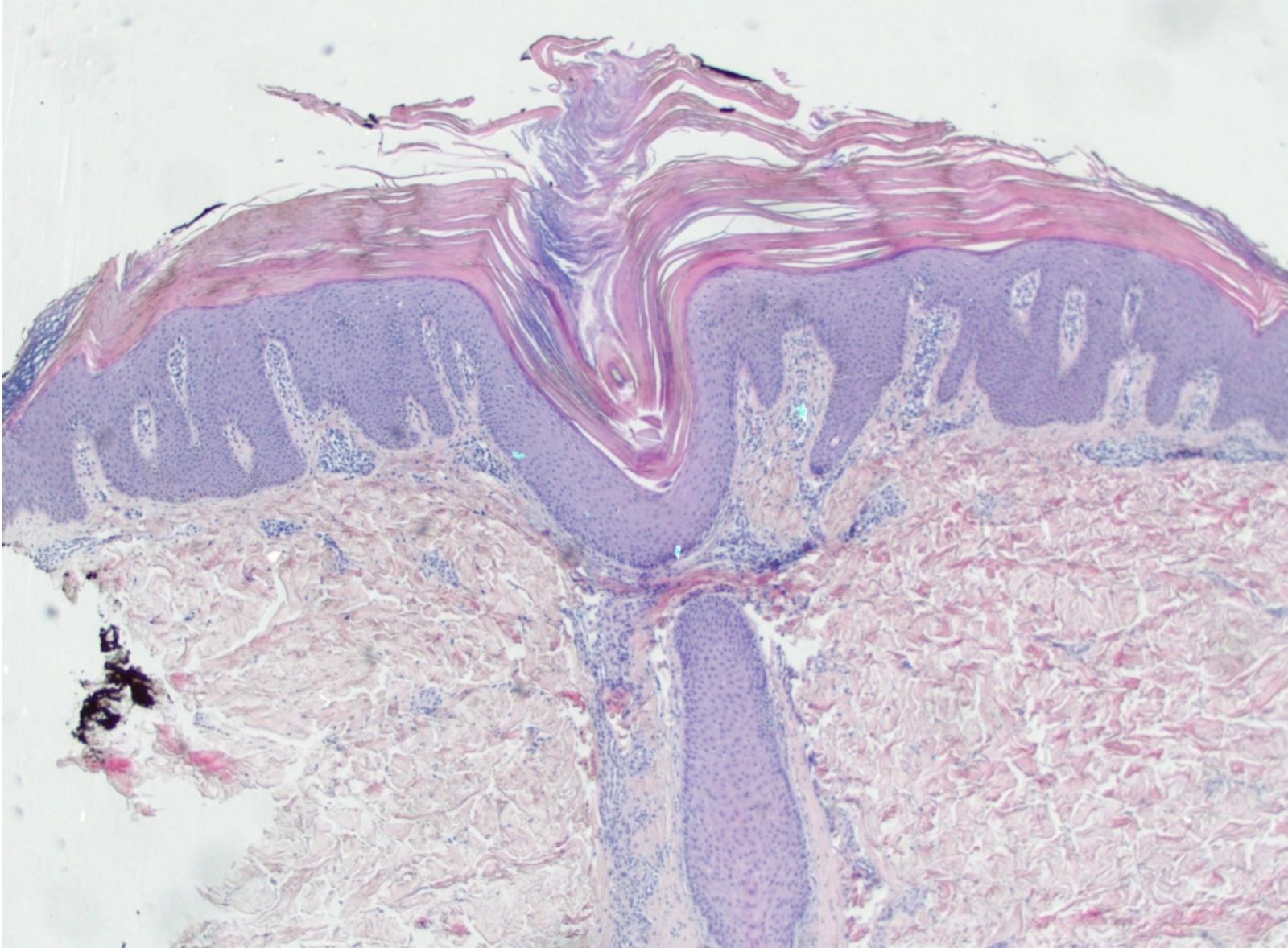
Pustular psoriasis: practical tips

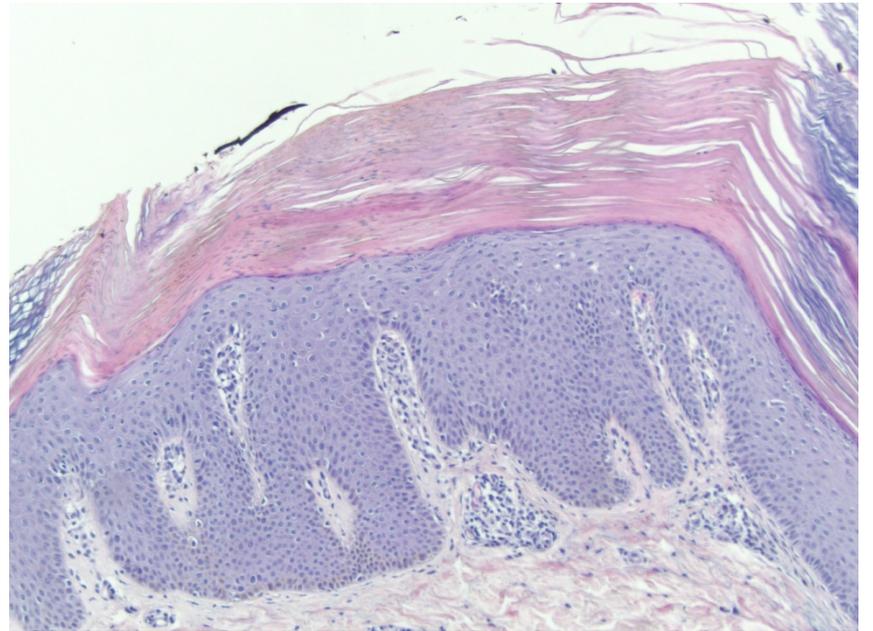
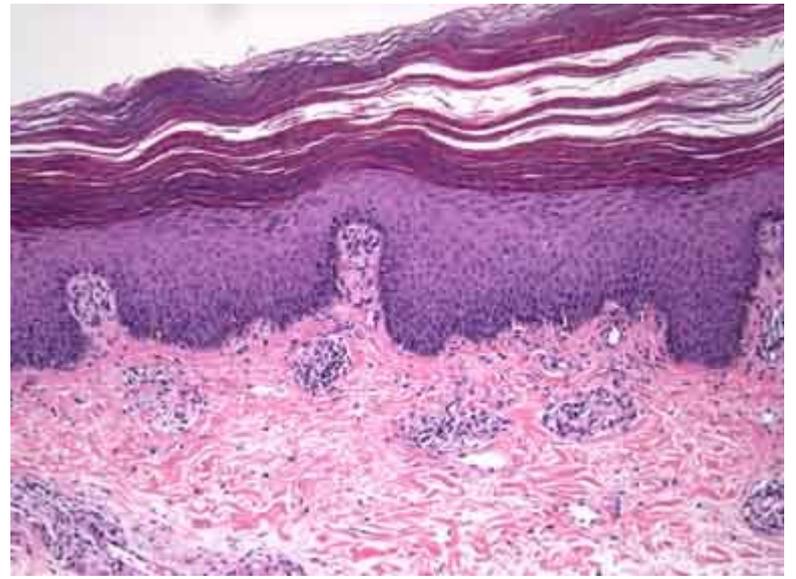
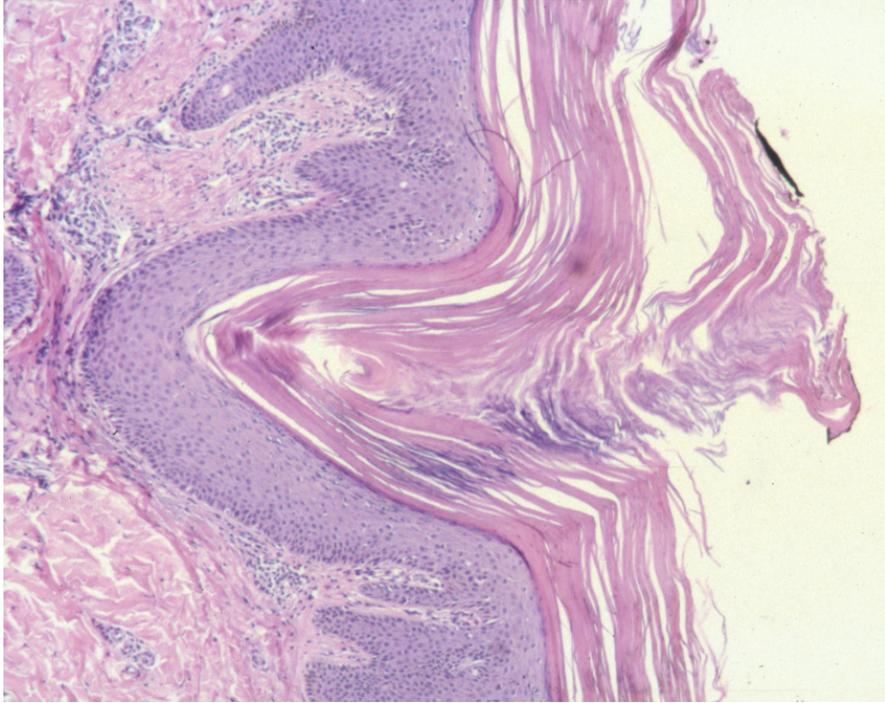
- Rule out a fungal infection with PAS or Grocott stains
- Eosinophils are not a feature of pustular psoriasis; if present consider fungal infection or AGEP/pustular drug eruption
- Patients often have history of psoriasis

Pityriasis rubra pilaris

- Clinical correlation: small follicular papules, confluent erythema with islands of spared skin and palmoplantar keratoderma
- Psoriasiform hyperplasia but normal or thickened granular layer
- Follicular plugging
- Checkerboard pattern of hyperkeratosis and parakeratosis







Pityriasis rubra pilaris: differential diagnosis

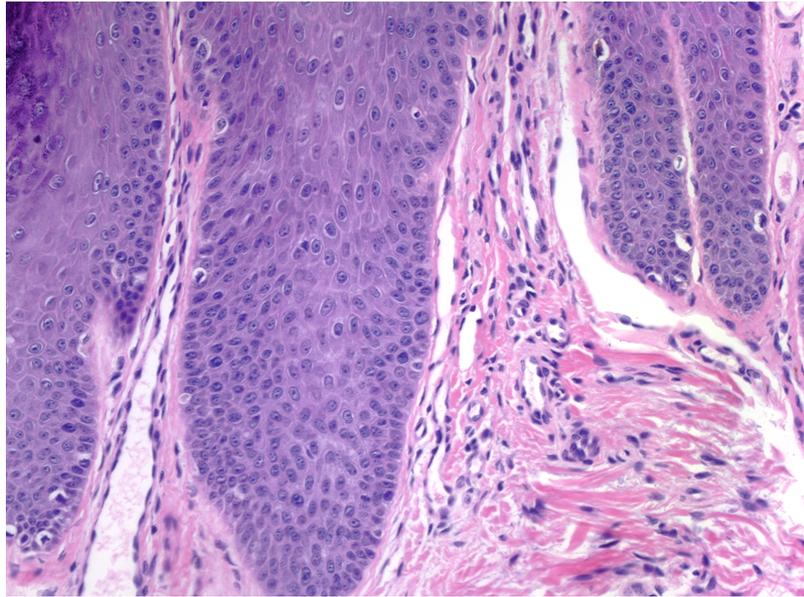
- Psoriasis (neutrophils in epidermis or stratum corneum; diminished or absent granular layer, no follicular plugging)
- Chronic spongiotic dermatitis (lacks the checkerboard pattern of parakeratosis, no follicular plugging)
- Seborrheic dermatitis: can be a difficult histological differential diagnosis because also neutrophils and follicular plugging BUT A VERY DIFFERENT CLINICAL PRESENTATION!

Pityriasis rubra pilaris: practical tips

- Biopsies of early lesions of PRP may be inconclusive. If there is a clinical suspicion of PRP and the biopsy specimens do not show characteristic morphology, a comment stating that a repeat biopsy from the most developed area of the eruption may help establish a diagnosis.
- The presence of follicular plugging even in the absence of a checkerboard pattern is suggestive in the appropriate clinical context.
- The checkerboard pattern of parakeratosis is often subtle.

Lichen simplex chronicus and prurigo nodularis

- Related entities that are the result of persistent scratching or rubbing
- Compact hyperkeratosis
- Acanthosis with thickened granular layer
- Vertically oriented, thickened collagen bundles in superficial dermis
- Sparse inflammatory infiltrate



Lichen simplex chronicus and prurigo nodularis: differential diagnosis

- Chronic spongiotic dermatitis (less prominent psoriasiform hyperplasia, does not have the vertical streaking of the papillary dermal collagen)
- Psoriasis (confluent parakeratosis, diminished or absent granular layer)
- Squamous cell carcinoma

Interface dermatitis

Interface dermatitis

- **Interface dermatitis with lichenoid pattern (lichenoid interface dermatitis):** characterized by basal vacuolization with scattered dyskeratotic keratinocytes and a band-like, or lichenoid, inflammatory infiltrate
 - lichen planus and variants
 - lichen planus-like keratosis (benign lichenoid keratosis)
 - lichenoid drug eruption
 - lichen striatus
 - lichen nitidus
 - histologic regression of many tumors

Interface dermatitis

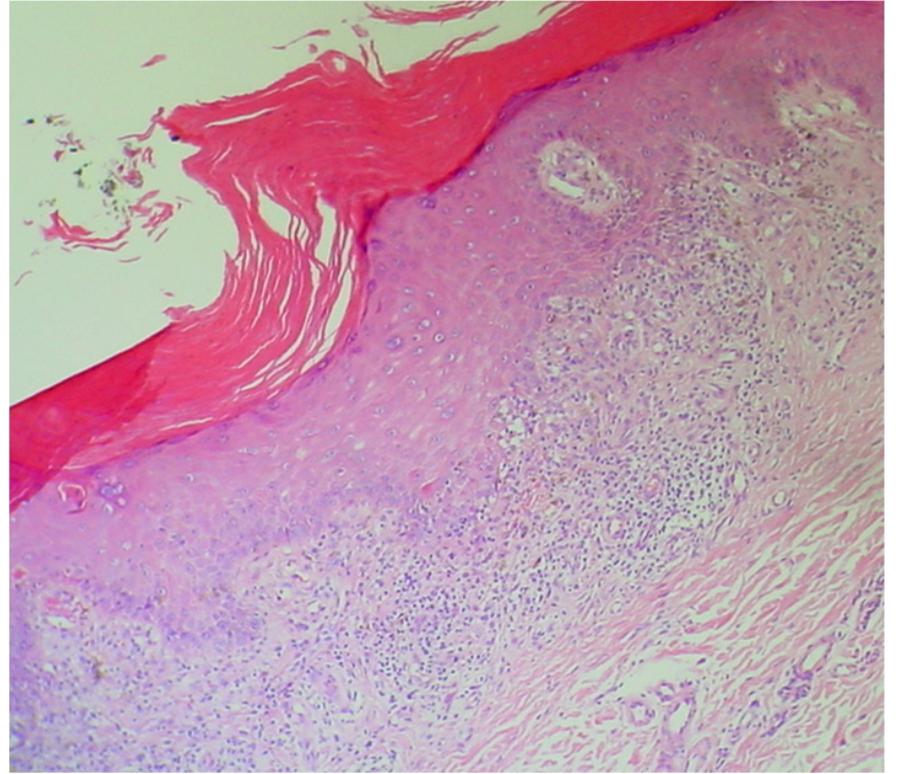
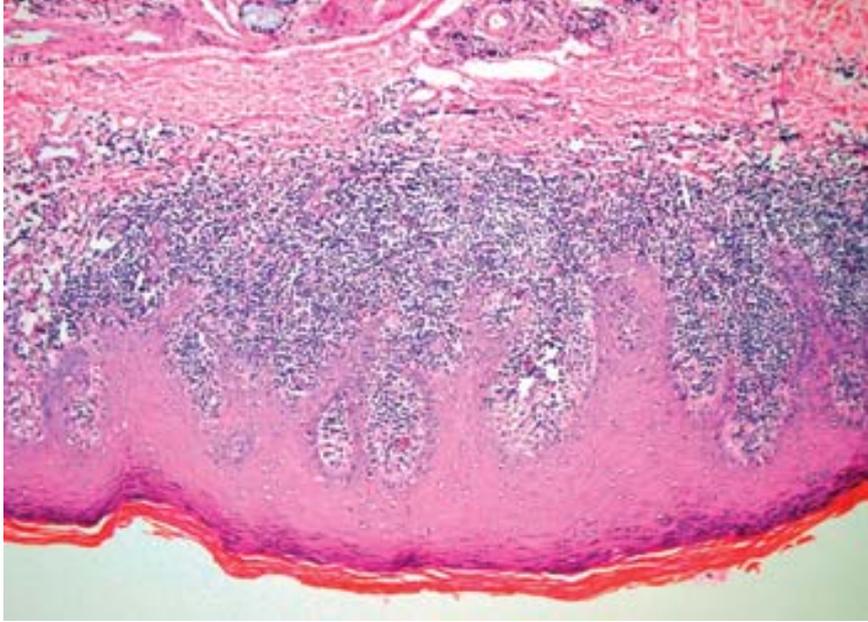
- **Interface dermatitis with a perivascular pattern of inflammation (vacuolar interface dermatitis):** a superficial or superficial and deep dermal perivascular infiltrate in addition to interface change

- erythema multiforme
- fixed drug eruption
- drug eruptions
- viral exanthems
- lupus erythematosus
- dermatomyositis
- graft-versus-host reaction
- pityriasis lichenoides
- vitiligo

Lichenoid interface dermatitis

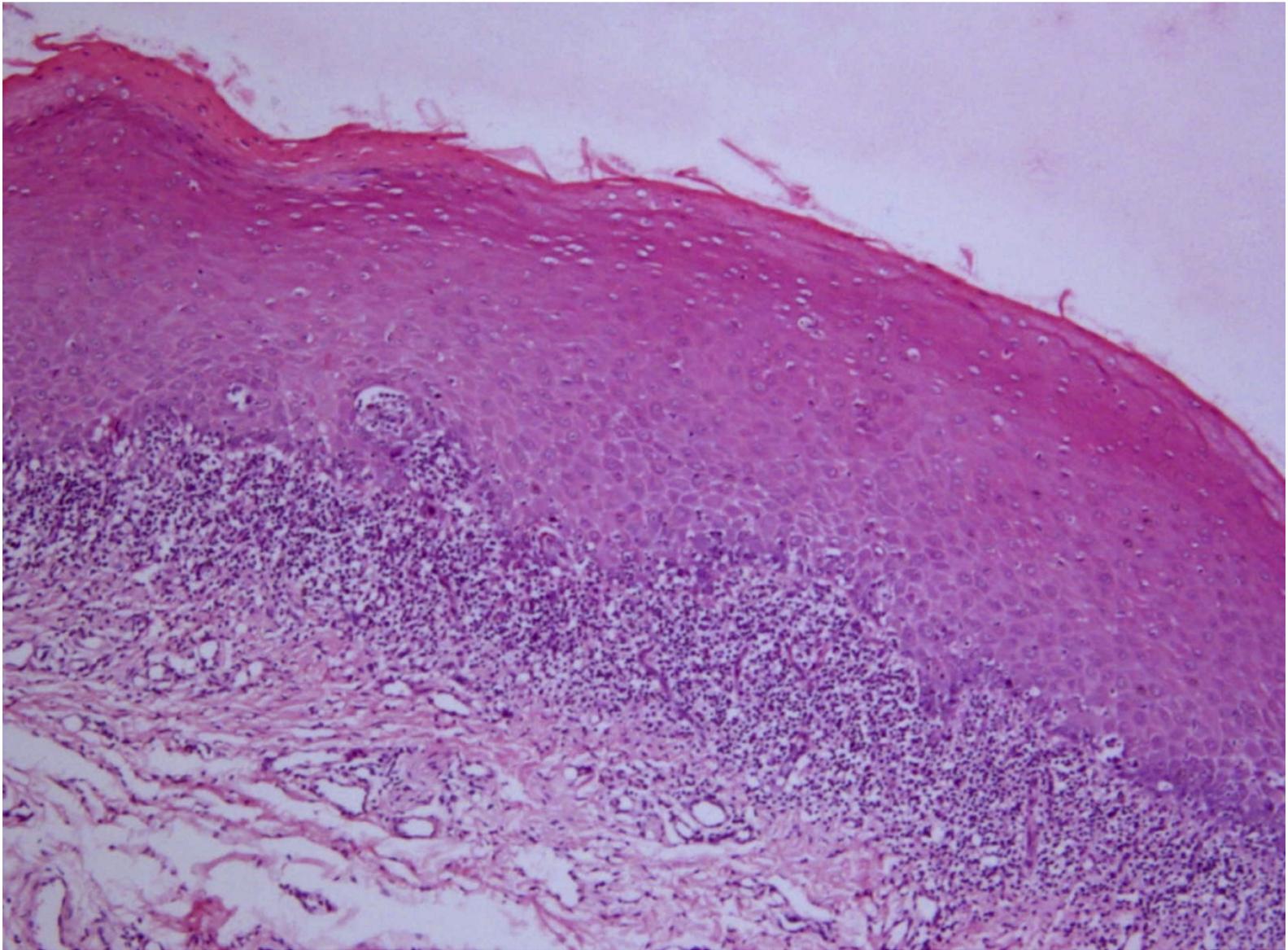
Lichen planus: key microscopic features

- Compact hyperkeratosis without parakeratosis
- Thickened granular layer
- Lichenoid infiltrate
- Interface change with basal vacuolization, dyskeratotic keratinocytes and saw-tooth pattern of dermoepidermal junction
- Typically no eosinophils



Lichen planus: variants

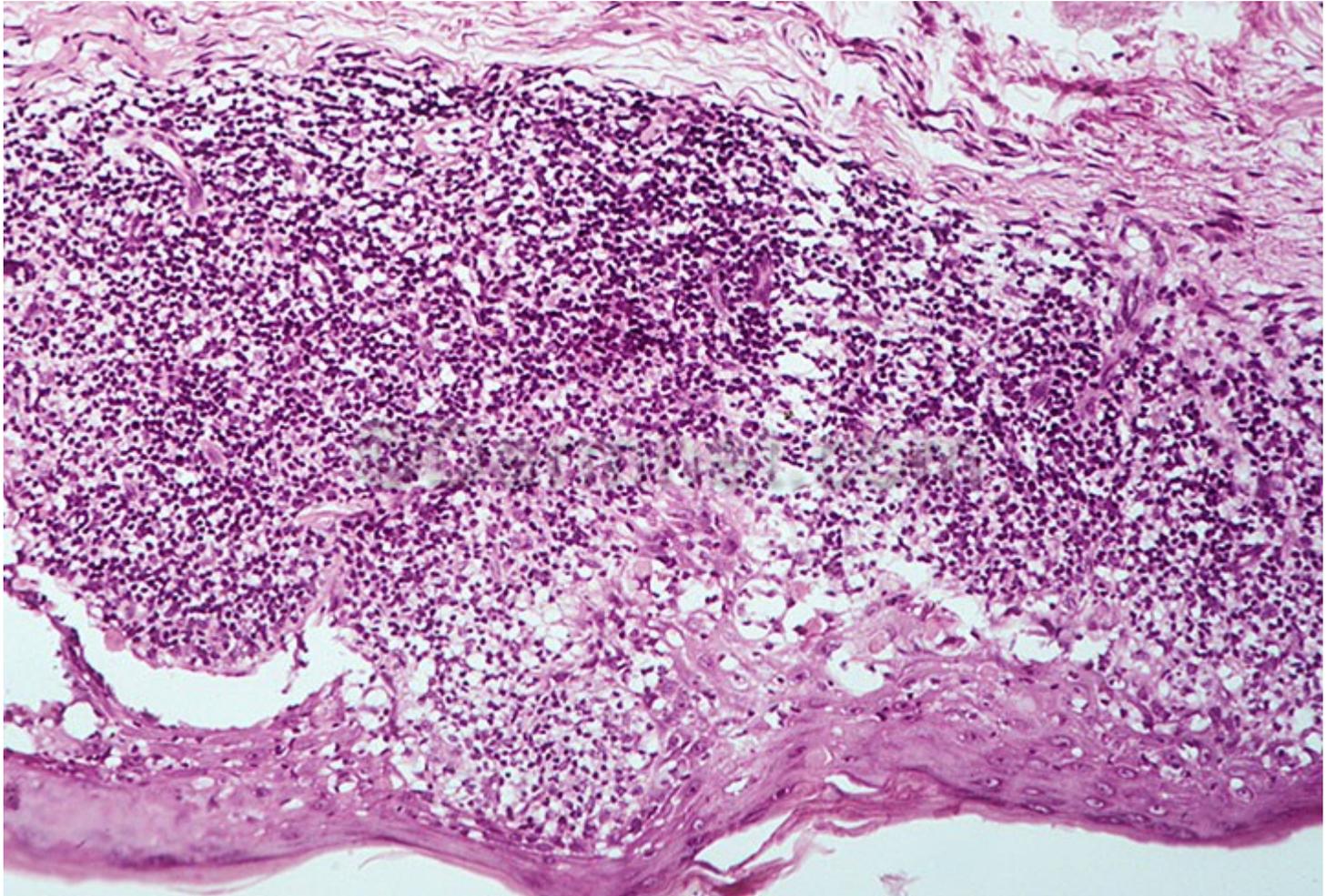
- **Hyperthrophic lichen planus:** resembles conventional LP but with marked acanthosis and eosinophils could be present
- **Atrophic lichen planus:** the epidermis is thinner than normal, and the interface change is subtler. Melanophages are frequently present in the dermis
- **Oral lichen planus:** epithelial changes more subtle than conventional LP, hyperkeratosis, may show parakeratosis, no sawtooth pattern, subtle evidence of formation of a granular layer



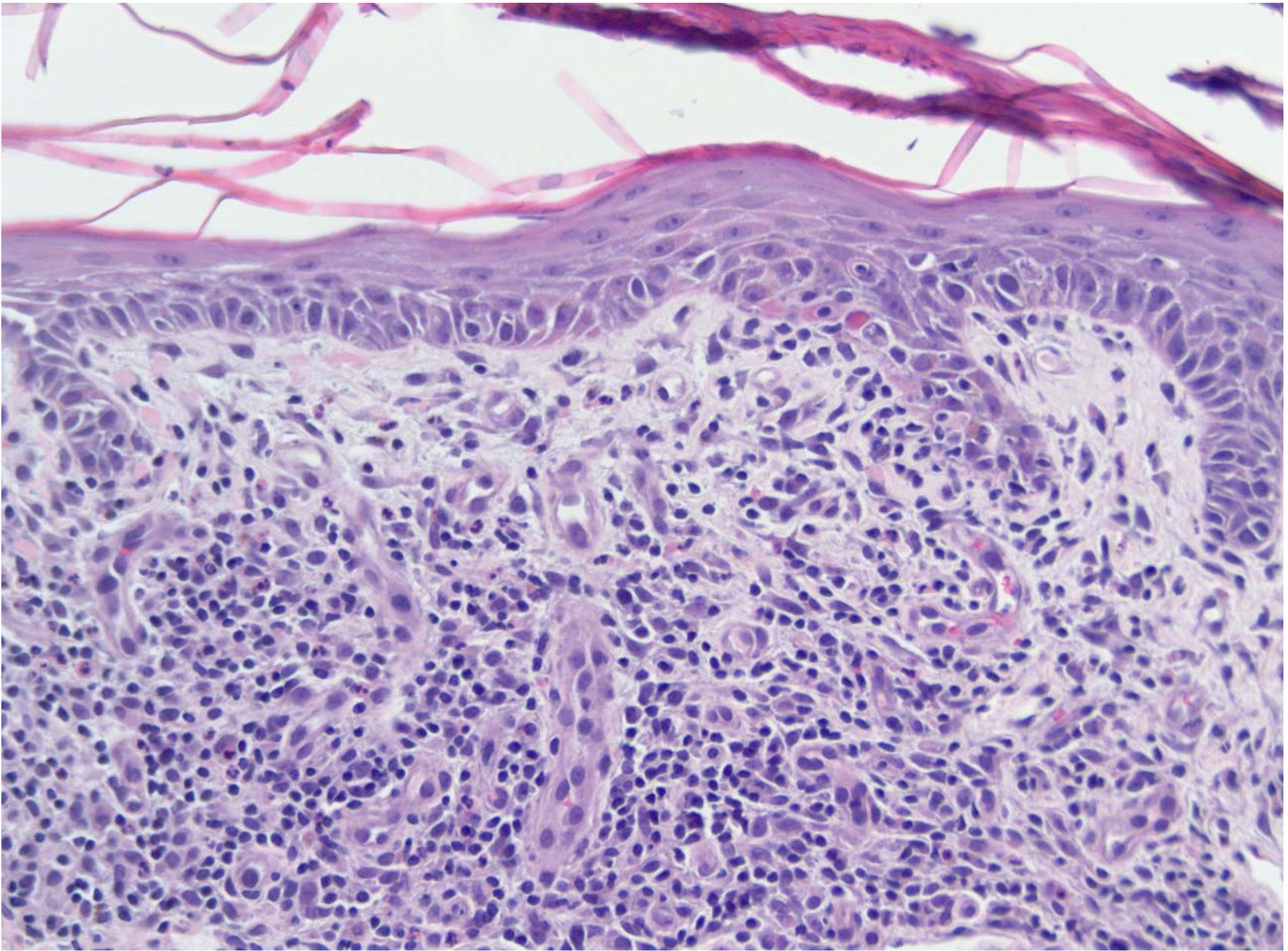
Oral lichen planus

Lichen planus: differential diagnosis

- *Benign lichenoid keratosis (lichen planus-like keratosis)*: clinical presentation is quite different (usually a solitary lesion presenting on the trunk) (no sawtooth pattern, no striking hypergranulosis)
- *Lichenoid drug eruption* (eosinophils, usually some parakeratosis)



Benign lichenoid keratosis



Lichenoid drug eruption

Lichen planus: practical tips

- If the clinical history is a solitary lesion, think benign lichenoid keratosis
- Eosinophils are not a typical feature of lichen planus with perhaps the exception of hypertrophic lichen planus. If present, consider lichenoid drug eruption
- Parakeratosis is not typical a feature of lichen planus. If present, the possibility of a lichenoid drug eruption should be considered
- In cases where the histologic features or clinical history are not clear cut, use a descriptive diagnosis of “lichenoid interface dermatitis, see comment”

Lichenoid drug eruption: key microscopic features

- Compact hyperkeratosis and parakeratosis
- Lichenoid infiltrate of lymphocytes and eosinophils
- Interface change

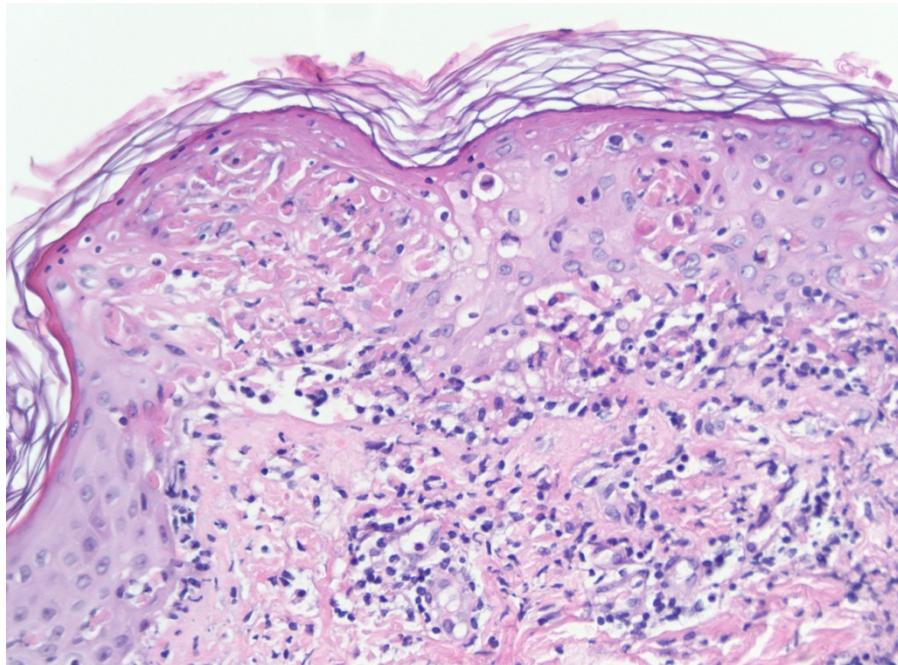
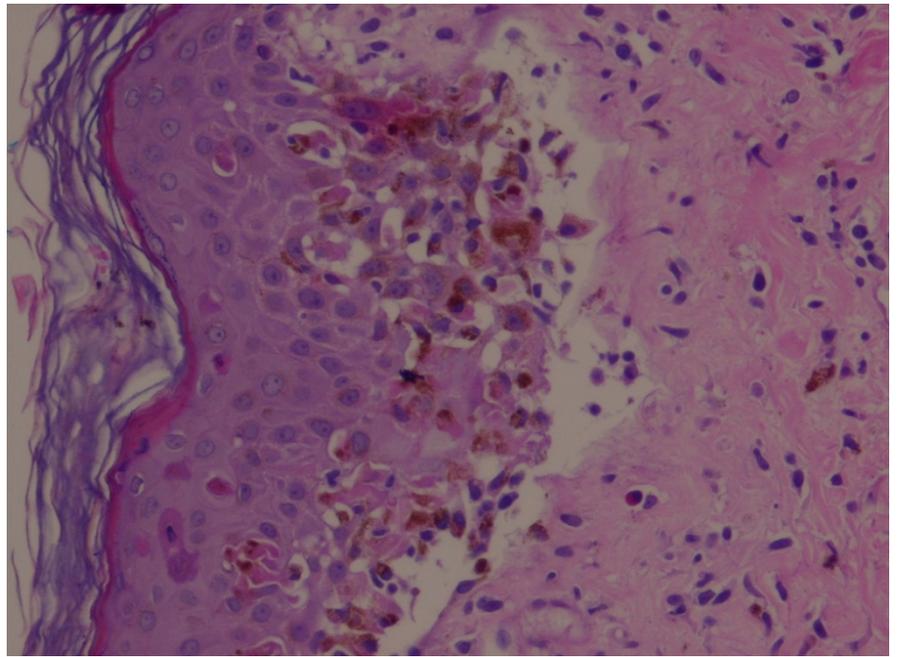
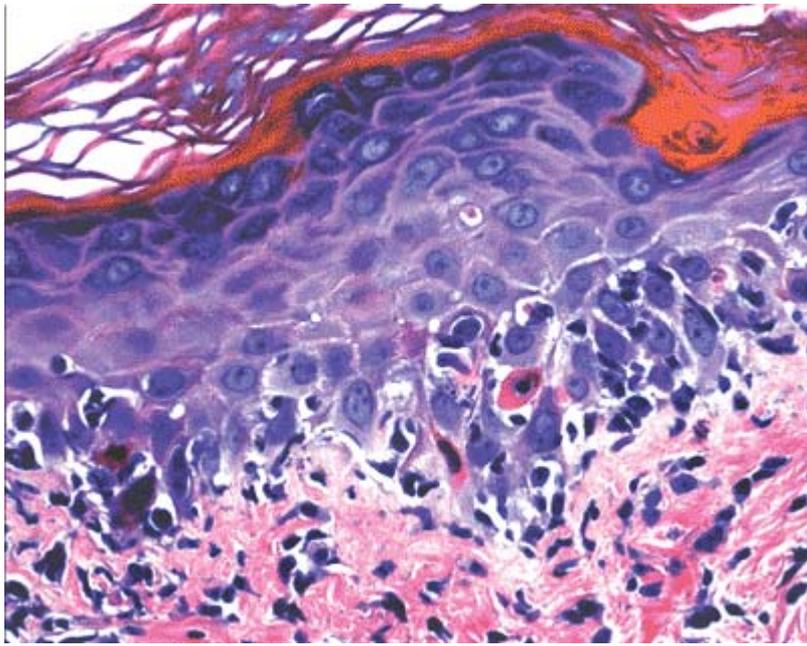
Lichenoid drug eruption: practical tips

- Parakeratosis is a frequent feature. Its presence argues for lichenoid drug eruption rather than lichen planus
- Eosinophils are conspicuous in the great majority of lichenoid drug eruptions.
- Lichenoid drug eruptions are typically more widespread than lichen planus
- Oral mucosa involvement is uncommon in lichenoid drug eruptions

Vacuolar interface dermatitis

Erythema multiforme/Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN)

- Histologically, they are similar to identical
- These entities are viewed as a spectrum of the same disease process
- Normal basket-weave stratum corneum
- Mild perivascular lymphocytic infiltrate (with or without scattered eosinophils)
- Basal vacuolization with dyskeratotic keratinocytes at all levels of the epidermis
- May have full thickness necrosis of epidermis

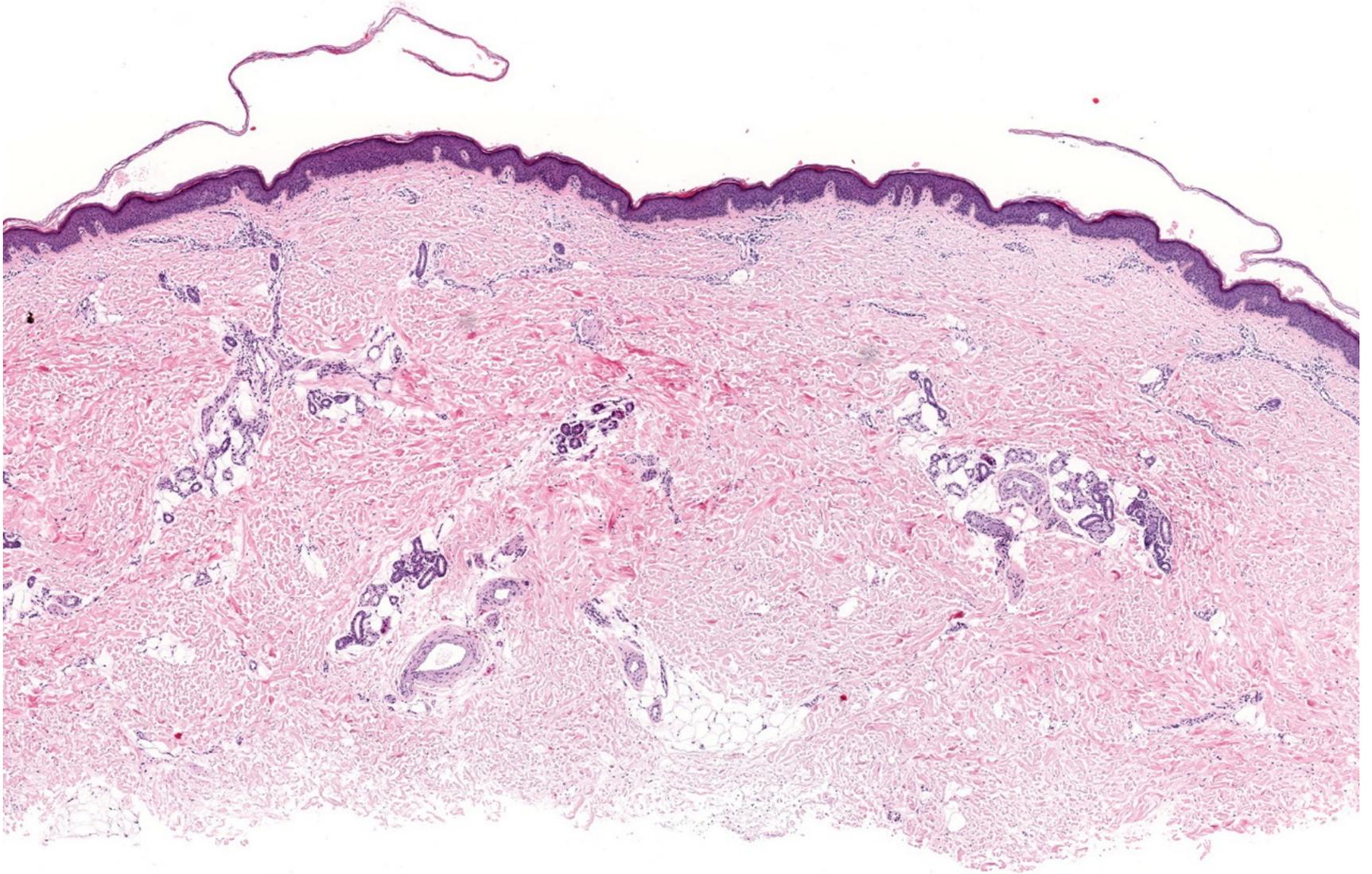


EEM/TEN: differential diagnosis

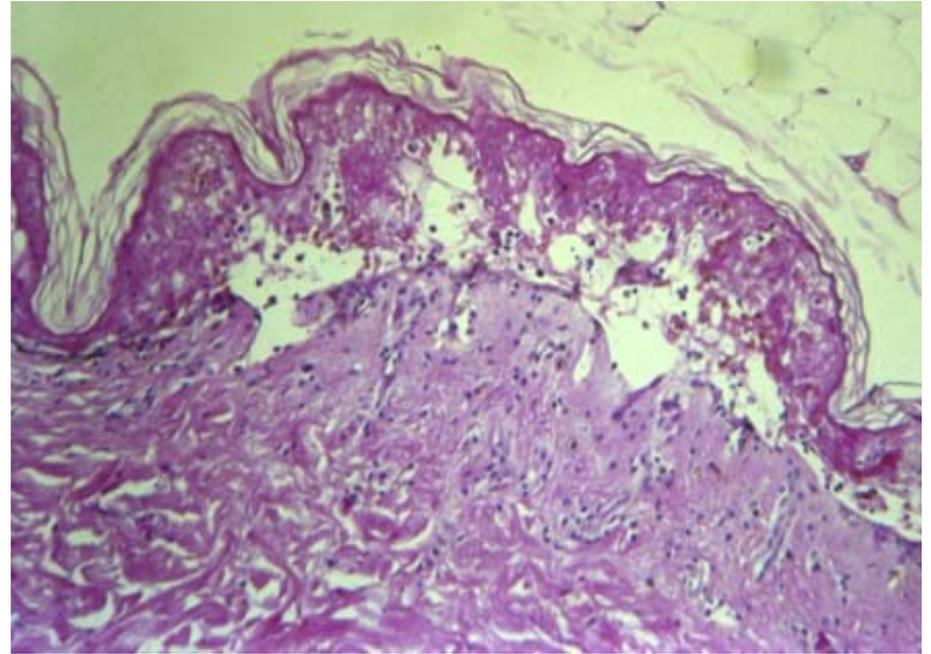
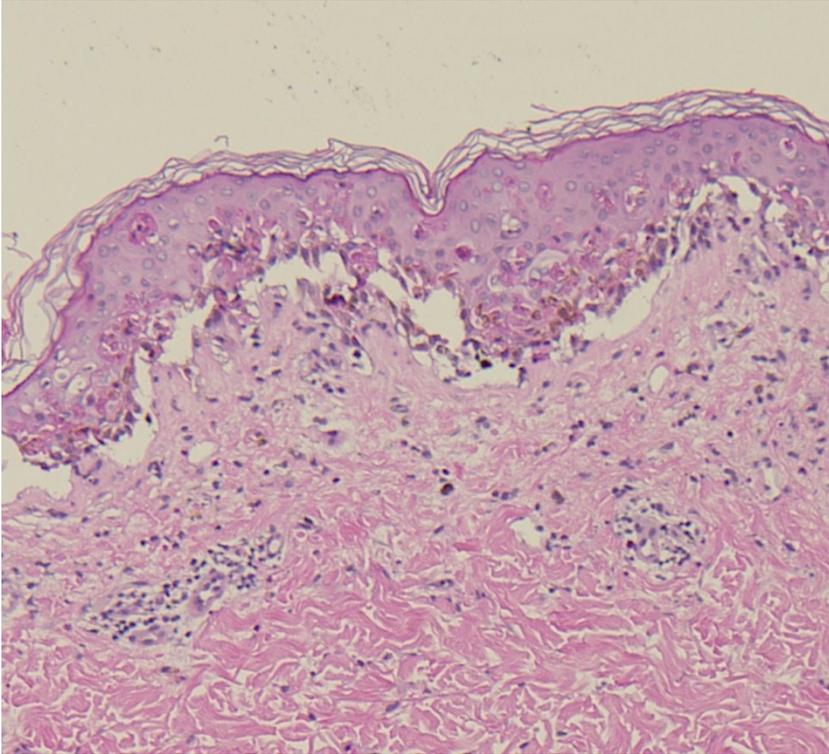
- Morbilliform (typical) drug eruption (epidermal damage is more pronounced in EEM!)
- GVHD (appropriate clinical history!)
- Connective tissue disease (LE and dermatomyositis) (epidermal changes like thickened basement membrane, parakeratosis and dermal mucin, immunofluorescence)

DD TEN and SSSS

- SSSS (Staphylococcal scalded skin syndrome): SSSS is characterized by a split between the stratum spinosum and stratum corneum, no interface change or prominent keratinocyte necrosis in contrast to toxic epidermal necrolysis (TEN)



Staphylococcal scalded skin syndrome



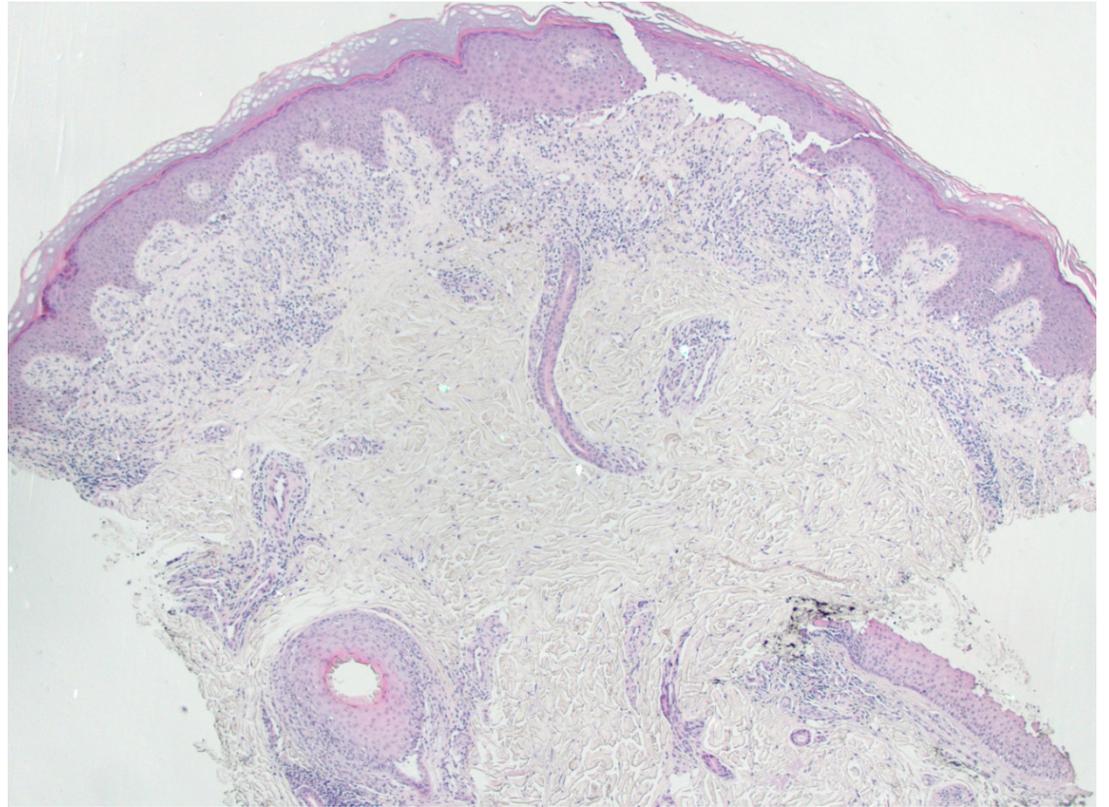
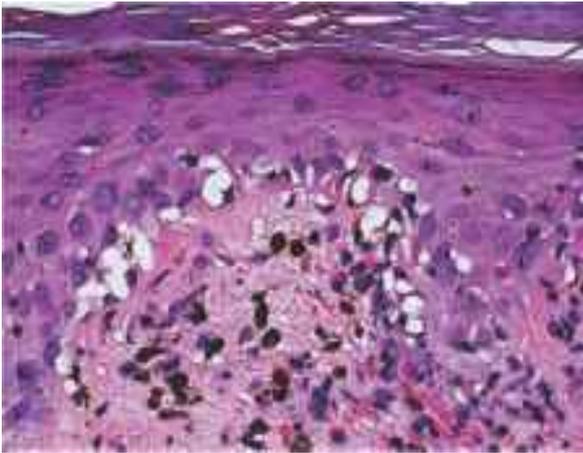
Toxic Epidermal Necrolysis (TEN)

EEM/TEN: practical tips

- Degree of epidermal damage is disproportionate to the density of the infiltrate
- Because this group has an acute onset, the epidermis retains its normal basket-weave pattern in the stratum corneum
- If there are large areas of full thickness necrosis, SJS or TEN is more likely. But these distinction is only made clinically!!

Fixed drug eruption: key microscopic features

- Normal basket-weave stratum corneum or parakeratosis; no hyperkeratosis
- Infiltrate of lymphocytes and eosinophils
- Scattered melanophages
- Interface change



Fixed drug eruption: differential diagnosis

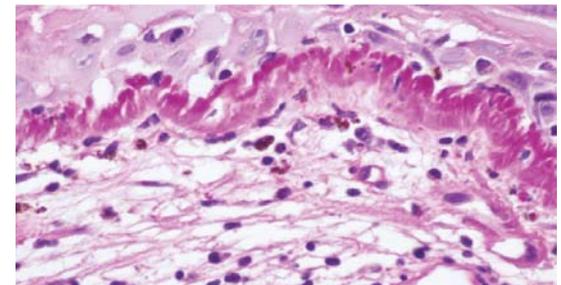
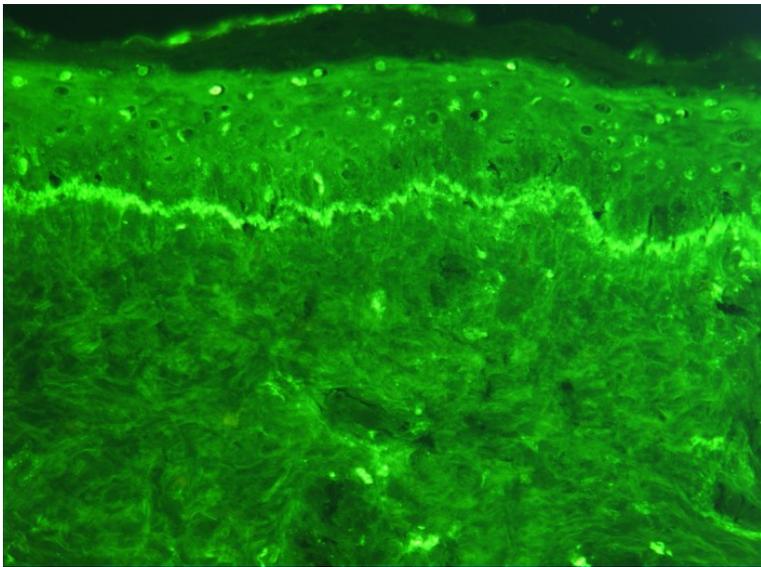
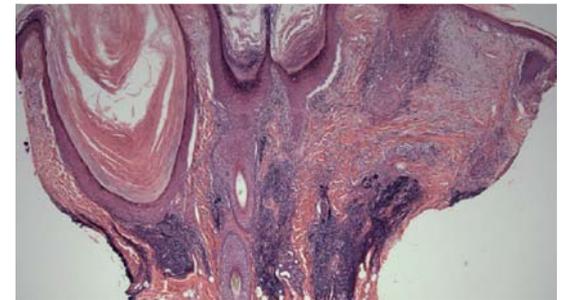
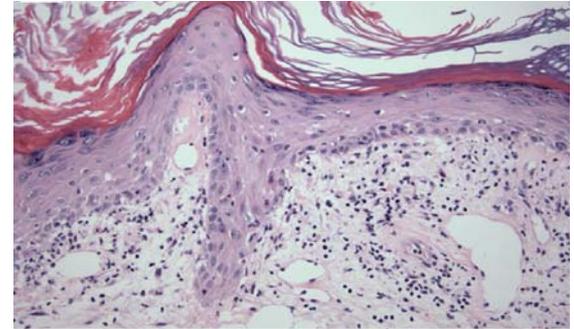
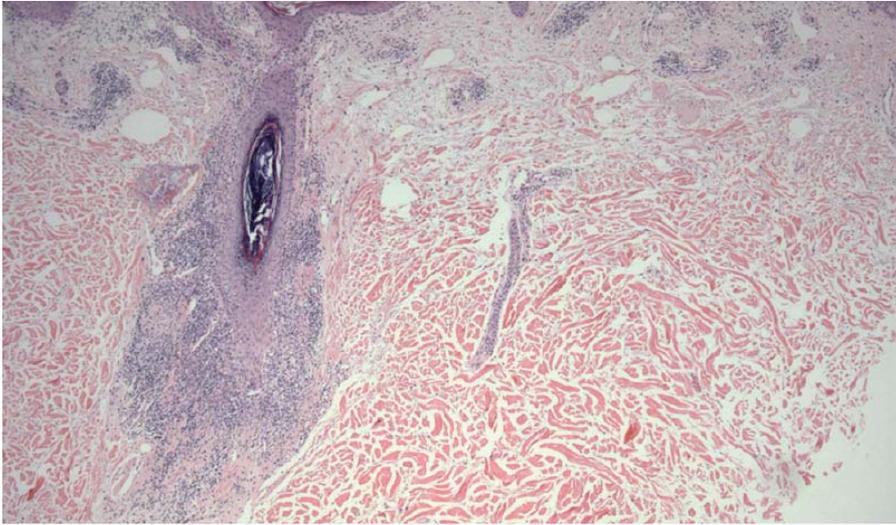
- EEM (less prominent dermal infiltrate)
- GVHD (less prominent dermal infiltrate, appropriate clinical history)
- Lichen planus
- Lichenoid drug eruption

Fixed drug eruption: practical tips

- Clinically localized, not widespread
- Only make a diagnosis of fixed drug eruption with a solid clinical history.
- Epidermal change limited: patchy keratosis to normal stratum corneum, granular layer not thickened
- Melanophages can be a clue to an evolving or recurrent fixed drug eruption
- Fixed drug eruptions have more prominent interface change than morbilliform drug eruptions

Lupus erythematosus (LE) discoid type:key microscopic features

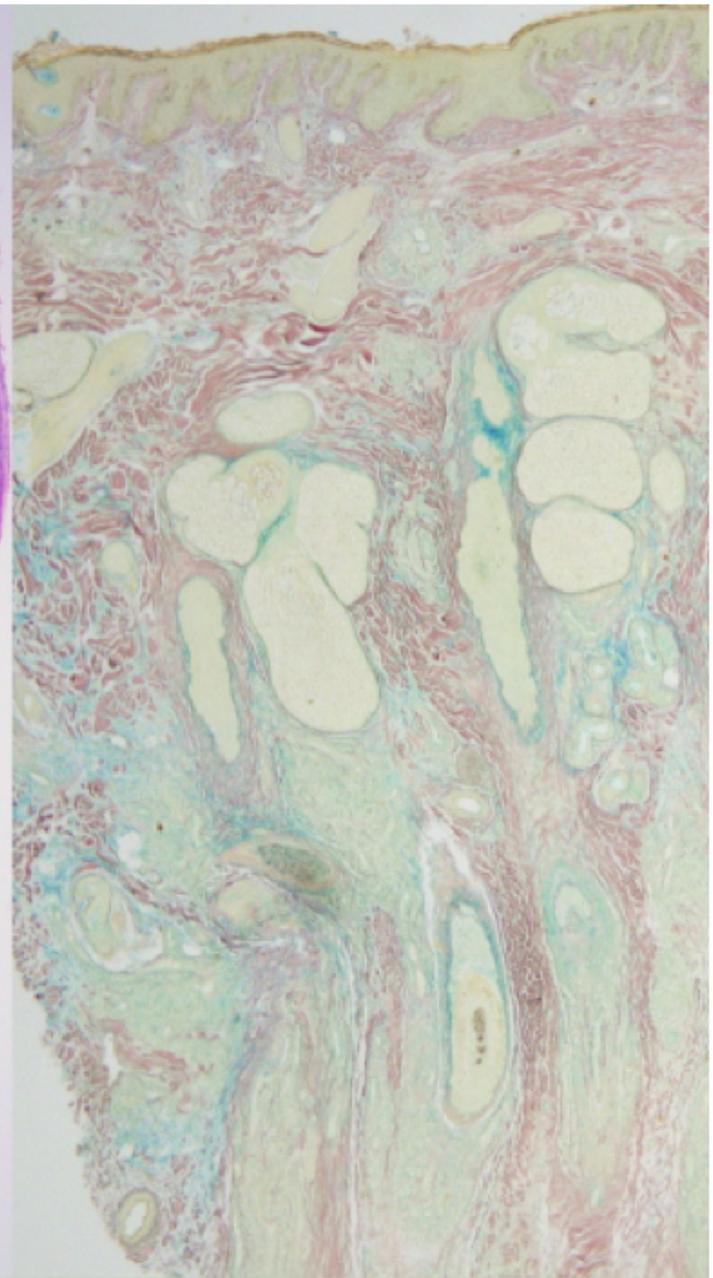
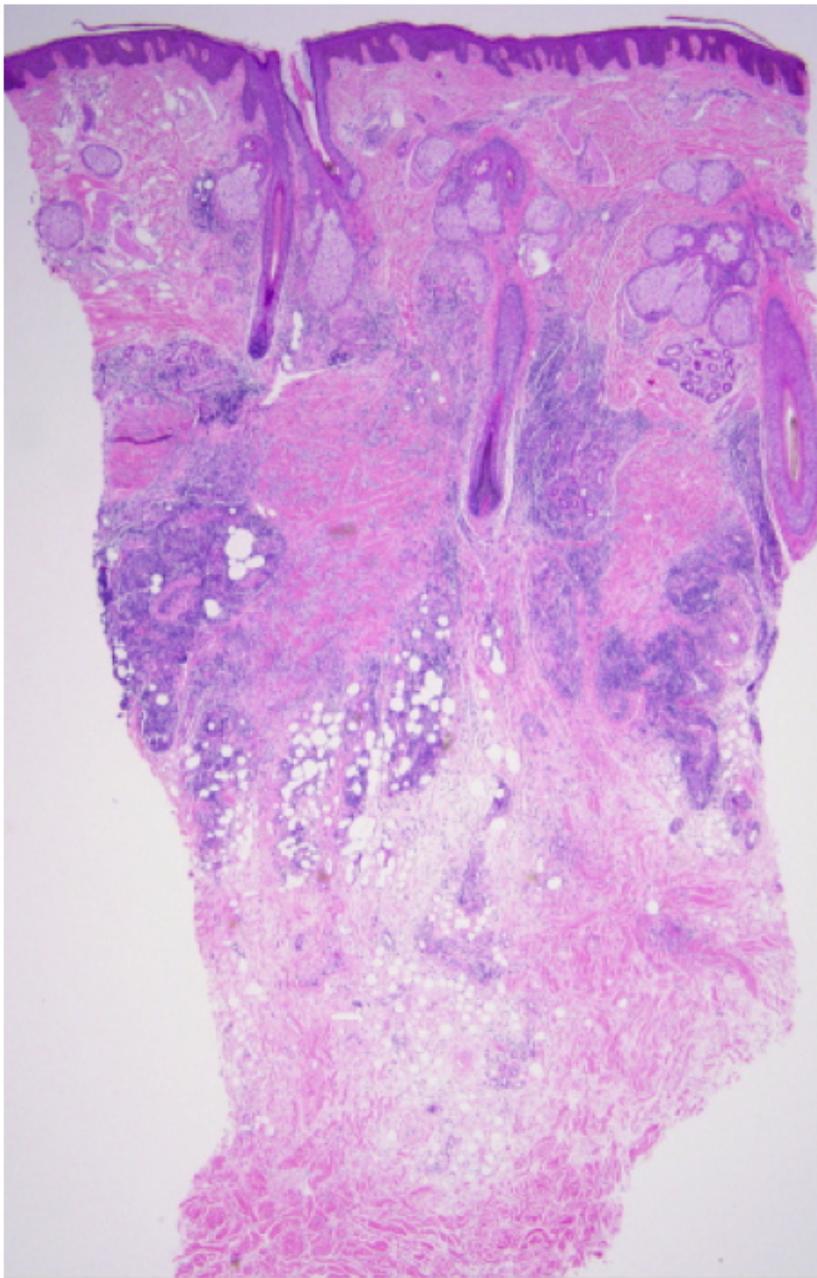
- Variable hyperkeratosis and parakeratosis, follicular plugging
- Interface change with basal vacuolization
- Epidermal basement membrane often thickened
- Superficial or superficial and deep perivascular or perivascular and periadnexal lymphocytic infiltrate
- Increased dermal mucin



Lupus erythematosus: lupus band (IgG)

LE variants

- Subacute LE: usually a less intense inflammatory infiltrate and more prominent atrophy.
- Systemic LE: prominent basal vacuolization but necrotic keratinocytes are rare, infiltrate typically less intense and usually in a superficial perivascular distribution
- Tumid LE: significant interface change typically absent, combination of a superficial and deep infiltrate with increased mucin is an important clue



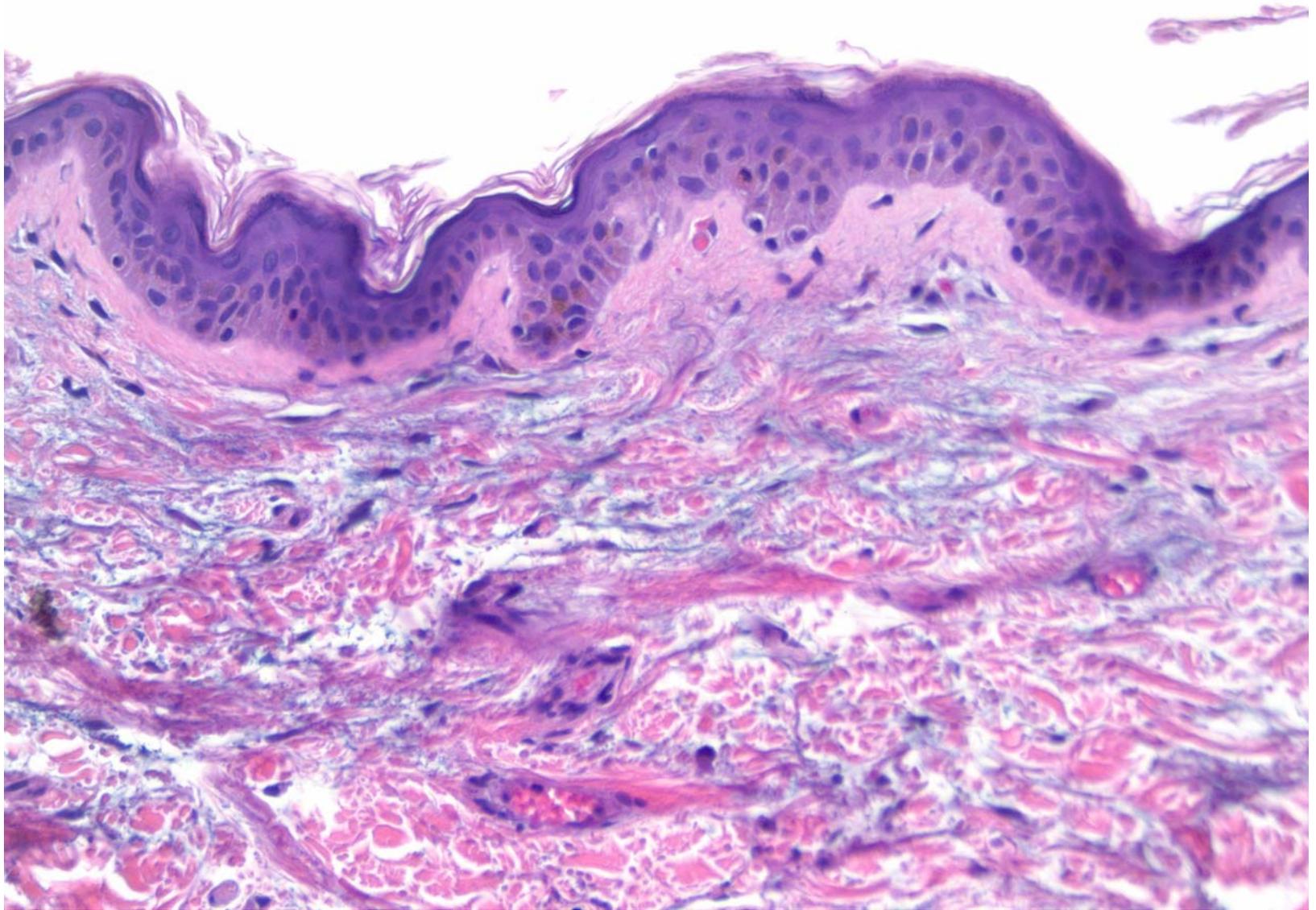
Tumid LE

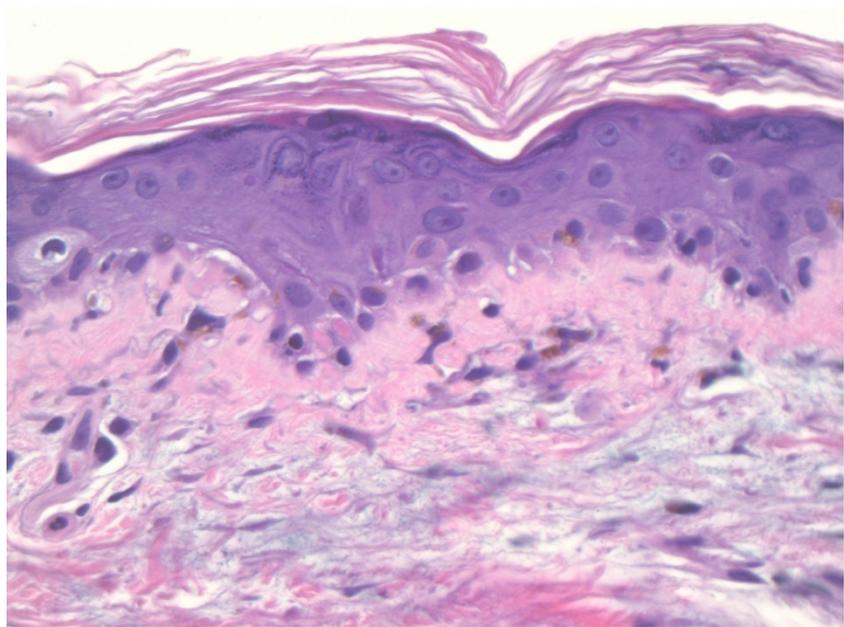
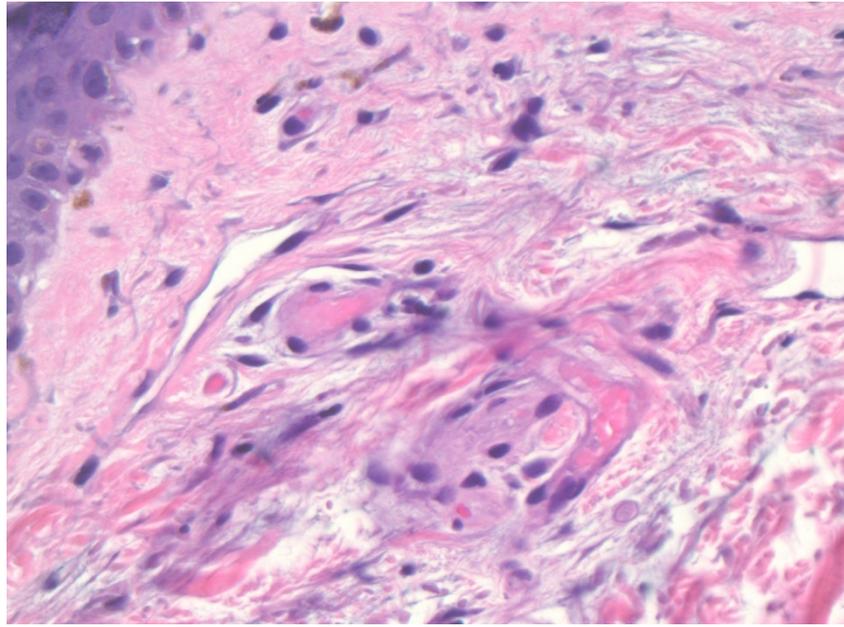
LE: practical tips

- Distribution is important: LE is a photo-distributed disease
- Eosinophils are not a feature of LE except in rare cases of drug-induced LE The presence of eosinophils raises the possibility of an arthropod bite reaction or drug eruption
- Colloidal iron studies may help highlight the dermal mucin
- Some cases of dermatomyositis and LE are histologically indistinguishable
- Tumid LE lacks interface change

Dermatomyositis: key microscopic features

- Basal vacuolization
- Mild superficial perivascular lymphocytic infiltrate
- Increased dermal mucin
- **Clinical correlation is important:** combination of muscle weakness and characteristic cutaneous findings of erythematous to violaceous slightly scaly lesions. The face, shoulders and extensor surfaces are most commonly involved





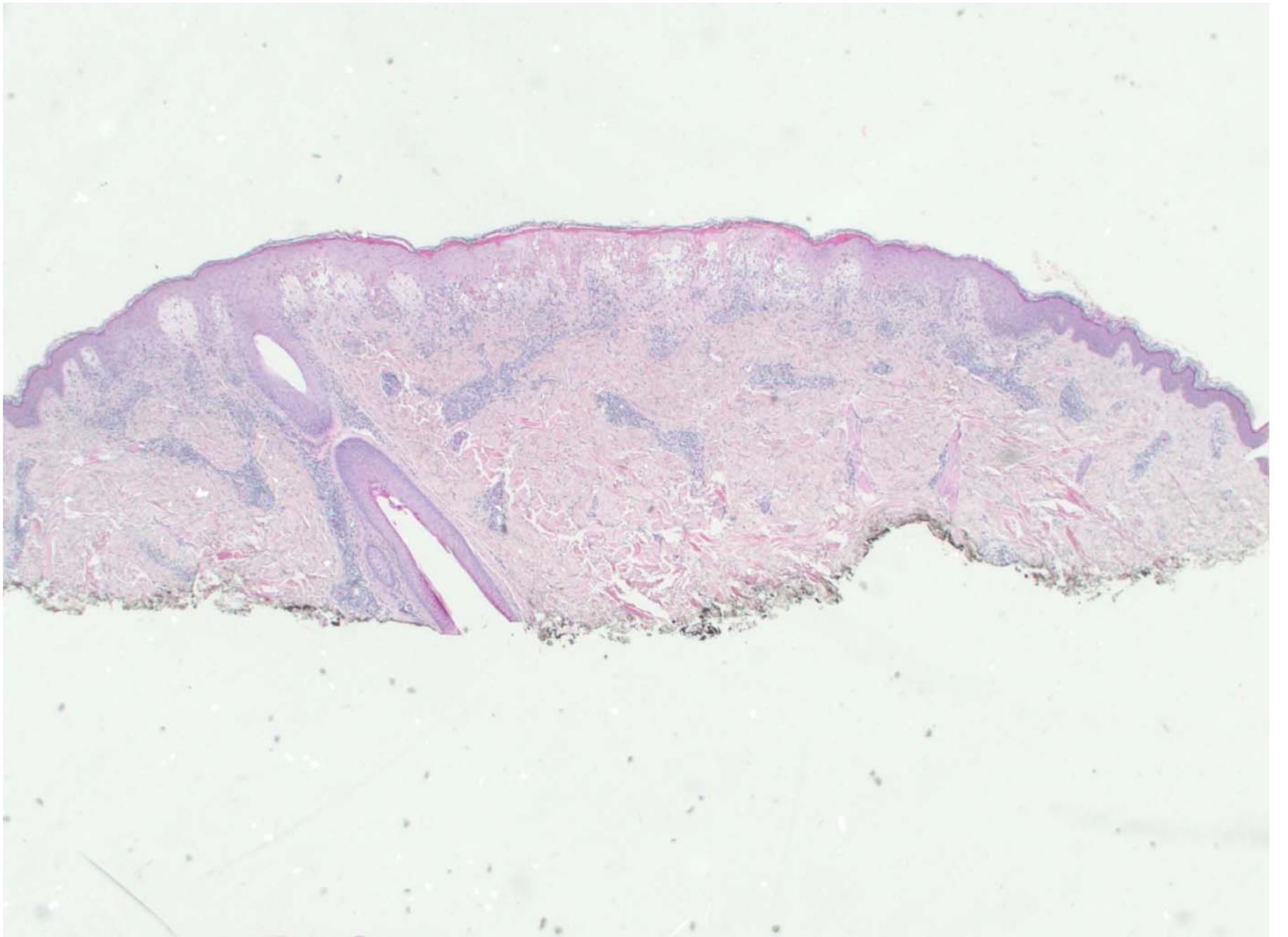
Dermatomyositis: practical tips

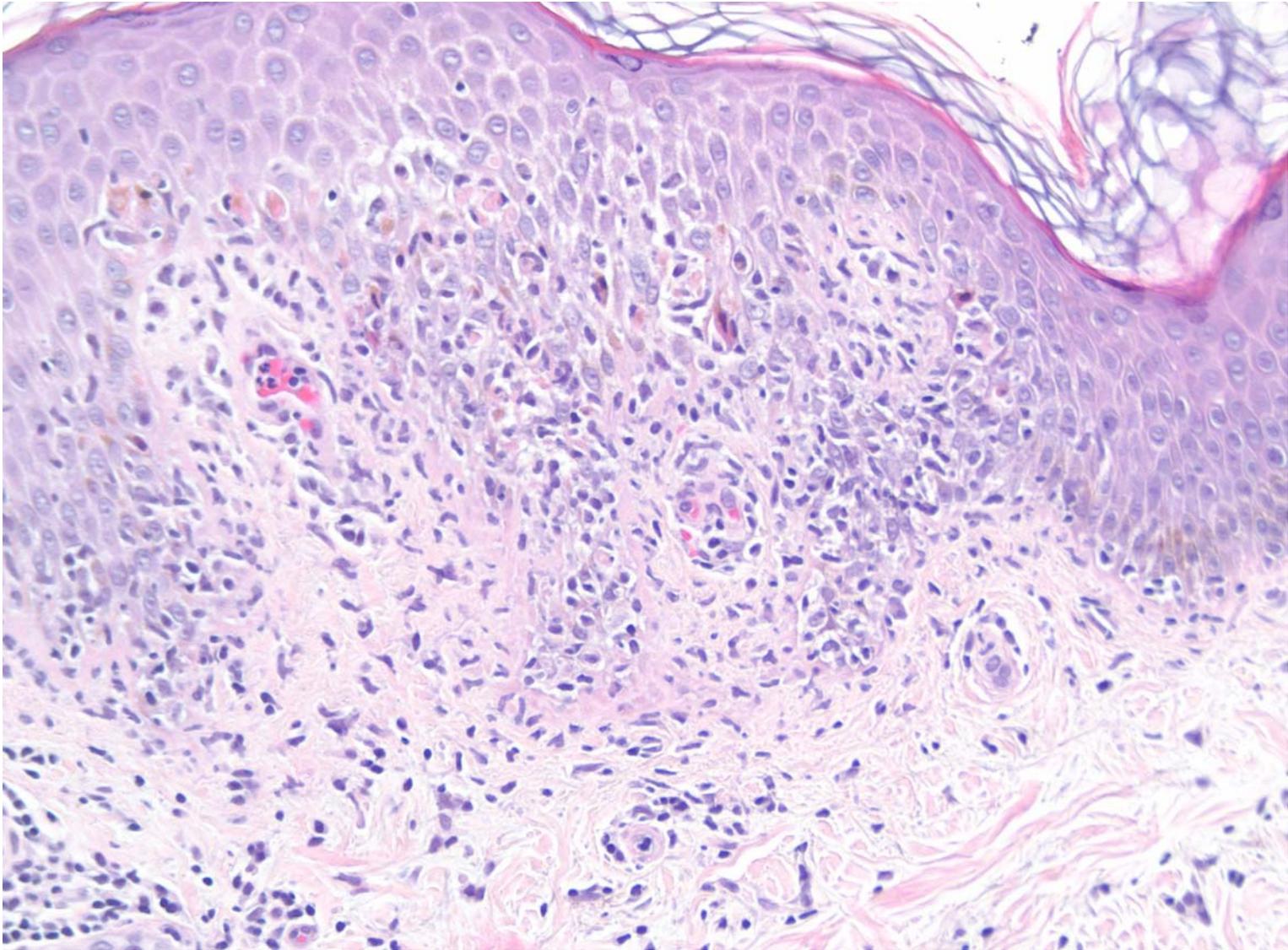
- The infiltrate is usually mild and restricted to the superficial dermis. If there is a deep component, consider the diagnosis of lupus erythematosus
- Eosinophils are not a feature. If present consider the diagnosis of a drug eruption
- Colloidal iron stains may help highlight the dermal mucin
- Dermatomyositis is pruritic, this clinical information can be a clue

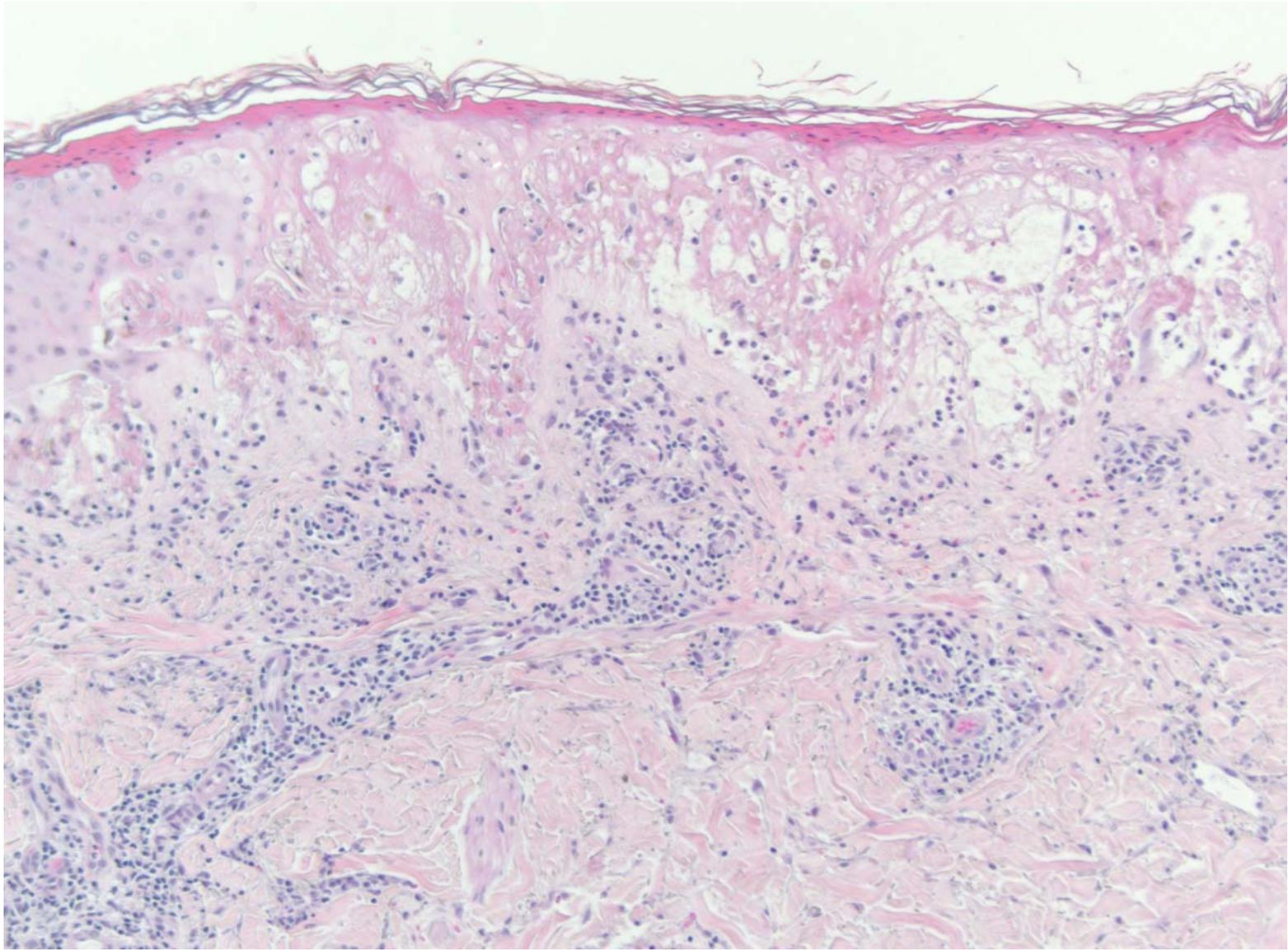
Pityriasis lichenoides et varioliformis acuta (PLEVA): key microscopic features

- Parakeratosis, spongiosis and basal vacuolization
- Dyskeratotic keratinocytes
- Superficial and deep perivascular lymphocytic infiltrate
- Extravasation of erythrocytes in papillary dermis









PLEVA: practical tips

- Maintain a high index of suspicion
- The presence of interface change with hemorrhage is an important clue
- Knowledge of the clinical history: PLEVA presents as hemorrhagic papules
- An ulcerated lesion of PLEVA has non-specific histologic features. Suggest re-biopsy of a more recent lesion

Perivascular dermatitis

perivascular dermatitis: definition

- The inflammatory infiltrate is concentrated around the vessels of the superficial and/or deep vascular plexus. **There is no significant epidermal change.**

Superficial perivascular dermatitis (1)

- **Lymphocytes predominant**

- drug reactions (morbilliform)
- viral exanthems
- chronic urticaria
- superficial annulare centrifugum (gyrate erythema)

- **Lymphocytes with extravasated erythrocytes and/or siderophages**

- Schamberg's disease and other forms of pigmented purpuric dermatosis
- stasis dermatitis (see spongiotic dermatitis)

Superficial perivascular dermatitis (2)

- **Eosinophils**

- urticaria

- urticarial hypersensitivity reaction (arthropod bite or drug)

- drug reactions (morbilliform)

- **Mast cells perivascular and interstitially**

- cutaneous mastocytosis (especially telangiectasia eruptiva macularis perstans or TMEP)

- **Plasma cells**

- syphilis

- rosacea

Superficial and deep perivascular dermatitis

- **Lymphocytes predominate**

- deep annular erythema (gyrate erythema)
- polymorphous light eruption
- perniosis (chilblains)
- lymphomatoid papulosis

- **Eosinophils**

- dermal hypersensitivity reaction (including arthropod bite reaction or drug)

- **Plasma cells**

- morphea
- syphilis
- Lyme disease (erythema chronicum migrans)

Morbilliform drug eruption: key microscopic features

- Epidermis normal or with mild interface change
- Usually mild superficial perivascular infiltrate but may be deep
- Infiltrate may be predominantly composed of lymphocytes or eosinophils, but eosinophils are usually present

Morbilliform drug eruption: practical tips

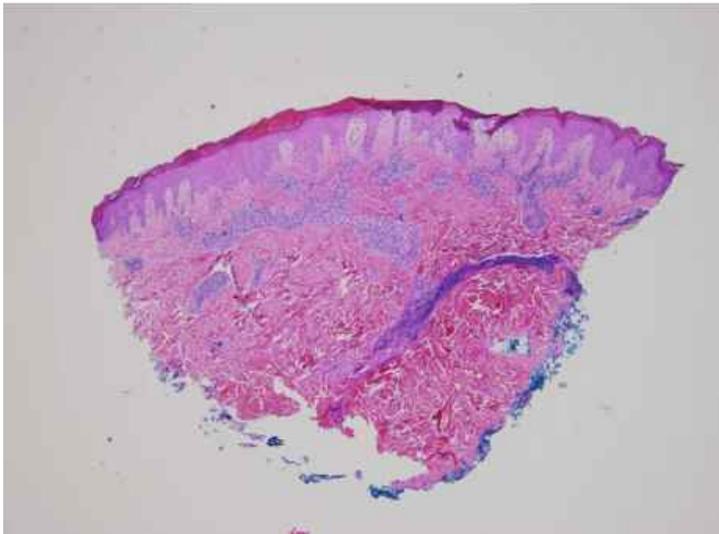
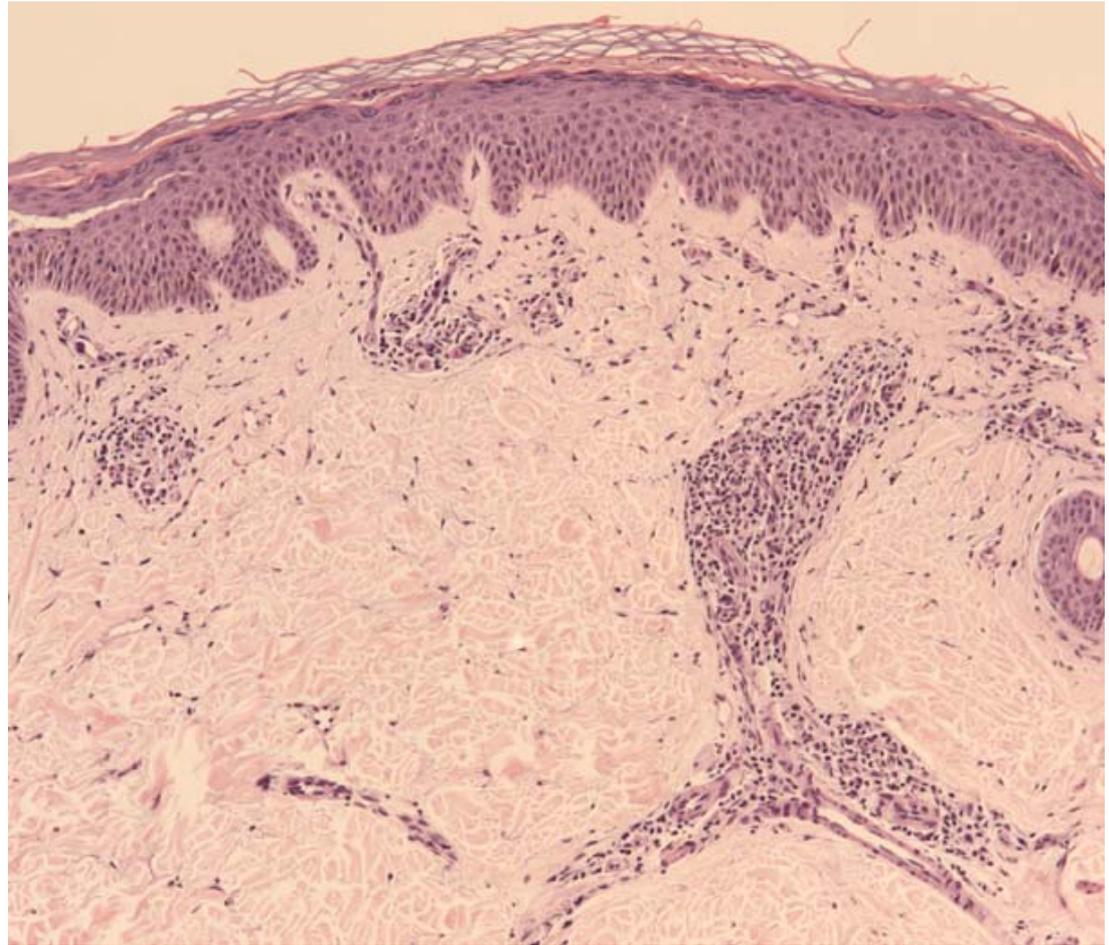
- Sparse infiltrate is a clue
- Usually widespread eruptions
- Clinical correlation is critical: call clinician and ask about new medications

Morbilliform drug eruption: differential diagnosis

- *Viral exanthema* (normally no eosinophils)
 - *Urticaria*: differentiation requires knowledge of the clinical presentation)
 - *Arthropod bite reaction* (but typically have a denser infiltrate)
- without a good clinical history, it is best to use a descriptive diagnosis!

Erythema annulare centrifugum: key microscopic features

- Superficial or superficial and deep perivascular pattern
- The superficial variant may show slight spongiosis and scale
- The deep variant generally lacks epidermal changes
- Coat-sleeve pattern of infiltrate



Erythema annulare centrifugum: differential diagnosis

- **Superficial pattern**

- pityriasis rosea (if spongiosis is evident)

- arthropod bite reaction or drug reaction (if eosinophils are observed)

- fungus infection (do a PAS stain)

- **Deep pattern**

- polymorphous light reaction

- chronic urticaria

- drug reaction

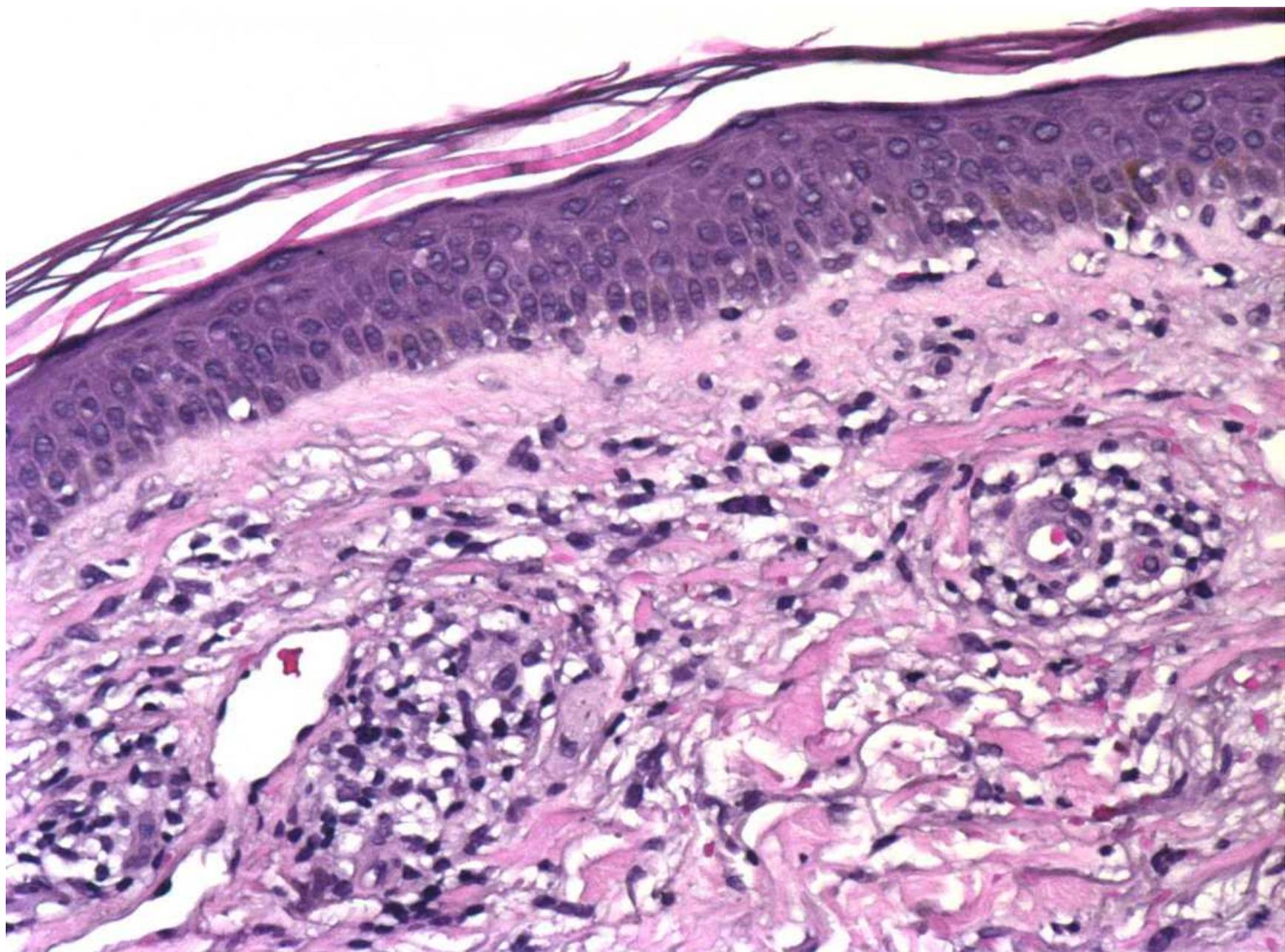
- fungus infection (do a PAS stain)

→all these entities do not have the coat-sleeve pattern!

→correlation with the clinical presentation! (annular, scaly erythematous plaques involving the trunk and proximal extremities)

Pigmented purpuric dermatosis (Schamberg's disease)

- Superficial perivascular dermatitis with little epidermal change; occasionally may have some spongiosis
- Mild superficial infiltrate with extravasated erythrocytes and siderophages, “lymphocytic vasculitis”
- Occasionally may have a lichenoid infiltrate
- No fibrinoid necrosis



Schamberg's disease: differential diagnosis

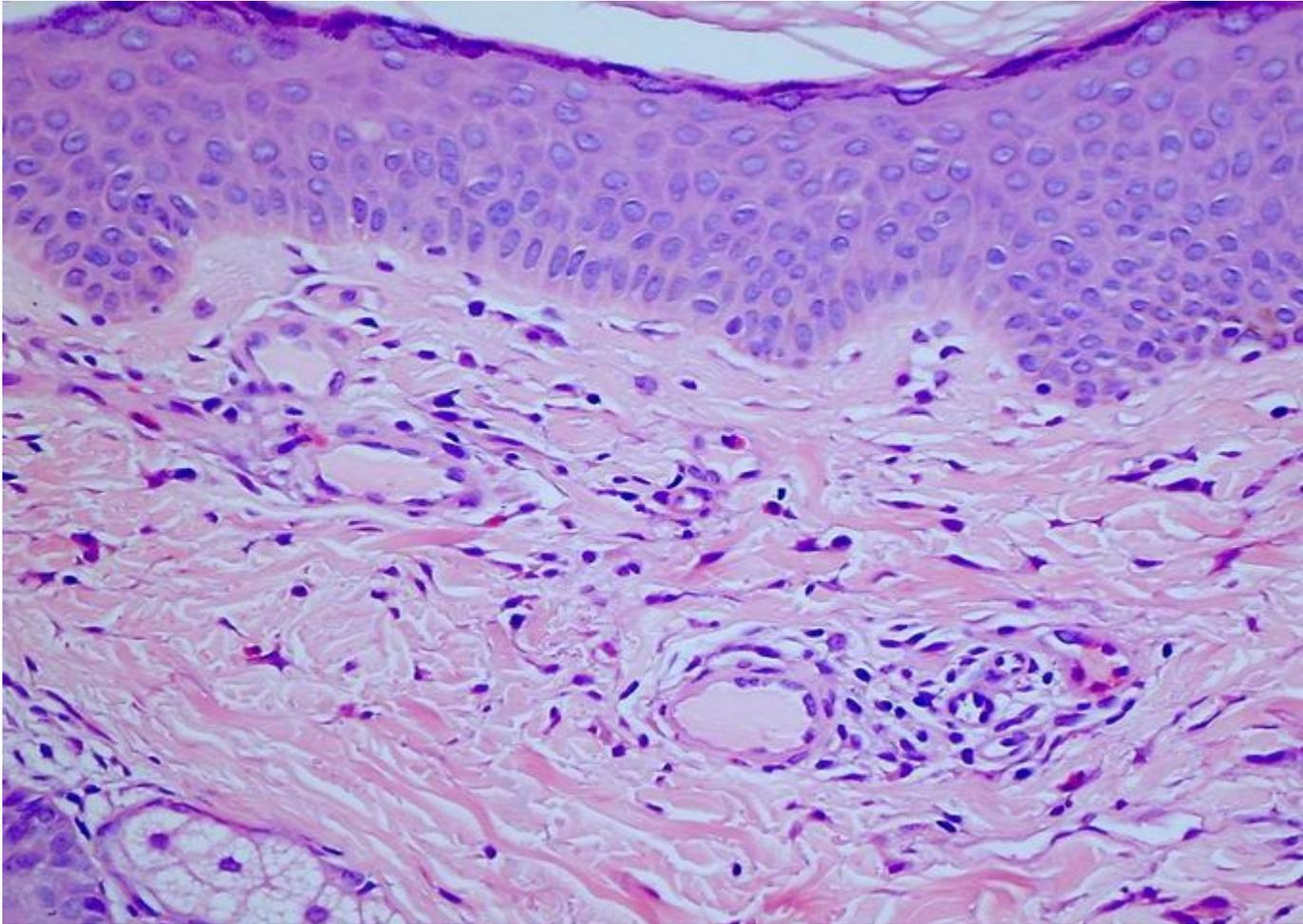
- Leukocytoclastic vasculitis (inflammatory component of neutrophils with leukocytoclasia and fibrin deposition/necrosis)
- Stasis dermatitis (lobular vascular proliferation in the superficial dermis)
- Pityriasis rosea (spongiotic type dermatitis)

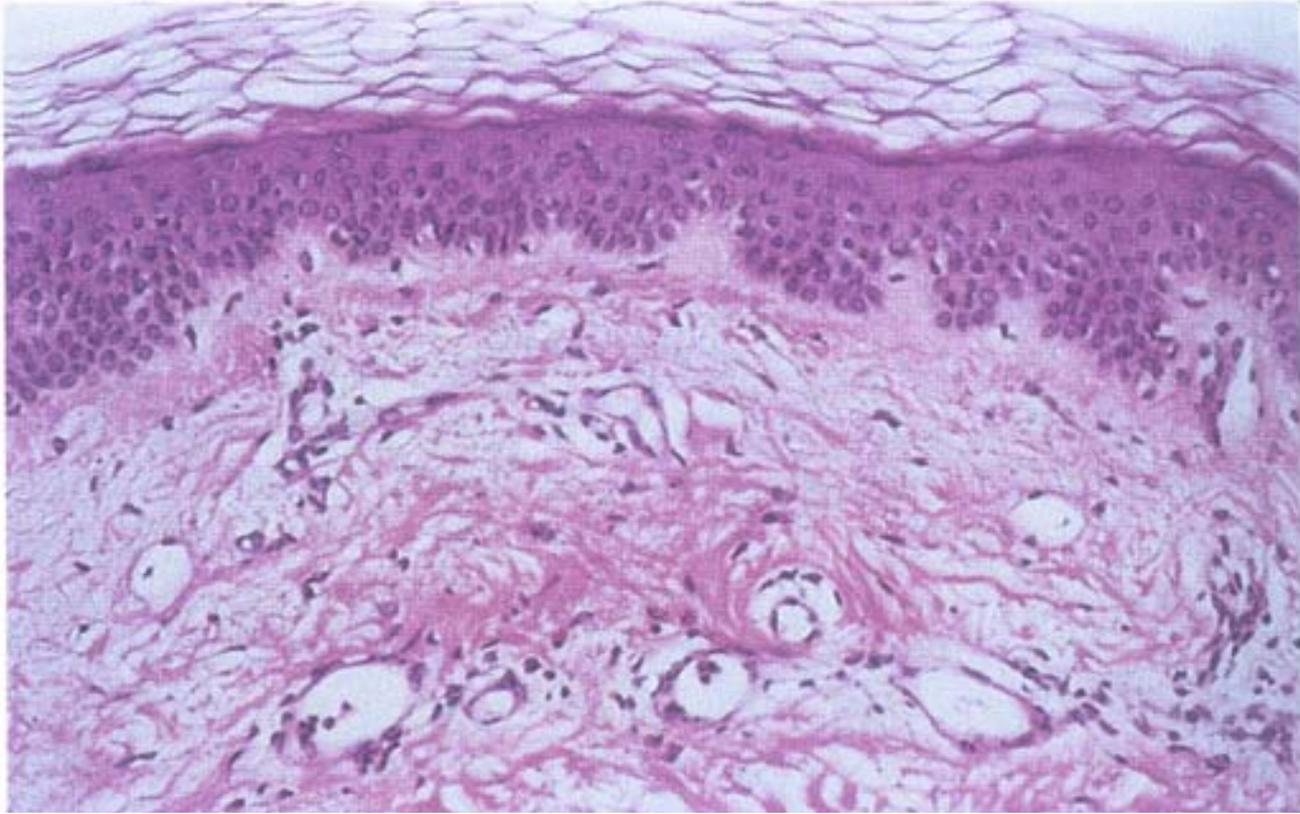
Schamberg's disease: practical tips

- Early lesions may demonstrate extravasated erythrocytes but no siderophages
- The absence of overt vascular damage helps distinguish pigmented purpuric dermatosis from leukocytoclastic vasculitis

Urticaria: key microscopic features

- Epidermis is unremarkable
- Papillary dermal edema
- Infiltrate may be superficial, or superficial and deep
- In contrast to arthropod bite and Wells' syndrome, the infiltrate is typically sparse
- Neutrophils and lymphocytes are often a component of the infiltrate
- Collections of neutrophils within vessel lumens is a helpful clue to the diagnosis





Urticaria: differential diagnosis

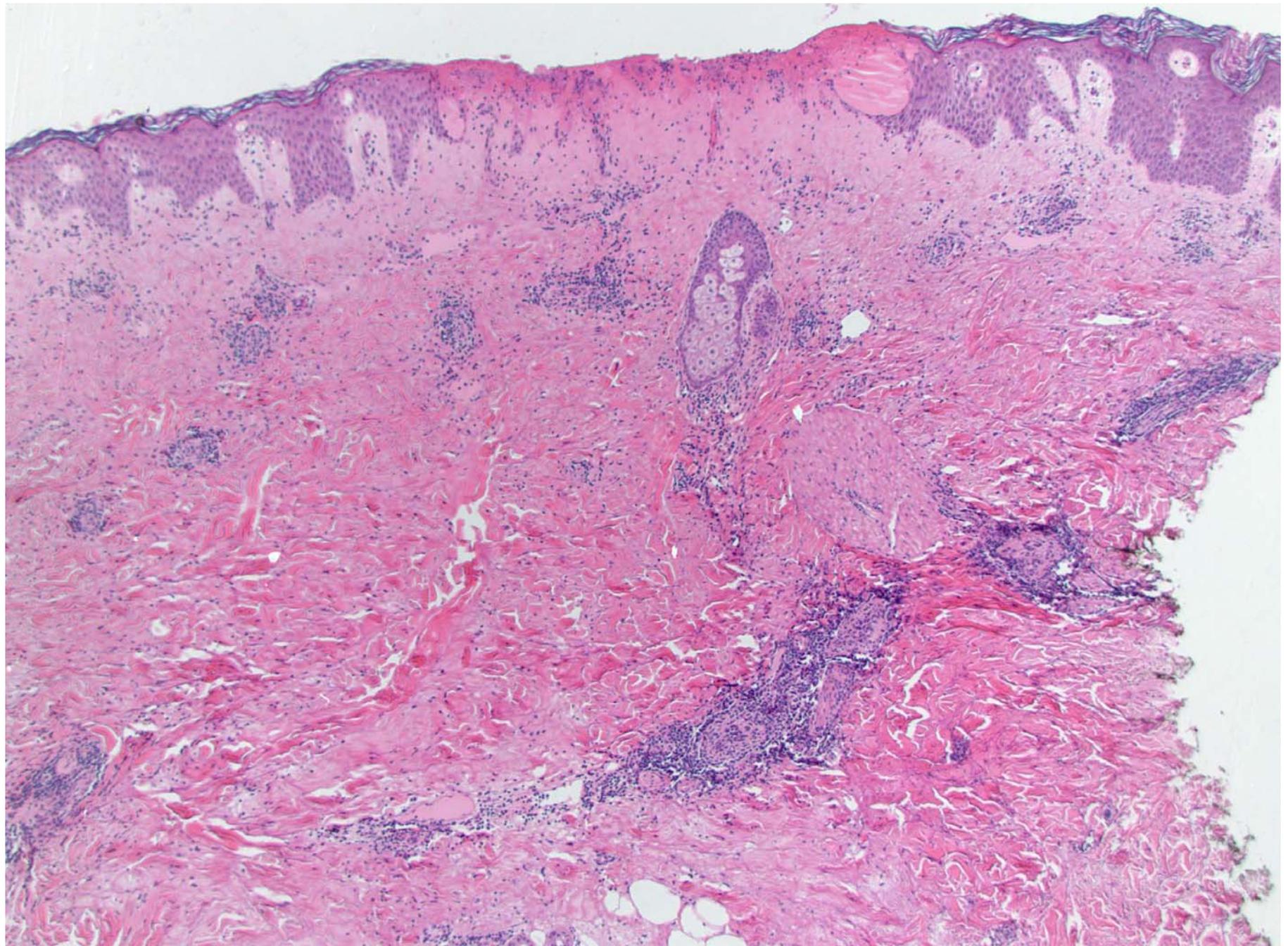
- Other hypersensitivity reactions: arthropod bite reactions or drug eruptions
- Mastocytosis (especially TMEP)

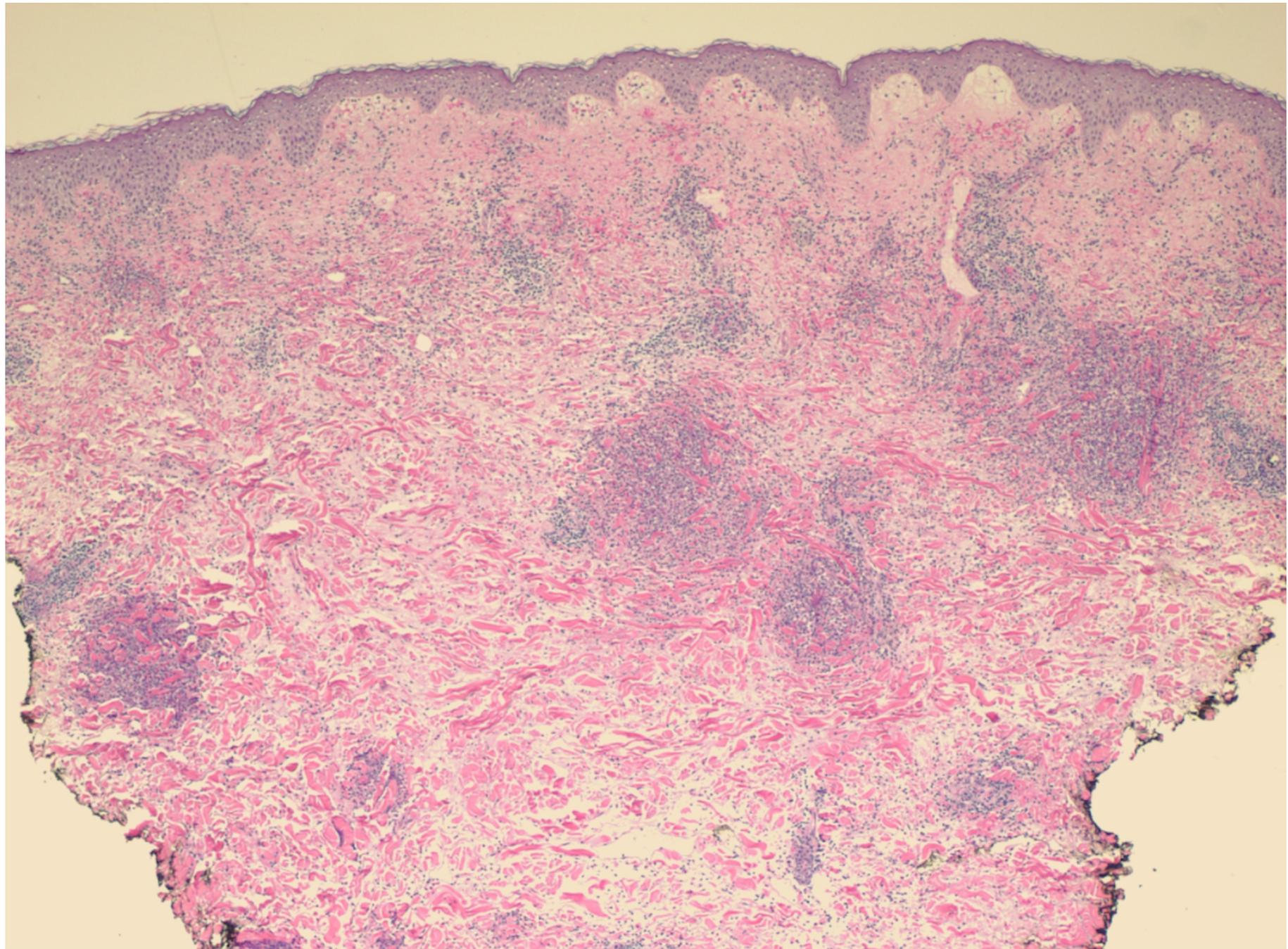
Urticaria: practical tips

- An unequivocal diagnosis of urticaria is not possible in the absence of good clinical information
- The infiltrate is usually mild in nature, such that at first glance the biopsy may superficially resemble normal skin on low power examination (“nothing lesions”)
- If a dense mixed infiltrate is present, consider entities such as arthropod bite reaction or drug

Arthropod bite reaction: key microscopic features

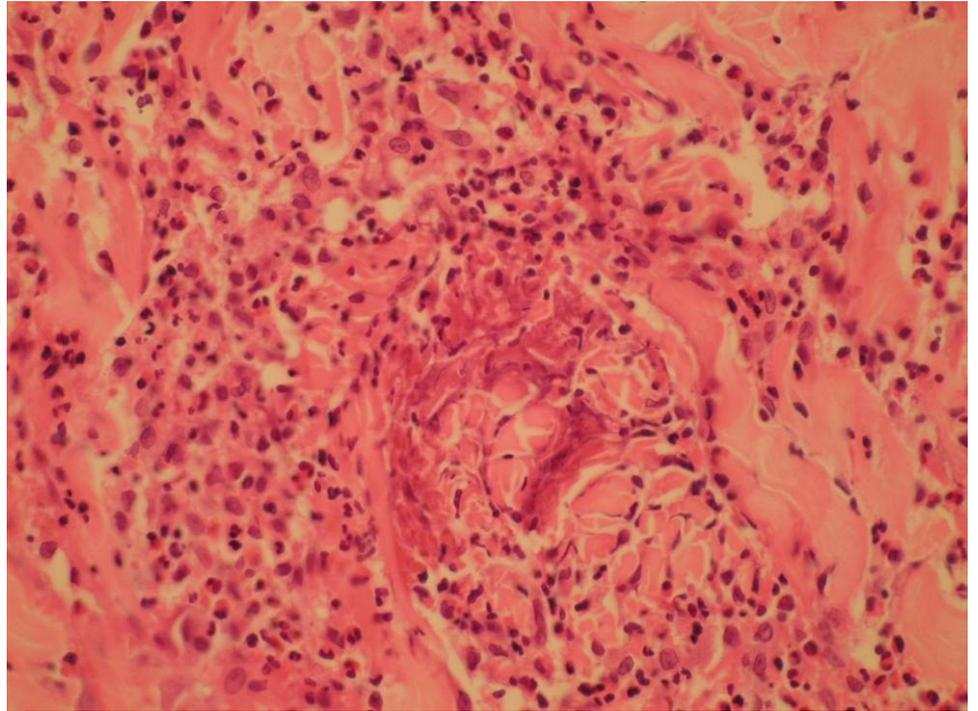
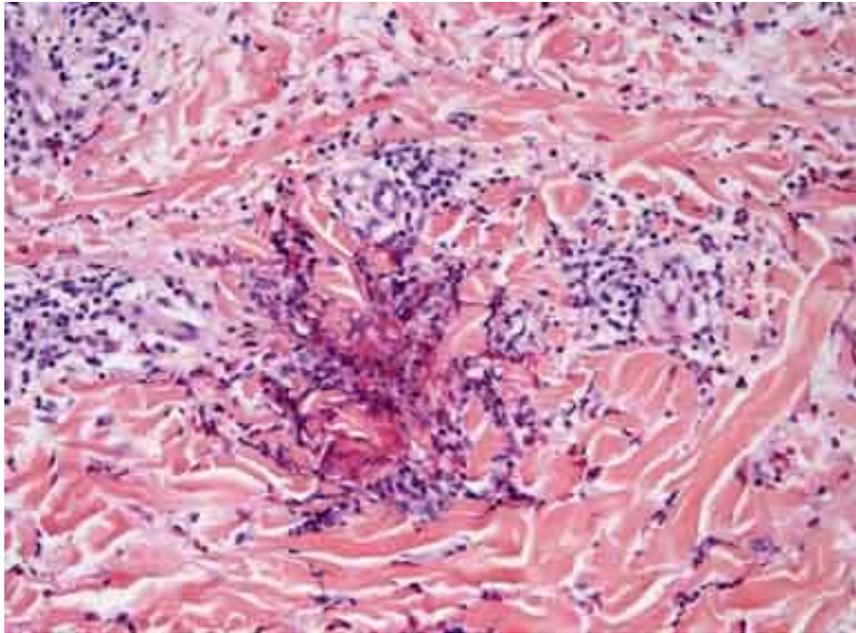
- Eosinophilic-rich, often wedge-shaped infiltrate that may extend into the subcutis
- An intraepidermal spongiotic vesicle may be present at the point of the punctum (early lesions)
- Late lesions are more commonly biopsied than early lesions, epidermis often unremarkable
- Flame figures may be seen in arthropod bite reactions (or any eosinophilic-rich dermatitis) and are not diagnostic of Wells' syndrome





“flame figures”

- Wells' syndrome: authentic disease??
Most authorities now believe Wells' is not an authentic disease but an exaggerated hypersensitivity response
- Arthropod bite reaction
- Drug eruptions
- Bullous pemphigoid
- Churg-Strauss syndrome



Arthropod bite reaction: differential diagnosis

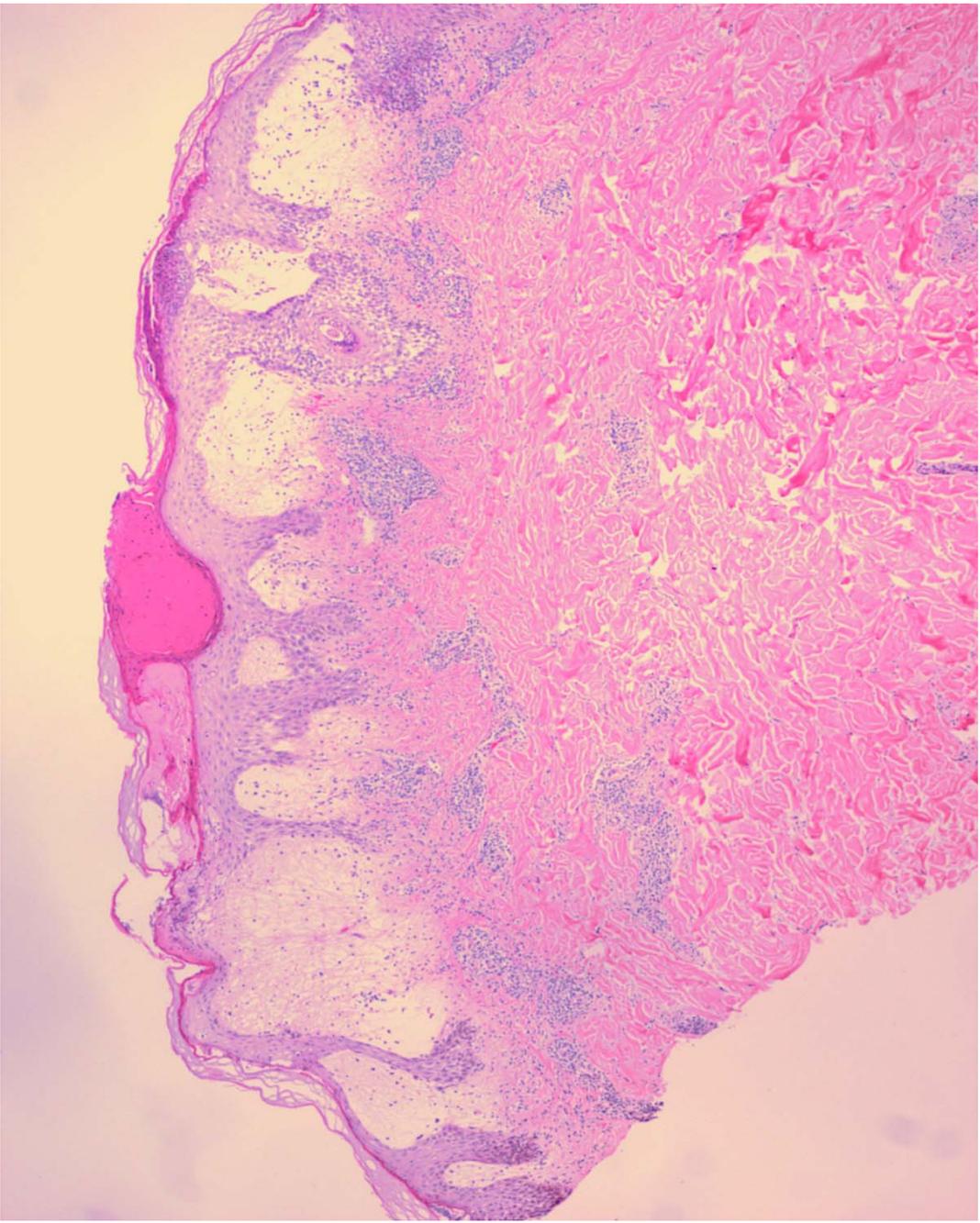
- Other dermal hypersensitivity reactions: urticaria, drug
- Eosinophilic cellulitis (Well's syndrome) (clinical correlation: large erythematous plaques on the trunk or extremities)
- Lymphomatoid papulosis

Arthropod bite reaction: practical tips

- Relatively commonly biopsied
- Infiltrate usually moderate to dense
- Numerous eosinophils: think arthropod bite reaction (exception: flea bites may have a prominent neutrophilic component)
- CD30+ cells may be seen in arthropod bite reactions, prompting consideration of LYP
- Eosinophils may be less conspicuous in older lesions

Polymorphous light eruption: key microscopic features

- On lower power, the infiltrate shows a gradual tapering with a predominance of lymphocytes
- Prominent subepidermal edema
- Occasional extravasated erythrocytes may be seen
- Epidermal alterations may be present including spongiosis and focal necrotic keratinocytes

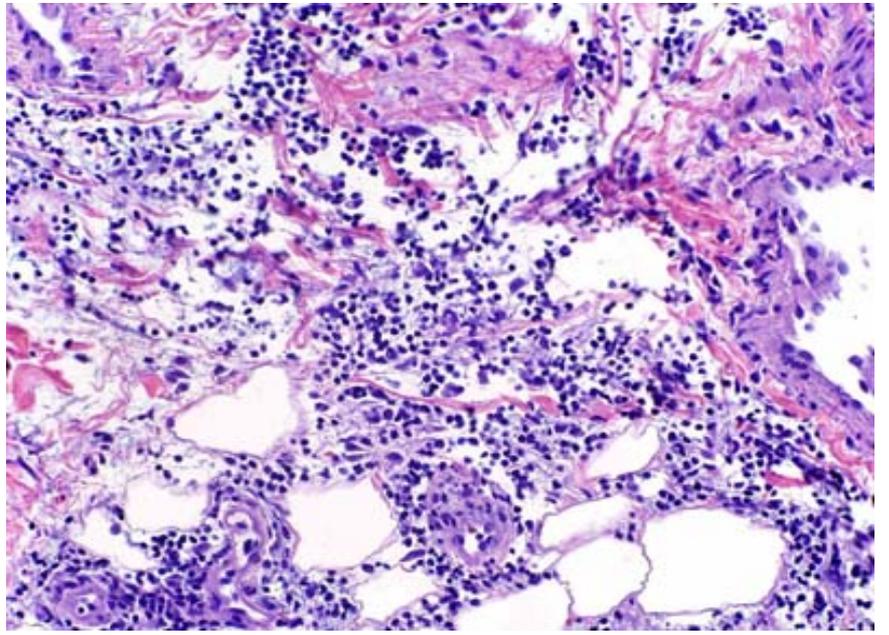
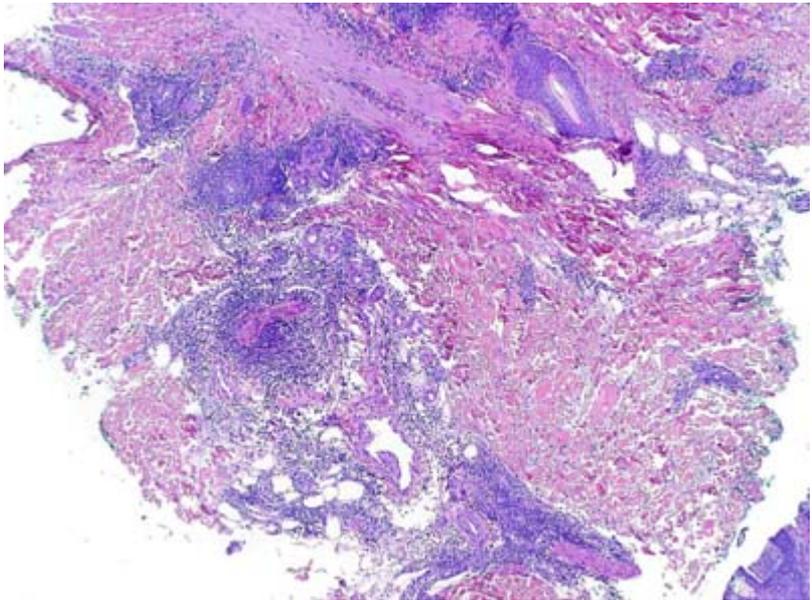
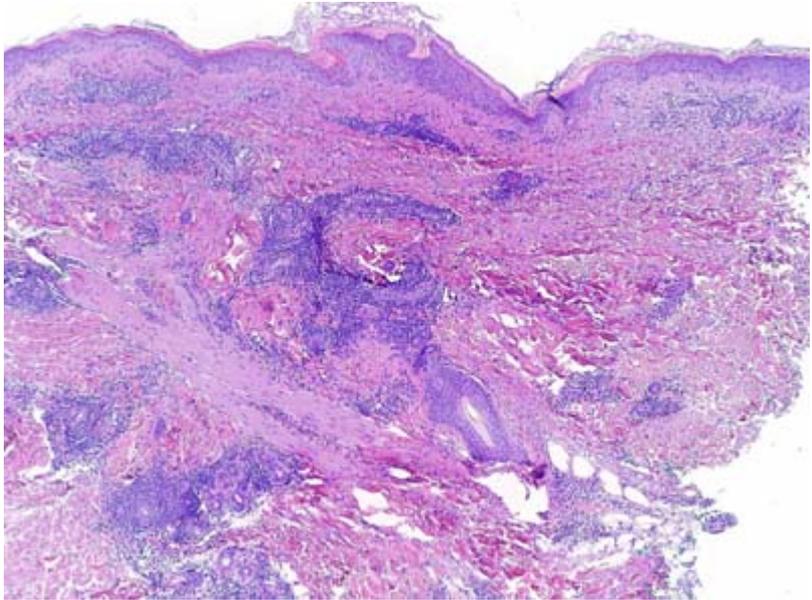


Polymorphous light eruption: differential diagnosis

- *Erythema annulare centrifugum* (no prominent edema)
 - *Arthropod bite reaction* (prominent component of eosinophils, usually absent in PLE)
 - *Lupus erythematosus (LE)* (no dermal mucinosis, no basement membrane zone thickening,....)=sometimes a difficult clinical and histologic differential diagnosis
- **clinical presentation of PLE is a helpful clue to the diagnosis:** pruritic eruption presenting in spring or early summer

Perniosis (chilblains): key microscopic features

- Epidermis usually unremarkable (may have focal interface change)
- Papillary dermal edema common
- Superficial and deep perivascular lymphocytic infiltrate
- Lymphocytic vasculitis
- Fluffy edema of vessel walls
- Peri-eccrine infiltrate



Perniosis: differential diagnosis

- PLE (no lymphocytic vasculitis, clinical presentation on the digits, especially toes, is not characteristic of PLE)
 - Chilblain lupus (essentially indistinguishable from the idiopathic form of perniosis) (interface change, when present, favors chilblains lupus)
- **clinical presentation of perniones**: painful erythematous nodules on the fingers and/or toes (acral sites), presents during cold damp weather, usually at the beginning of or at the end of winter

Nodular and diffuse dermatitis

Nodular and diffuse dermatitis: definition

- **Nodular** pattern: discrete nodular collections of inflammatory cells that are not vasculocentric. There are areas of uninvolved dermis
- **Diffuse** pattern: dense dermal inflammation without intervening areas of sparing

Diffuse dermatitis

- **Lymphocytes predominant:** cutaneous lymphoid hyperplasia (cutaneous pseudolymphoma)
- **Neutrophils predominant:** acute febrile neutrophilic dermatosis (Sweet's syndrome)
- **Eosinophils predominant:** eosinophilic cellulitis (Wells' syndrome), lymphomatoid papulosis
- **Mast cells predominant:** urticaria pigmentosa
- **Plasma cells predominant:** plasmacytoma, myeloma
- **“Histiocytoid” cells predominant:** lepromatous leprosy
- **Mixed cell types:** granuloma faciale, syphilis (plasma cells)

Nodular dermatitis

- Granulomatous dermatitis

Different types of granulomas

- Tuberculoid granuloma
- Sarcoidal granuloma
- Palisaded granuloma
- “interstitial granulomatous pattern”
- Suppurative granuloma

Granulomatous dermatitis

- Sarcoidosis
- Granuloma annulare
- Rheumatoid nodule
- Necrobiosis lipoidica
- Necrobiotic xanthogranuloma
- Cutaneous Crohn's disease
- Granulomatous rosacea
- Foreign body reaction
- Infection
- Actinic granuloma
- Granulomatous drug eruption

Nodular and diffuse dermatitis

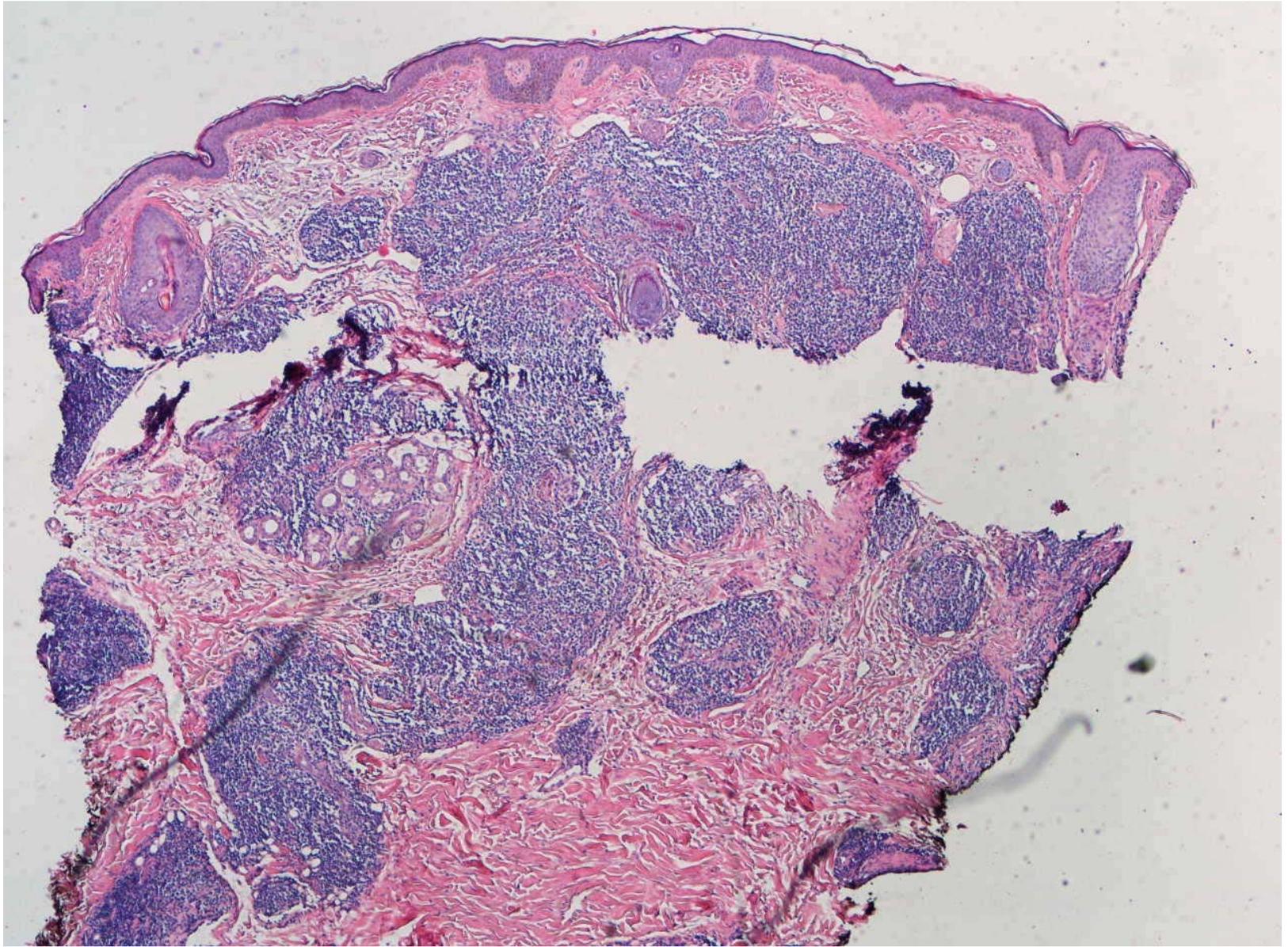
- Lymphoid hyperplasia/pseudolymphoma
- Neutrophilic dermatosis (e.g. Sweet's syndrome/acute febrile neutrophilic dermatosis)
- Granuloma faciale
- **Granulomatous dermatitis**

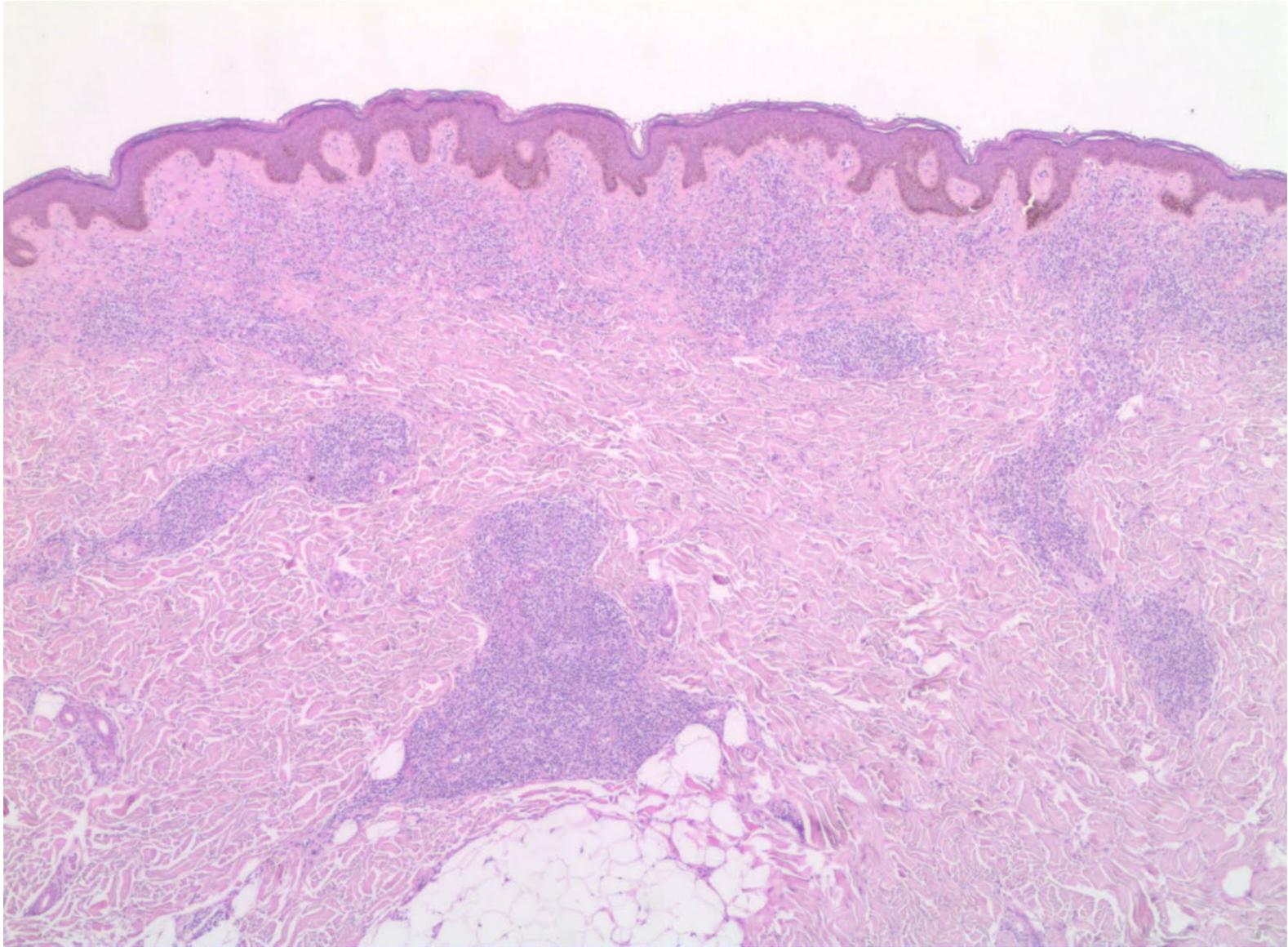
Reactive lymphoid hyperplasia: key microscopic features

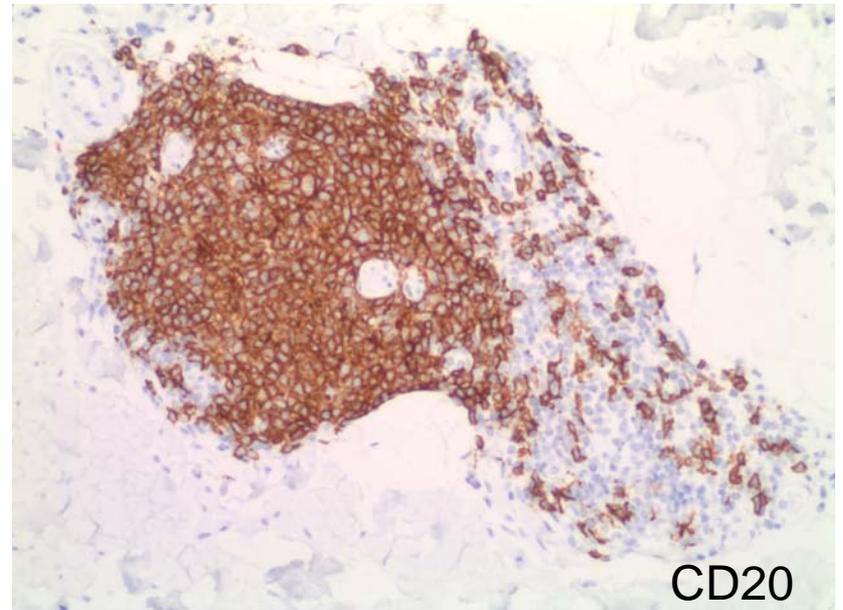
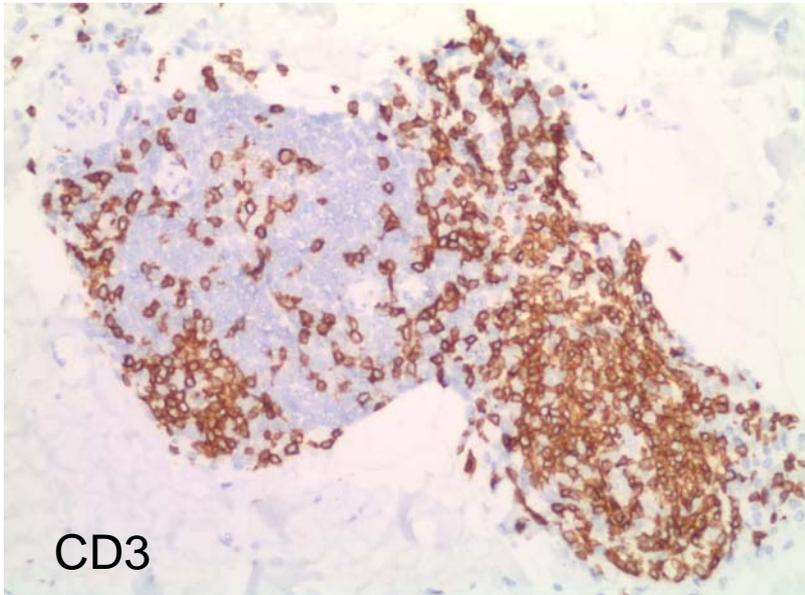
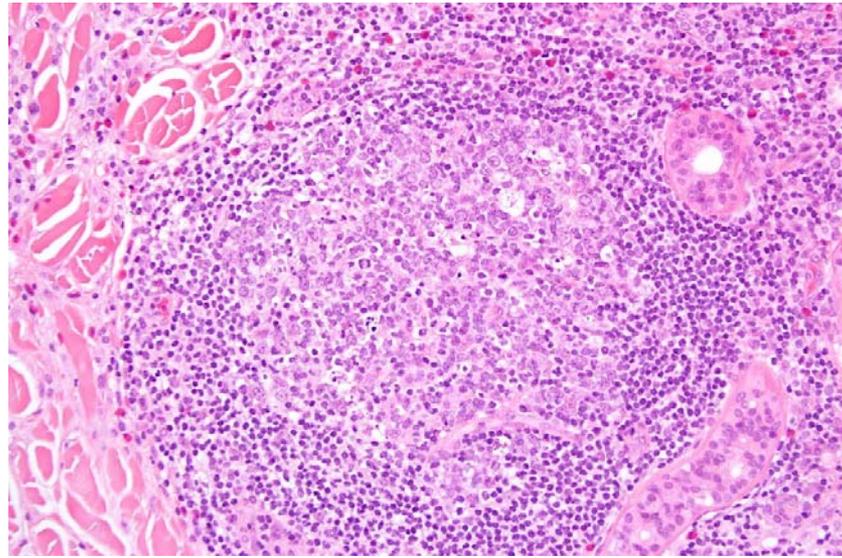
- Polarized reactive germinal centers with tingible body macrophages
- Predominantly T-cells surrounding the germinal centers
- B-cells are largely restricted to germinal centers
- Plasma cells and eosinophils may be present
- No light chain restriction

Reactive lymphoid hyperplasia/pseudolymphoma: practical tips

- Differentiation from low-grade B-cell lymphoma (follicular center, marginal zone) may be quite difficult
 - Features that favor lymphoid hyperplasia:
 - polarized germinal centers with tingible body macrophages
 - clinical correlation is essential for a correct diagnosis
 - "top-heavy" (superficial and mid-dermal) infiltrate with preservation of adnexal structures
 - mixed cell infiltrate, B-cells generally limited to germinal centers
 - lack of light chain restriction
 - however, be aware that these are not hard and fast rules!
- immunophenotypic studies are almost always required. Molecular studies may be helpful in border-line cases**







Sweet syndrome: key microscopic features

- Diffuse infiltrate of neutrophils
- Leukocytoclasia but no vasculitis
- **Clinical correlation!** (“acute febrile neutrophilic dermatose”: acute onset of fever and leukocytosis associated with arthralgias and erythematous plaques, most often in middle-aged women after a nonspecific respiratory or gastrointestinal infection)

Table 1. Diagnostic Criteria for Sweet Syndrome*

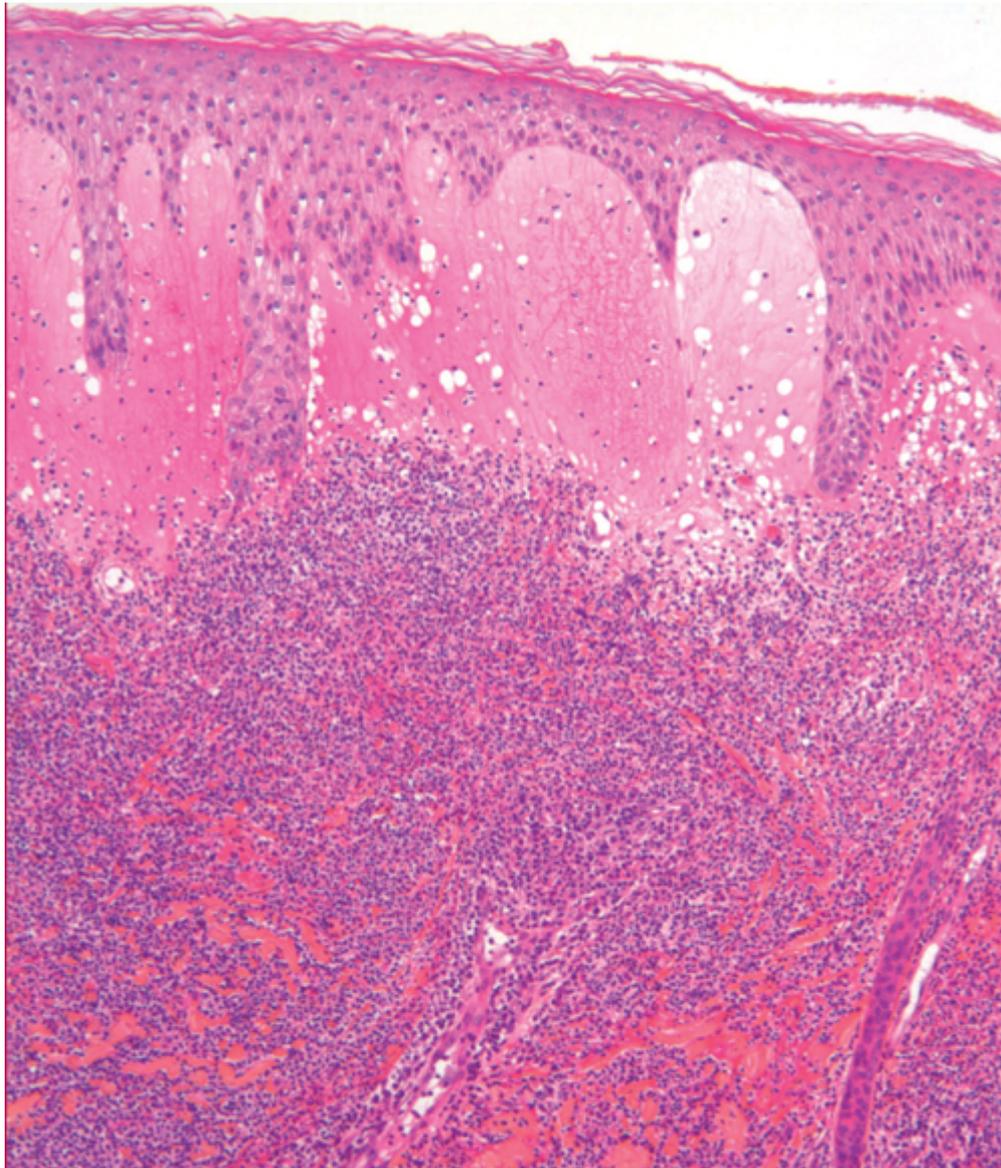
Major criteria

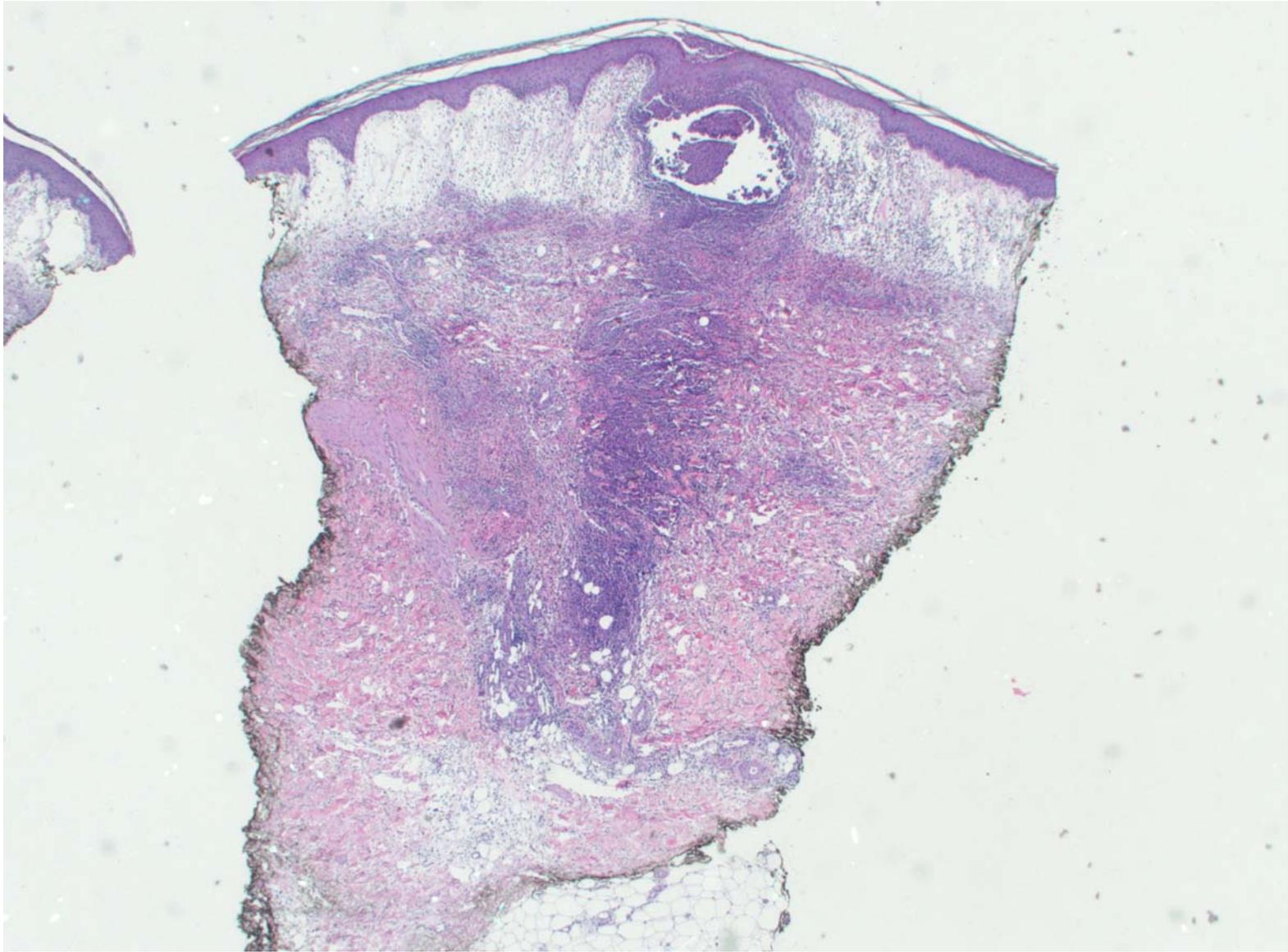
1. Abrupt onset of tender erythematous plaques or nodules
2. Dense neutrophilic infiltrate on biopsy

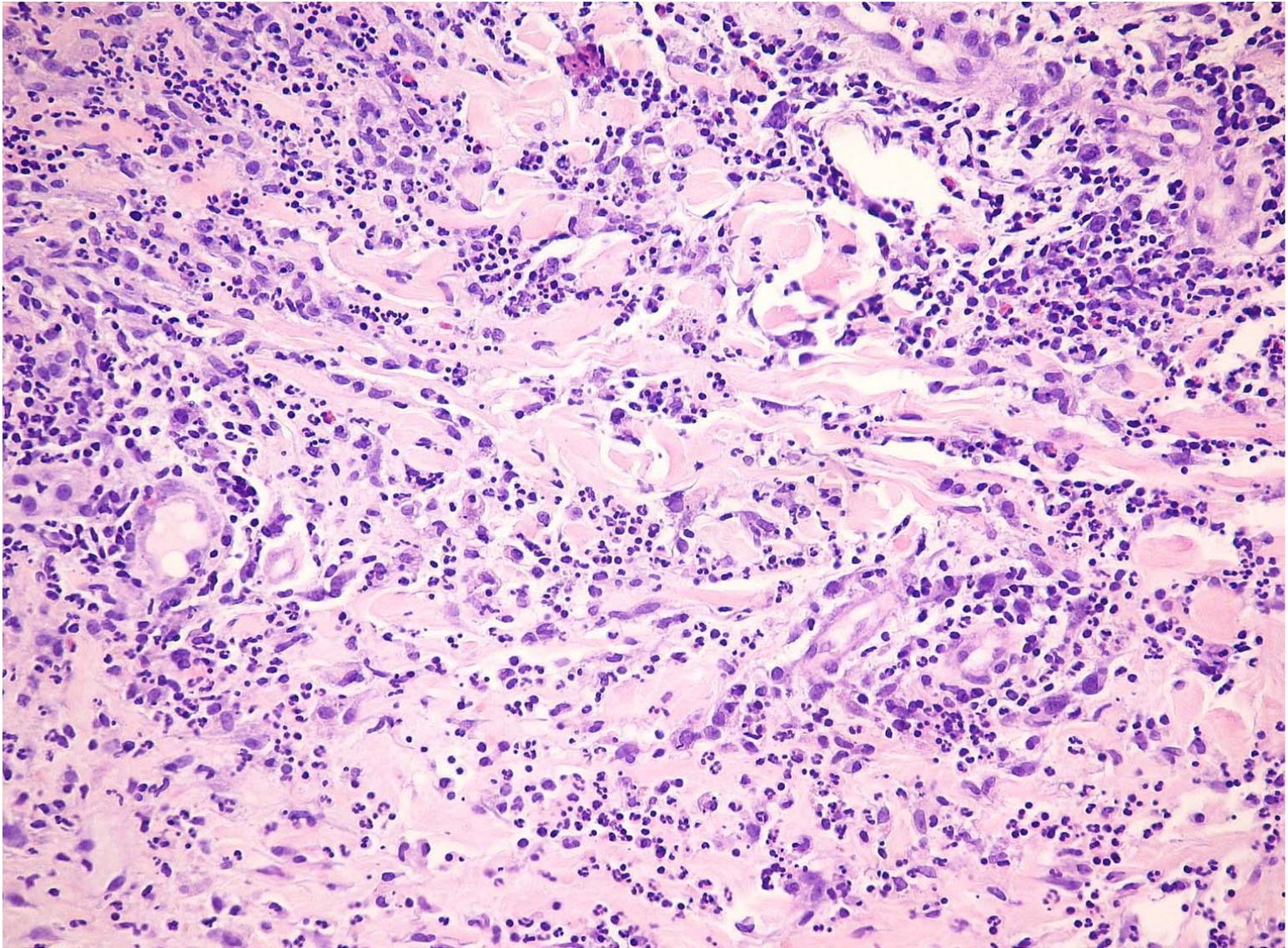
Minor criteria

1. Fever, temperature $>38^{\circ}\text{C}$
2. Association with an underlying hematologic malignancy, inflammatory disease, or pregnancy or preceded by an upper respiratory or gastrointestinal tract infection
3. Excellent response to treatment with systemic corticosteroids
4. Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate >20 mm/h; positive C-reactive protein; leukocyte count $>10 \times 10^3/\mu\text{L}$; $>70\%$ neutrophils

*Adapted from Honigsmann et al.⁶ The presence of both major criteria and 2 of the 4 minor criteria is required for the diagnosis of Sweet syndrome.







Sweet syndrome: differential diagnosis

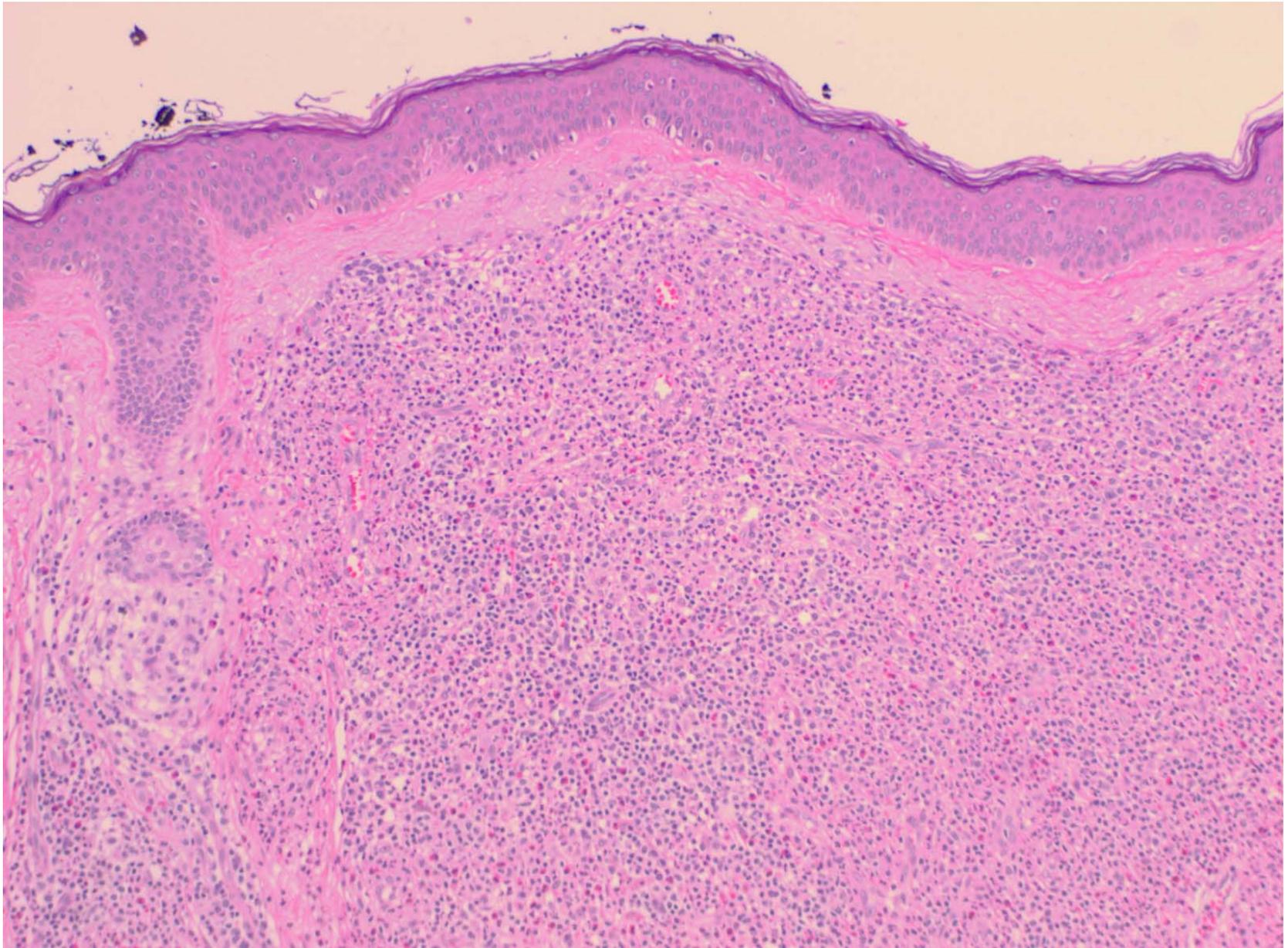
- **Exclude an infectious etiology!!**
- Other neutrophilic dermatoses (e.g. bowel bypass syndrome, rheumatoid neutrophilic dermatosis)
- **Pyoderma gangrenosum** (clinical correlation: ulcers with a raised undermined border and diffuse dermal neutrophilic infiltrate)=diagnosis of exclusion
- Granuloma faciale

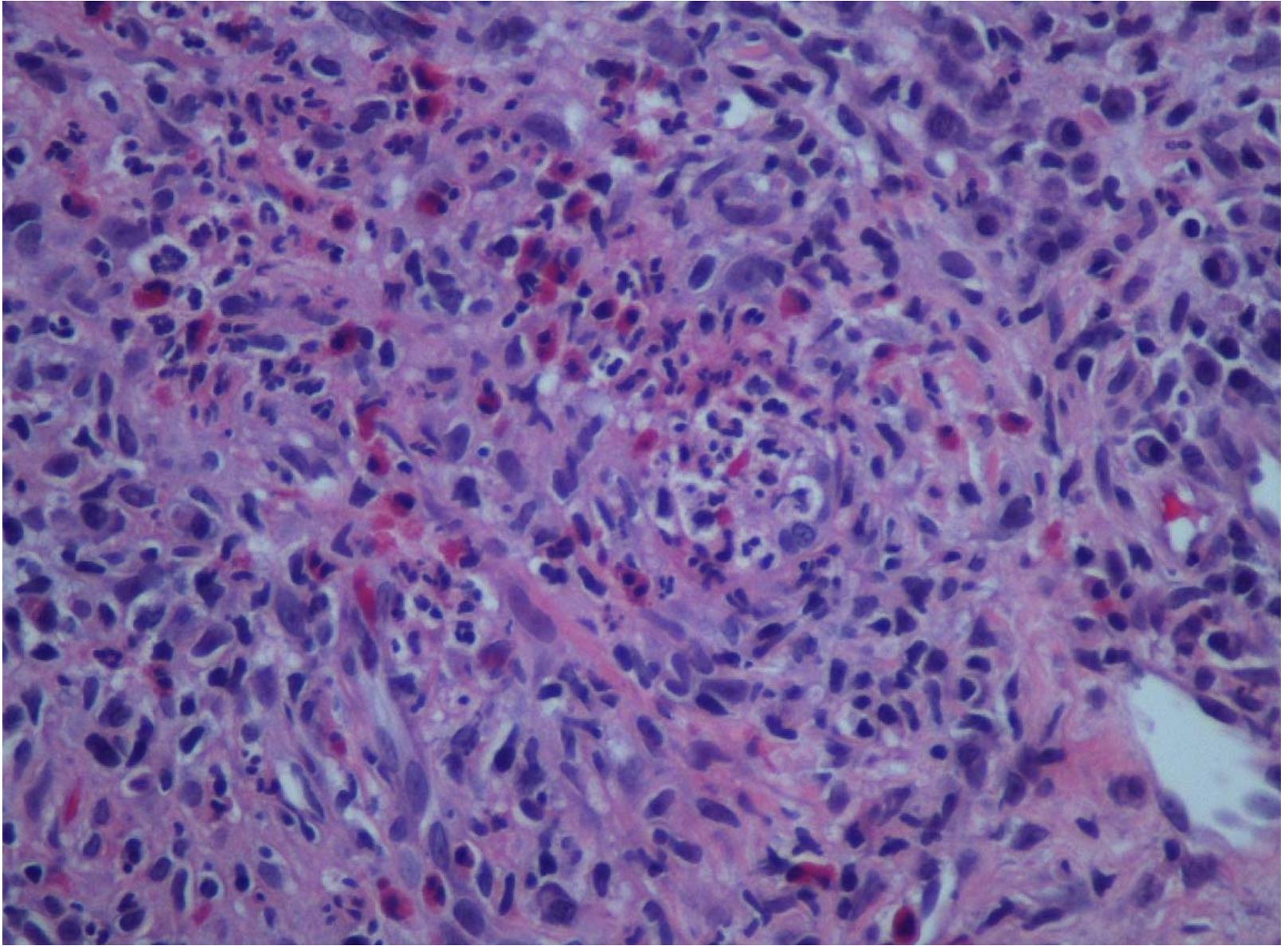
Sweet syndrome: practical tips

- No true vasculitis
- Ulceration uncommon in Sweet syndrome
- If an infectious process is a clinical consideration, tissue culture should be pursued
- If Sweet syndrome is considered clinically, but infiltrate looks histiocytic, consider immunostains for myeloperoxidase to exclude histiocytoid Sweet syndrome

Granuloma faciale: key microscopic features

- Polymorphous infiltrate with neutrophils, eosinophils, and plasmacells, and sparing of adventitial dermis is diagnostic (forming a Grenz zone)
- Evidence of leucocytoclastic vasculitis may be seen in early cases
- Extravasated erythrocytes and hemosiderin may be observed and contribute to the reddish-brown color of the lesions clinically





Granuloma faciale: differential diagnosis

- Sweet's syndrome
 - Arthropod bite reaction or other hypersensitivity reaction
- however the morphology of GF (mixed nature of the infiltrate) and the clinical presentation (single or multiple asymptomatic reddish-brown nodules that typically involve the face) is fairly distinctive!

Granuloma faciale: practical tips

- Polymorphous infiltrate is key to diagnosis
- Polymorphous infiltrate helps distinguish granuloma faciale from Sweet's syndrome
- May see vasculitis in early lesions; remember, *it is rare to see other forms of vasculitis on face!*

Granulomatous dermatitis

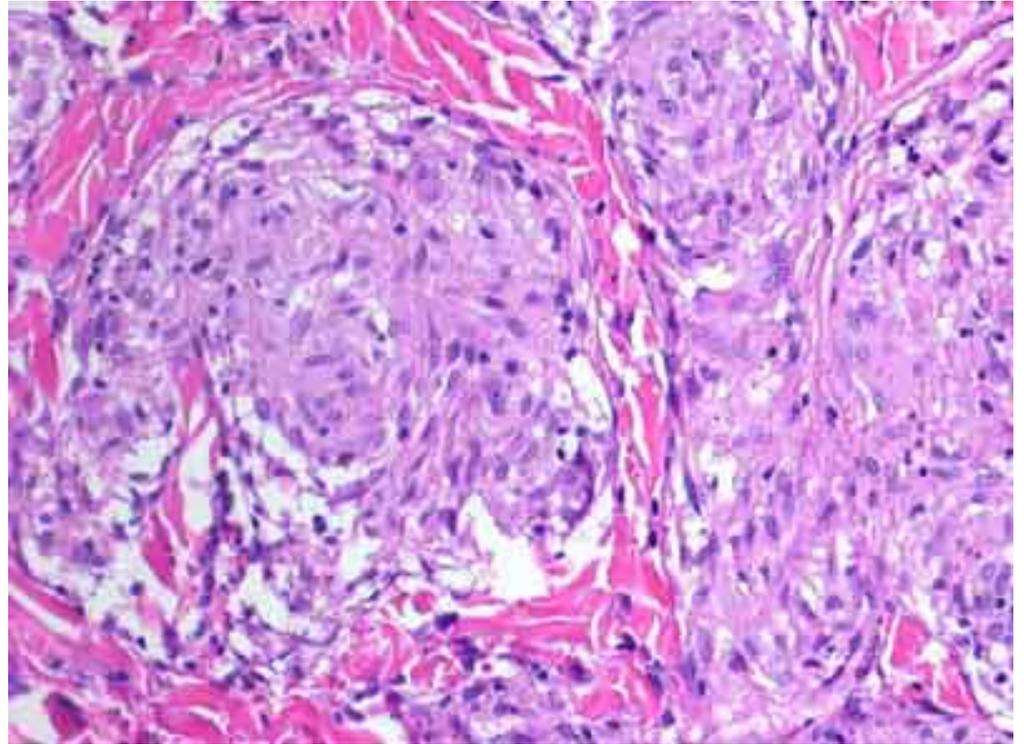
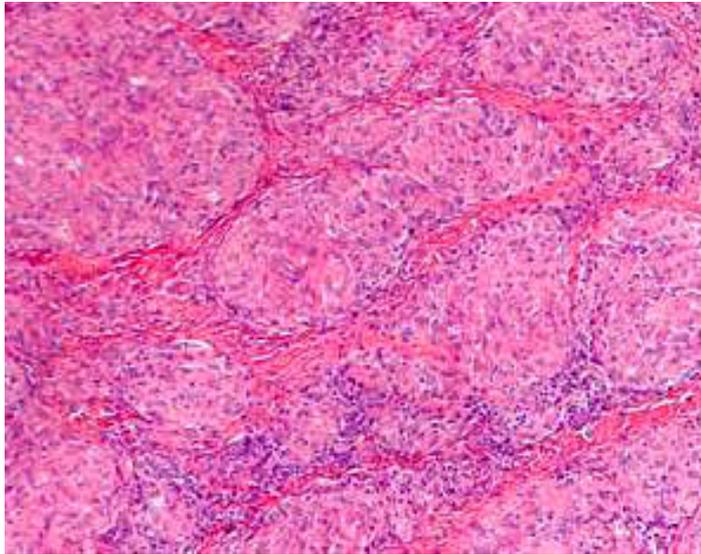
- A broad spectrum of disorders can manifest with a “granulomatous reaction”
- Not all granulomatous dermatitides contain granulomas per se
- Granulomas= discrete nodular aggregates of epithelioid histiocytes=most specific hallmark of granulomatous dermatitis

Different types of granulomas

- Tuberculoid granuloma
- Sarcoidal granuloma
- Palisaded granuloma
- “interstitial granulomatous pattern”
- Suppurative granuloma

Sarcoidal granuloma

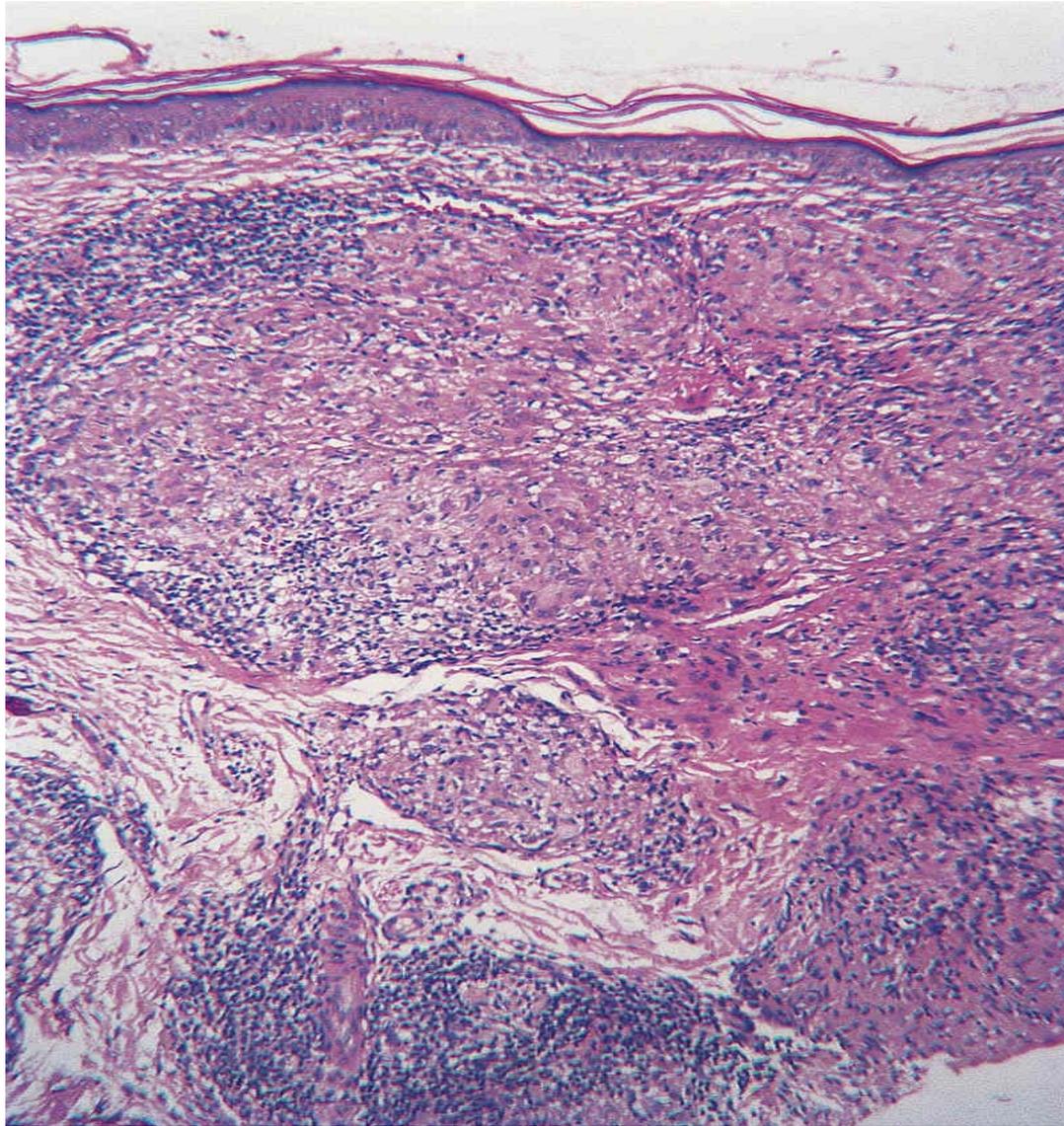
- Relatively circumscribed collection of epithelioid histiocytes (epithelioid granulomas)
- Poorly developed lymphocytic cuff (“naked granuloma”)
- No caseation necrosis
- “scar sarcoidosis”: foreign body within the sarcoidal granuloma
- sarcoidosis



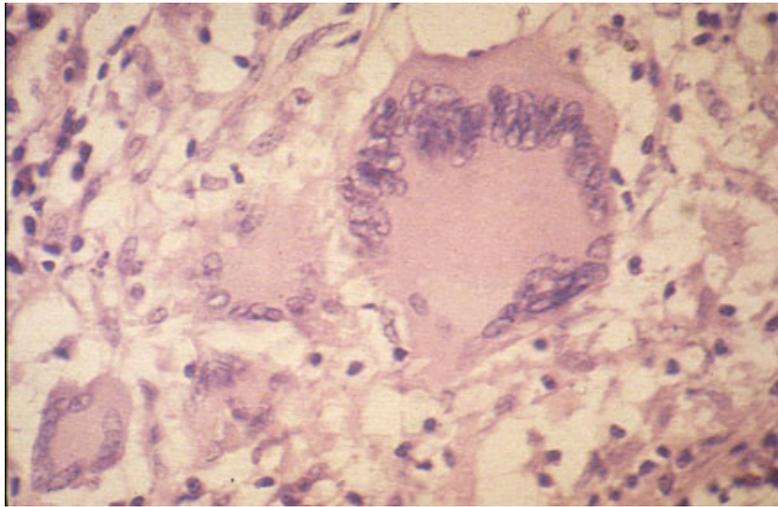
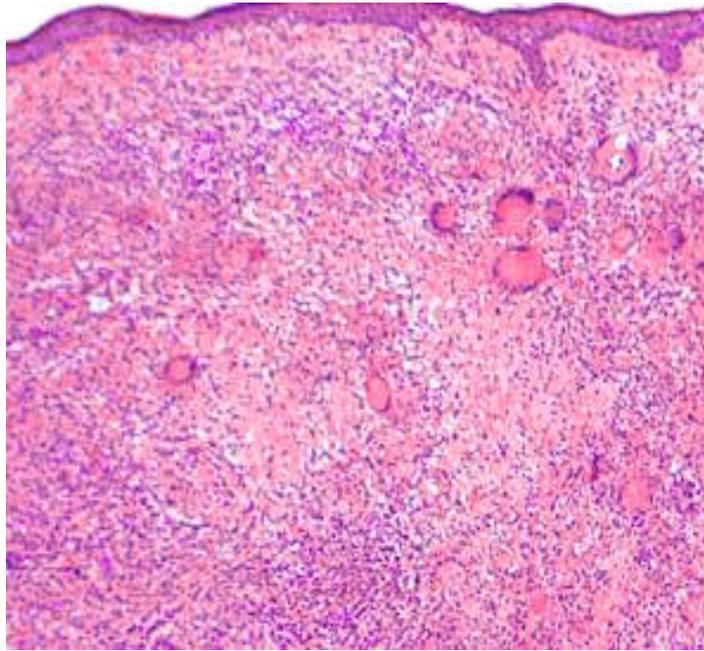
sarcoidosis

Tuberculoid granuloma

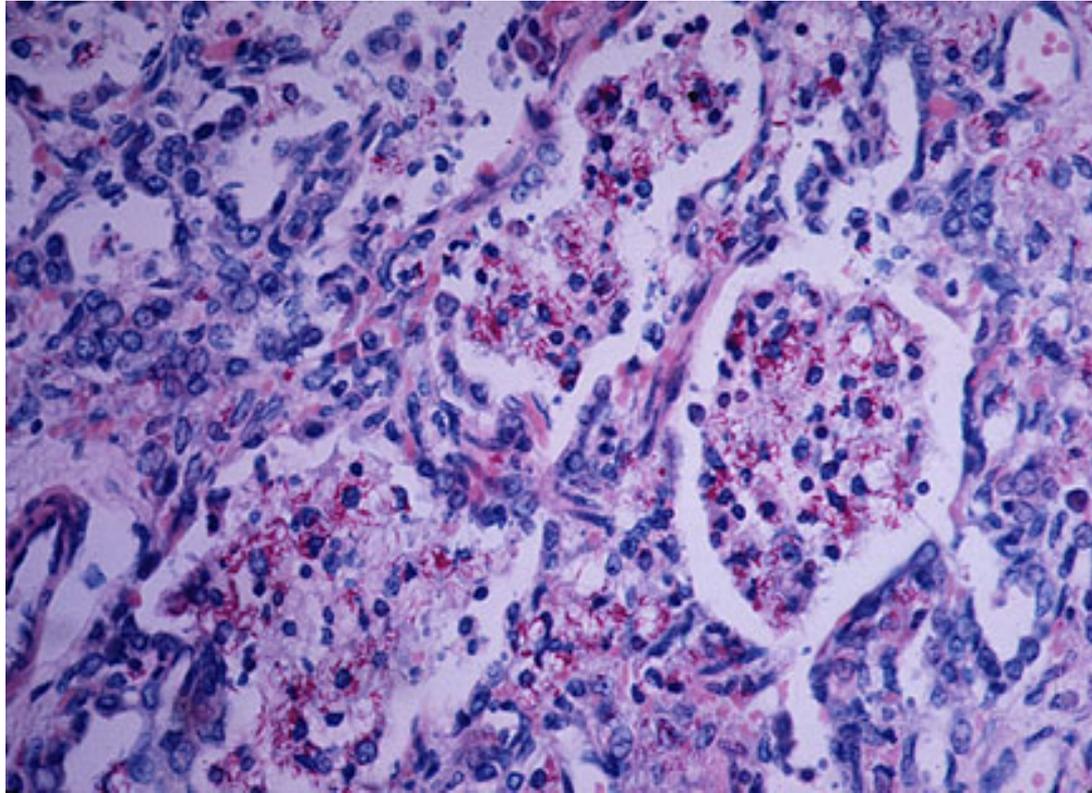
- Relatively circumscribed collection of epithelioid histiocytes (epithelioid granulomas) sometimes Langhans giant cells
- Surrounded by a cuff of lymphocytes (not naked granulomas)
- Necrosis/caseation is often present
- Tuberculosis (lupus vulgaris), other infections (fungal, bacterial, lepra, Leishmania,...), foreign body reaction, granulomatous rosacea, (rare: sarcoidosis, Crohn's disease)



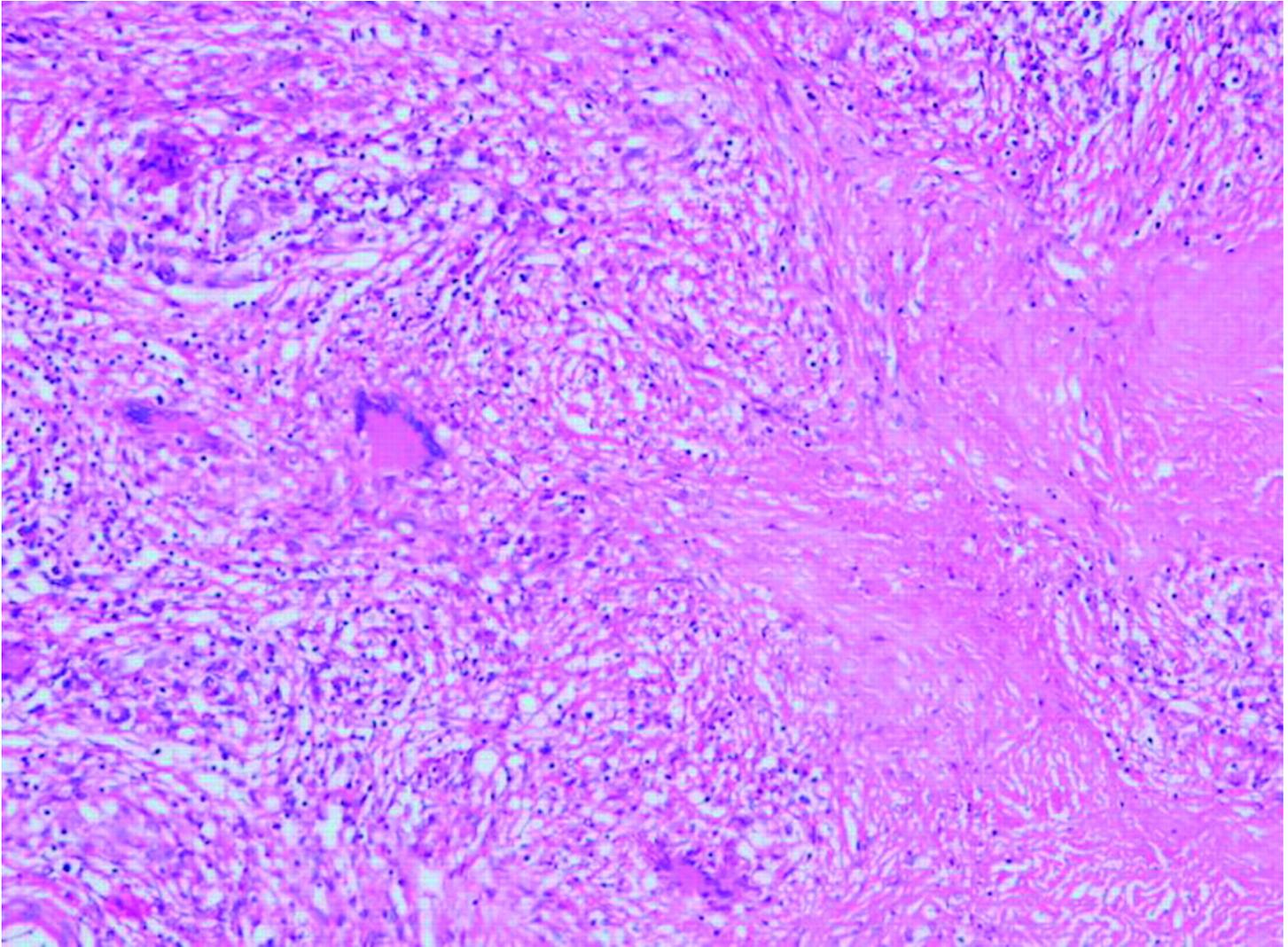
Lupus vulgaris



Lupus vulgaris



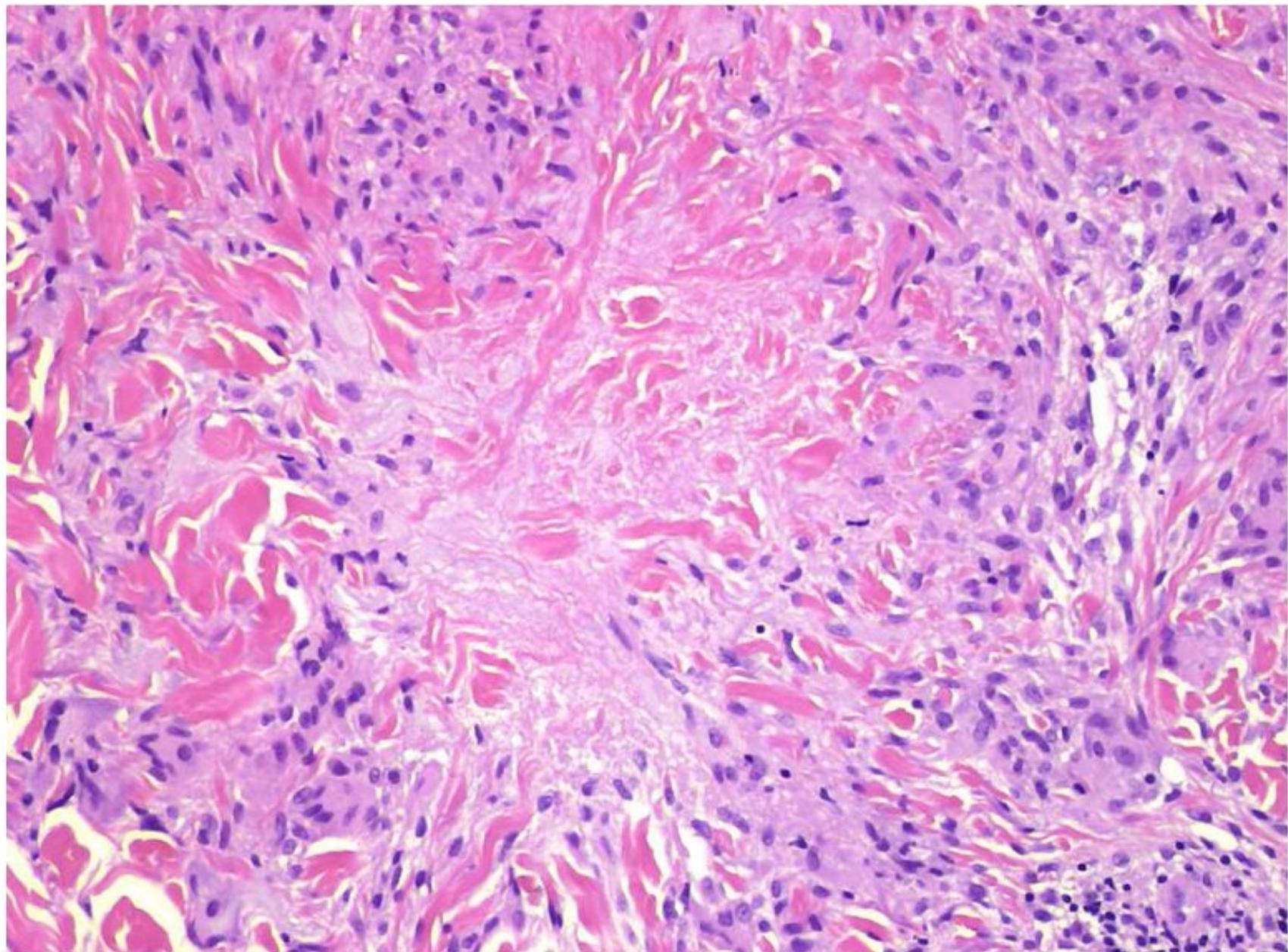
Lupus vulgaris



Tuberculosis (lung)

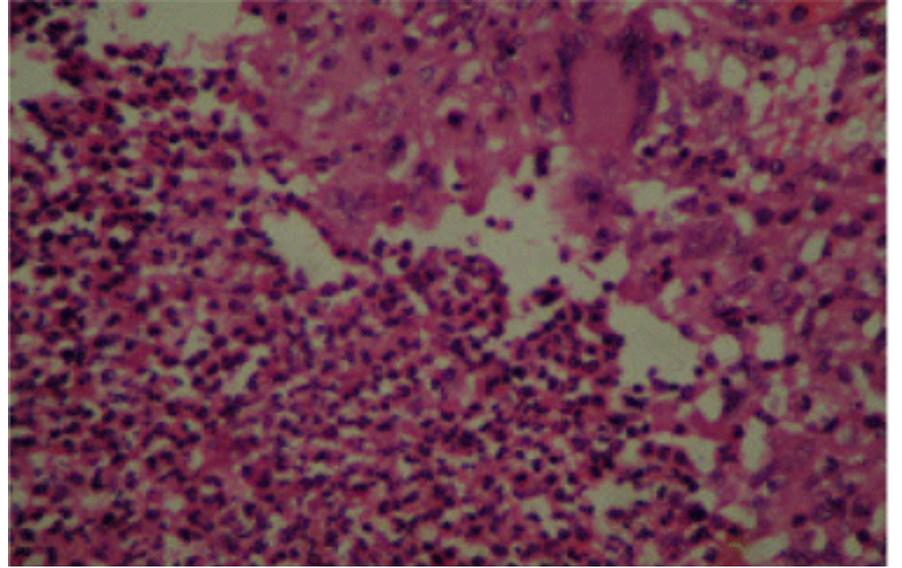
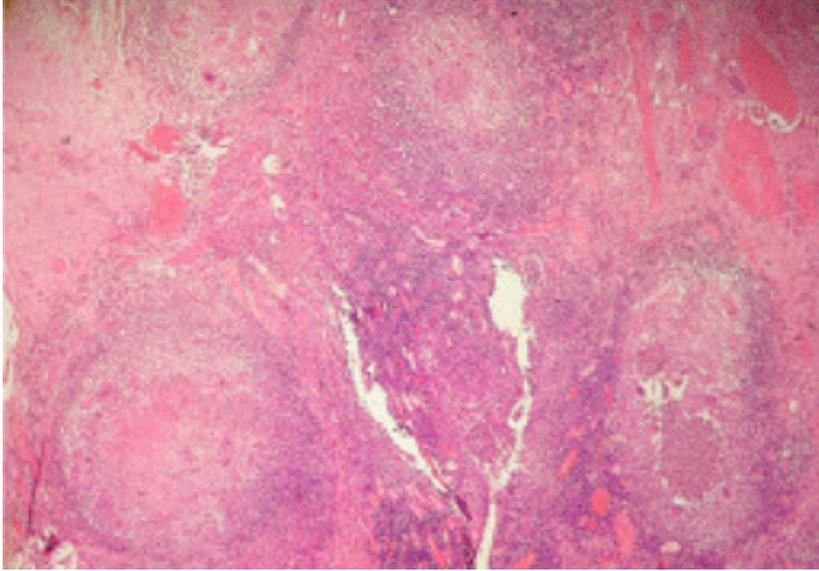
Palisaded granuloma

- Interstitial infiltrate of histiocytes admixed with other inflammatory cells, principally lymphocytes, and zones of altered collagen
- The inflammatory infiltrate surrounds the zones of altered collagen in a “wall-like or fence-like” fashion (palisading)
- No caseation necrosis
- Granuloma annulare, necrobiosis lipoidica, necrobiotic granuloma, rheumatic nodule, (rare: infection, foreign body reaction)



Suppurative granuloma

- Relatively circumscribed collection of (epithelioid) histiocytes
- Central collections of granulocytes (microabscesses)
- Infectious etiology!!, foreign body reaction



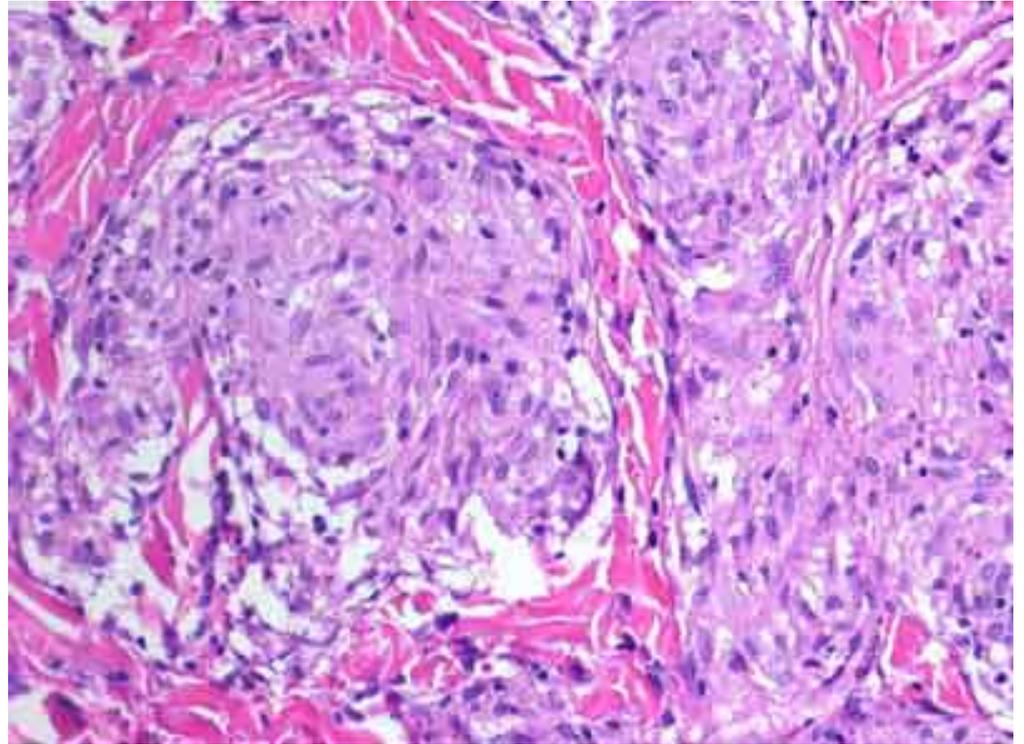
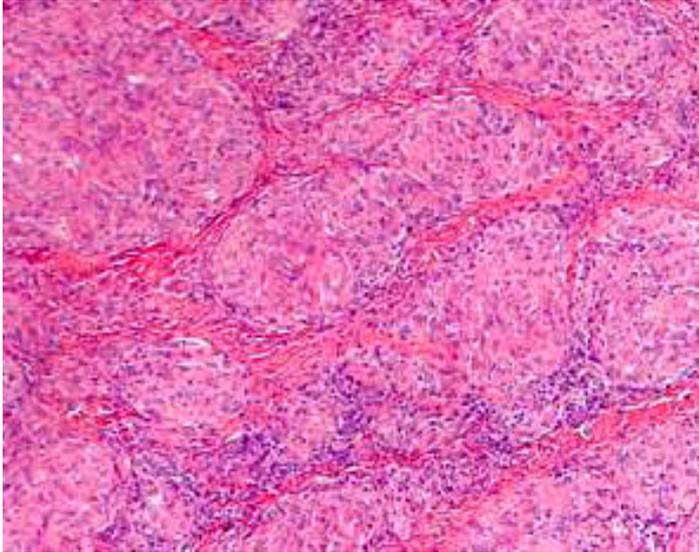
Suppurative granuloma

Interstitial granulomatous pattern

- Diffuse and interstitial dermal collections of histiocytes without formation of true granulomas
- Interstitial variant of granuloma annulare, lichen nitidus (also example of interface dermatitis)

Sarcoidosis: key microscopic features

- Epithelioid granulomas
- Poorly developed lymphocytic cuff
- Schaumann or asteroid body (stellate eosinophilic inclusions within multinucleated histiocyte)
- Scar sarcoidosis



sarcoidosis

Sarcoidosis: differential diagnosis

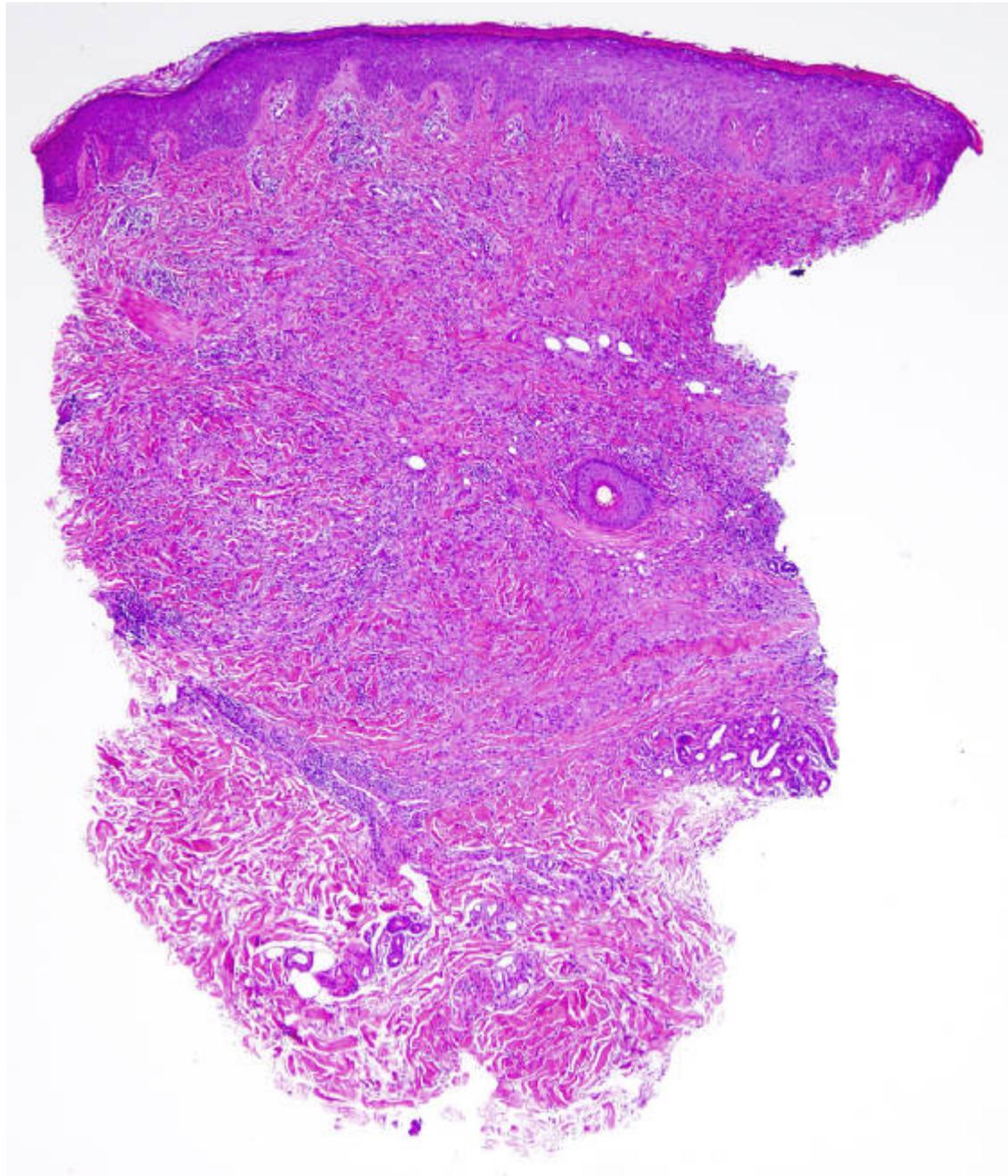
- **Exclude infection** (PAS, Grocott, ZN,....stains)
- *Cutaneous Crohn's disease* (usually presents in a perianal location, cutaneous manifestations of Crohn's disease may precede gastrointestinal involvement)
- *Necrobiosis lipoidica* (altered collagen, lymphoid aggregates, lymphoplasmacytic infiltrate)

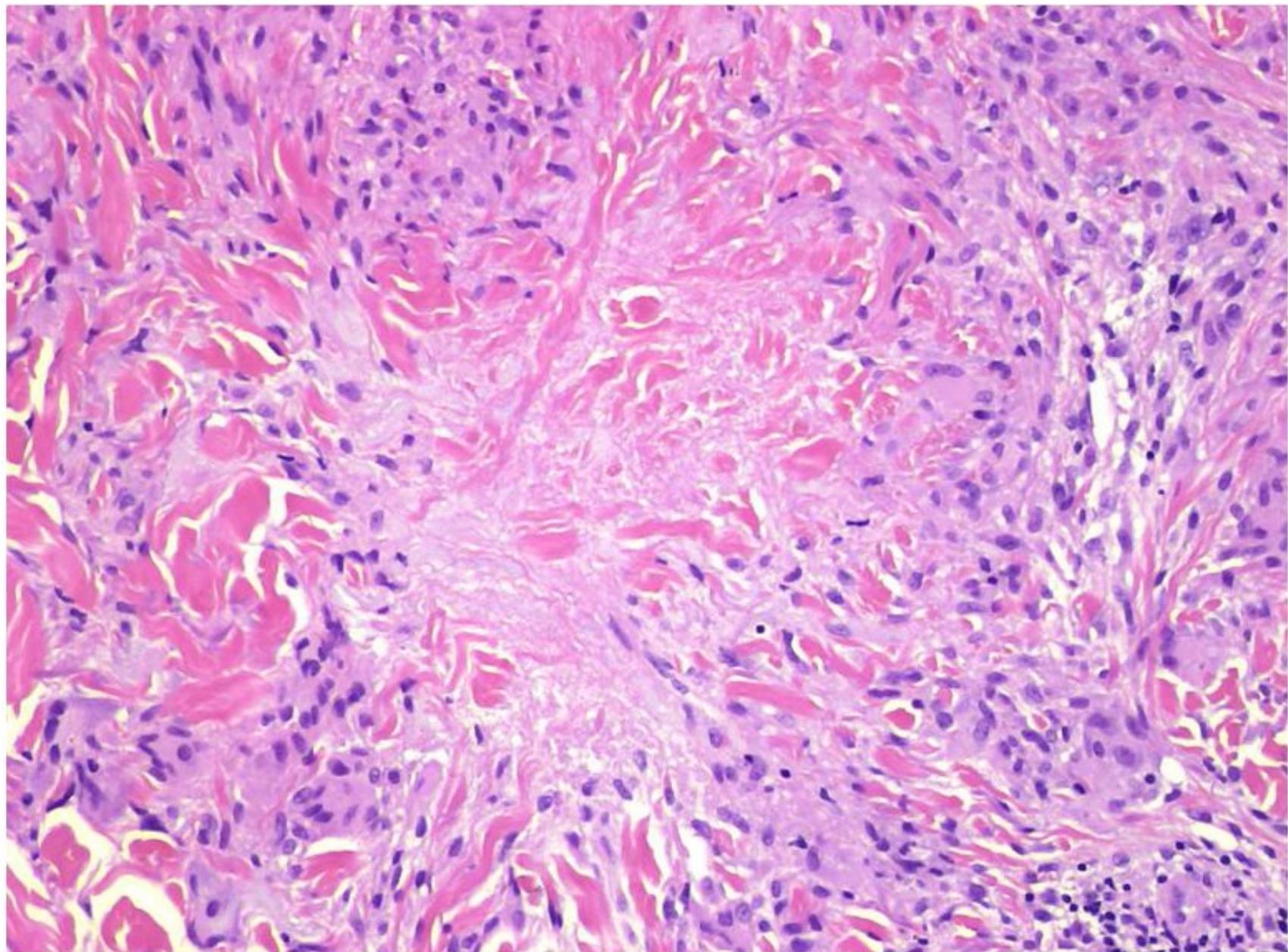
Sarcoidosis: practical tips

- Sarcoidosis is a diagnosis of exclusion
- Special stains and tissue culture should be liberally used, especially if there is no history of sarcoidosis
- Polarizable foreign material has been described in patients with sarcoidosis

Granuloma annulare: key microscopic features

- Regional involvement of dermis
- Palisading granuloma with interstitial infiltrate of histiocytes surrounding altered collagen fibers
- Altered collagen in granuloma has dermal mucin
- Interstitial pattern of granuloma annulare: infiltrate of histiocytes intercalating around altered collagen bundles





Granuloma annulare variants

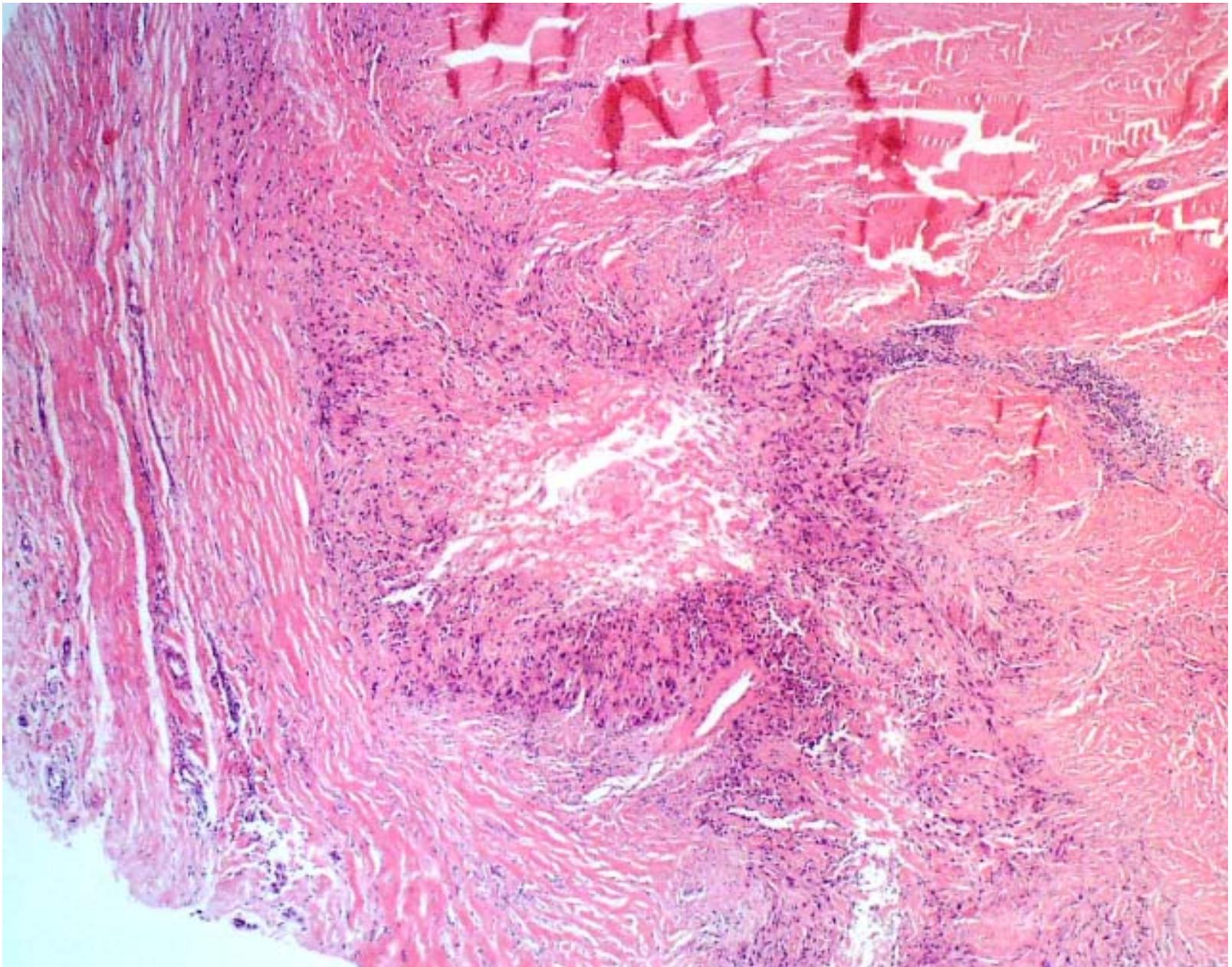
- *Interstitial (“incomplete”) GA*
- *Perforating GA* (transepidermal extrusion of the altered collagen fibers)
- *Subcutaneous GA* (predominantly or exclusively in the subcutaneous fat)

Granuloma annulare: differential diagnosis

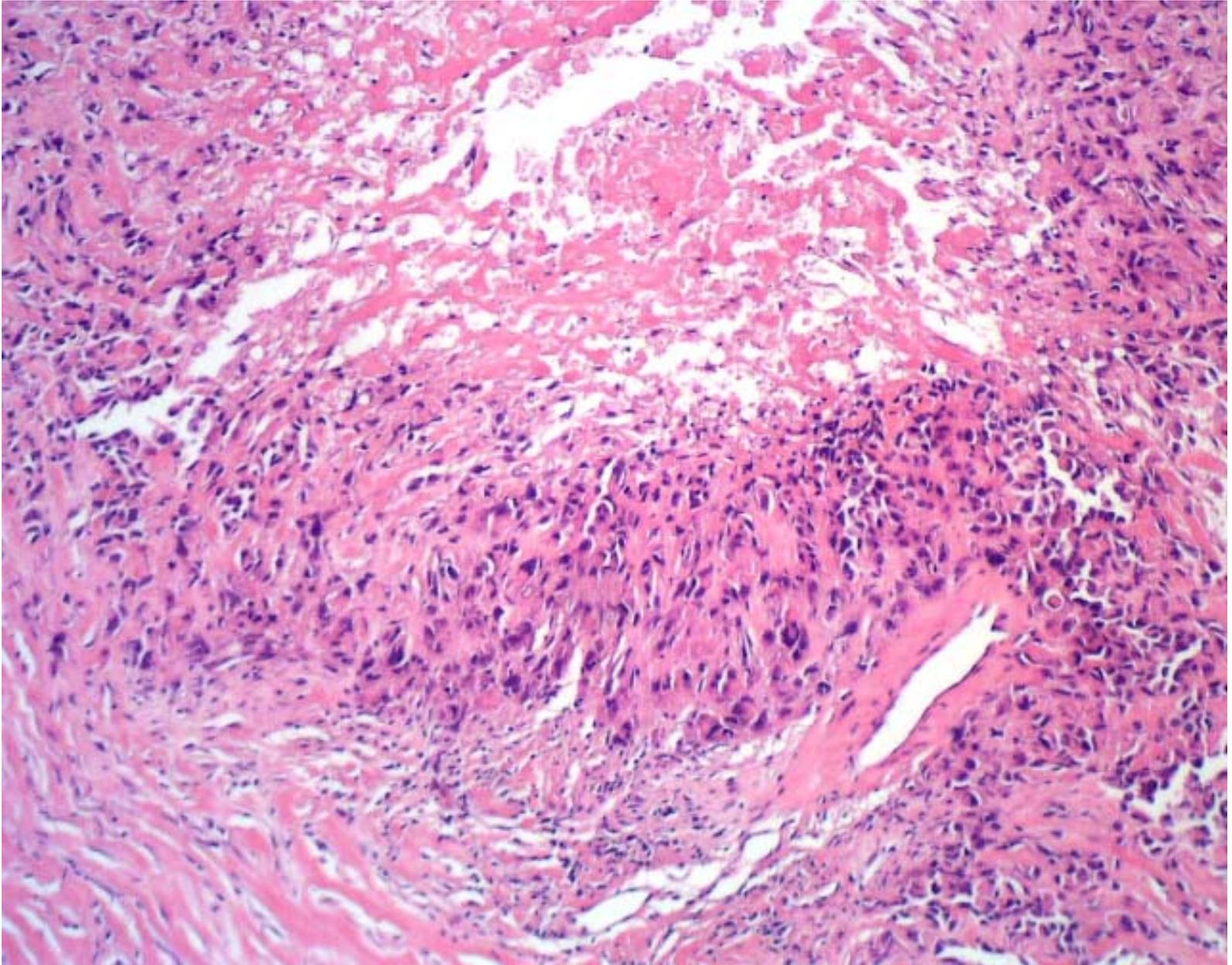
- *Necrobiosis lipoidica* (dermis more diffusely affected, tiered pattern of inflammatory infiltrate, lymphoid aggregates with plasma cells)
- *Rheumatoid nodule* (association with a joint, located in the deep dermis/subcutis, central zone of fibrin lacking dermal mucin) (difficult DD deep variant GA)
- *Interstitial granulomatous drug eruption* (difficult DD interstitial variant GA)
- *Actinic granuloma* (in sun damaged skin, phagocytosis of actinically damaged collagen by multinucleated giant cells)
- *Infectious pathology*

Granuloma annulare: **important differential diagnosis**

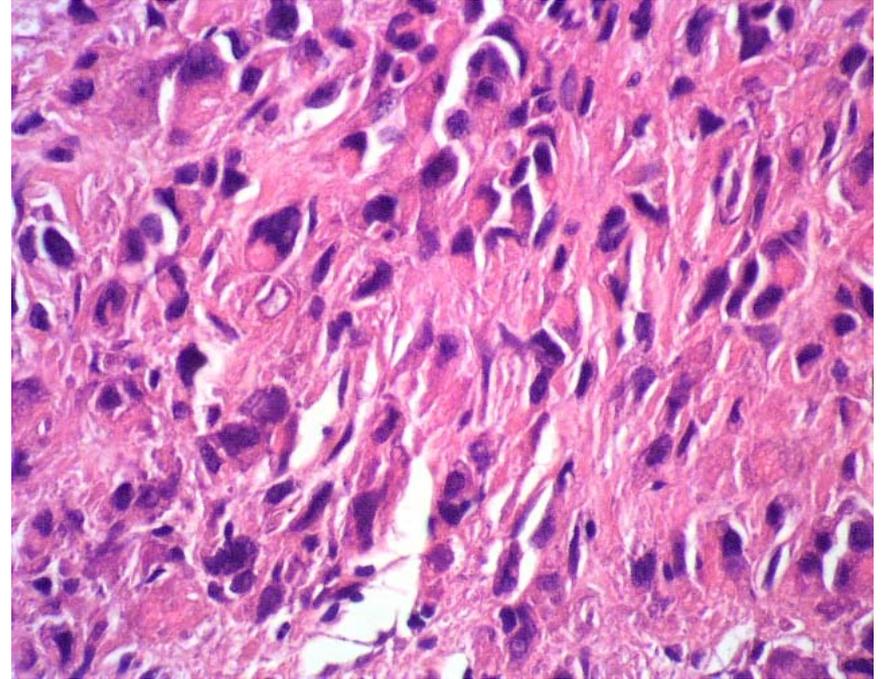
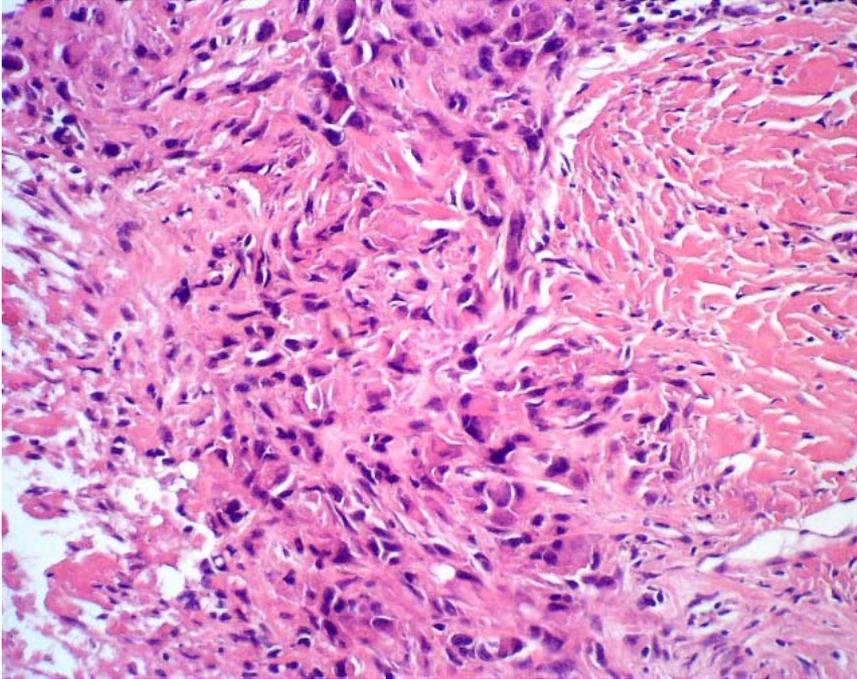
- **EPITHELIOID SARCOMA** (DD especially in the deep variant of a granuloma annulare): look for cytonuclear atypia, pleiomorphism and “dirty” necrosis. Immunohistochemistry: CK-pan+, EMA+, CD34 + (50%), CD68-, INI1-



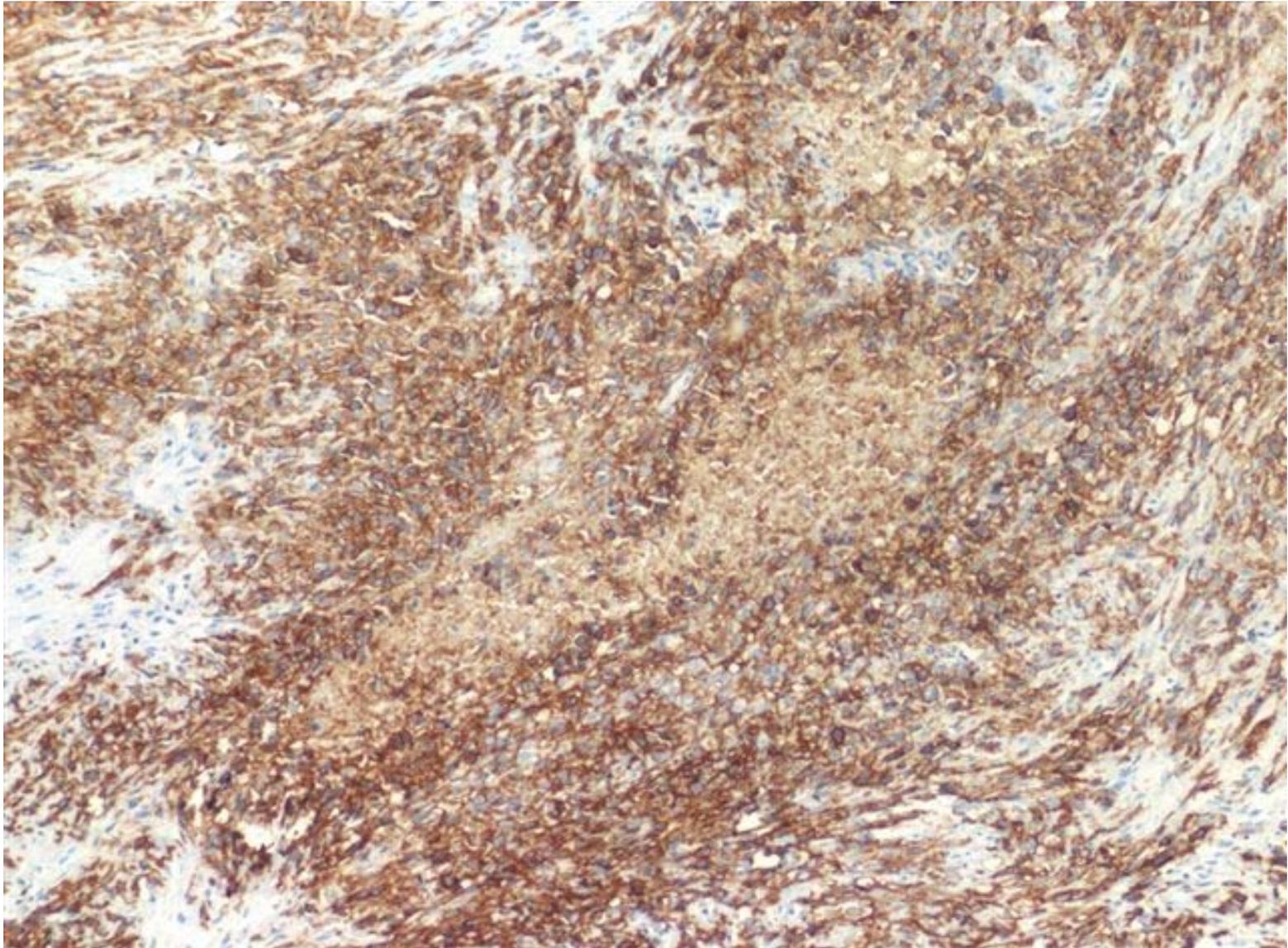
Epithelioid sarcoma



Epithelioid sarcoma



Epithelioid sarcoma



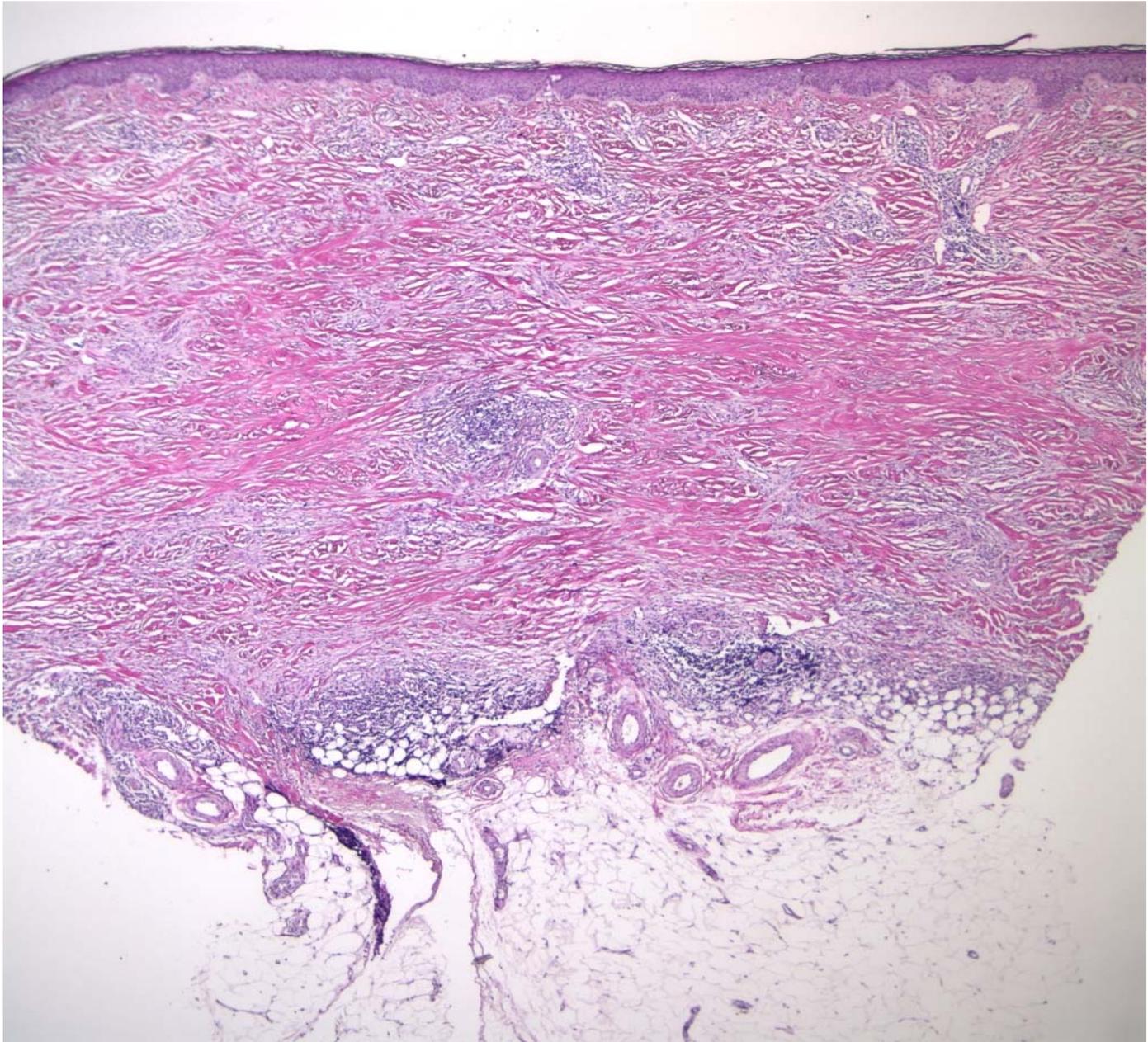
Epithelioid sarcoma: pan-CK

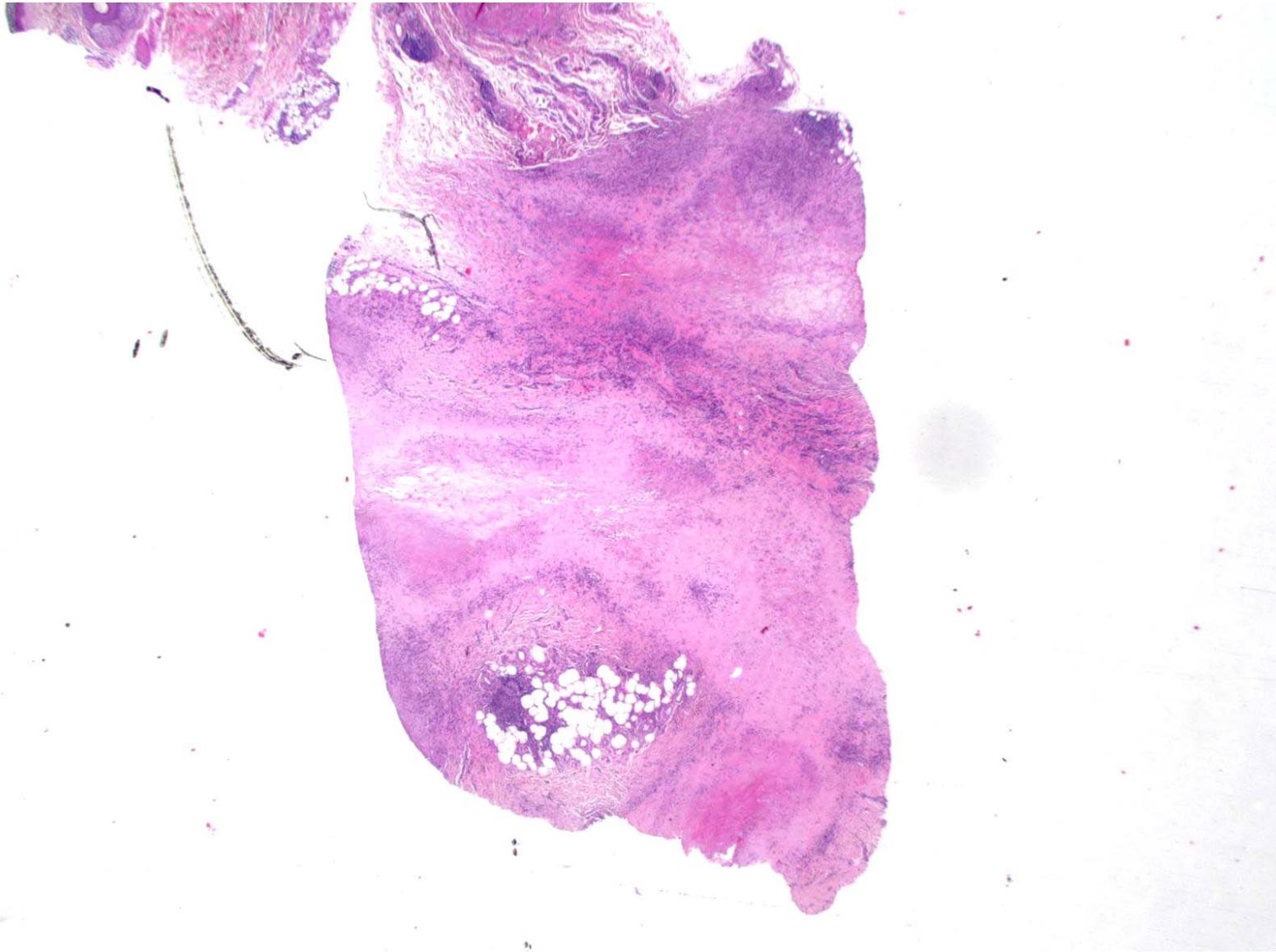
Granuloma annulare: practical tips

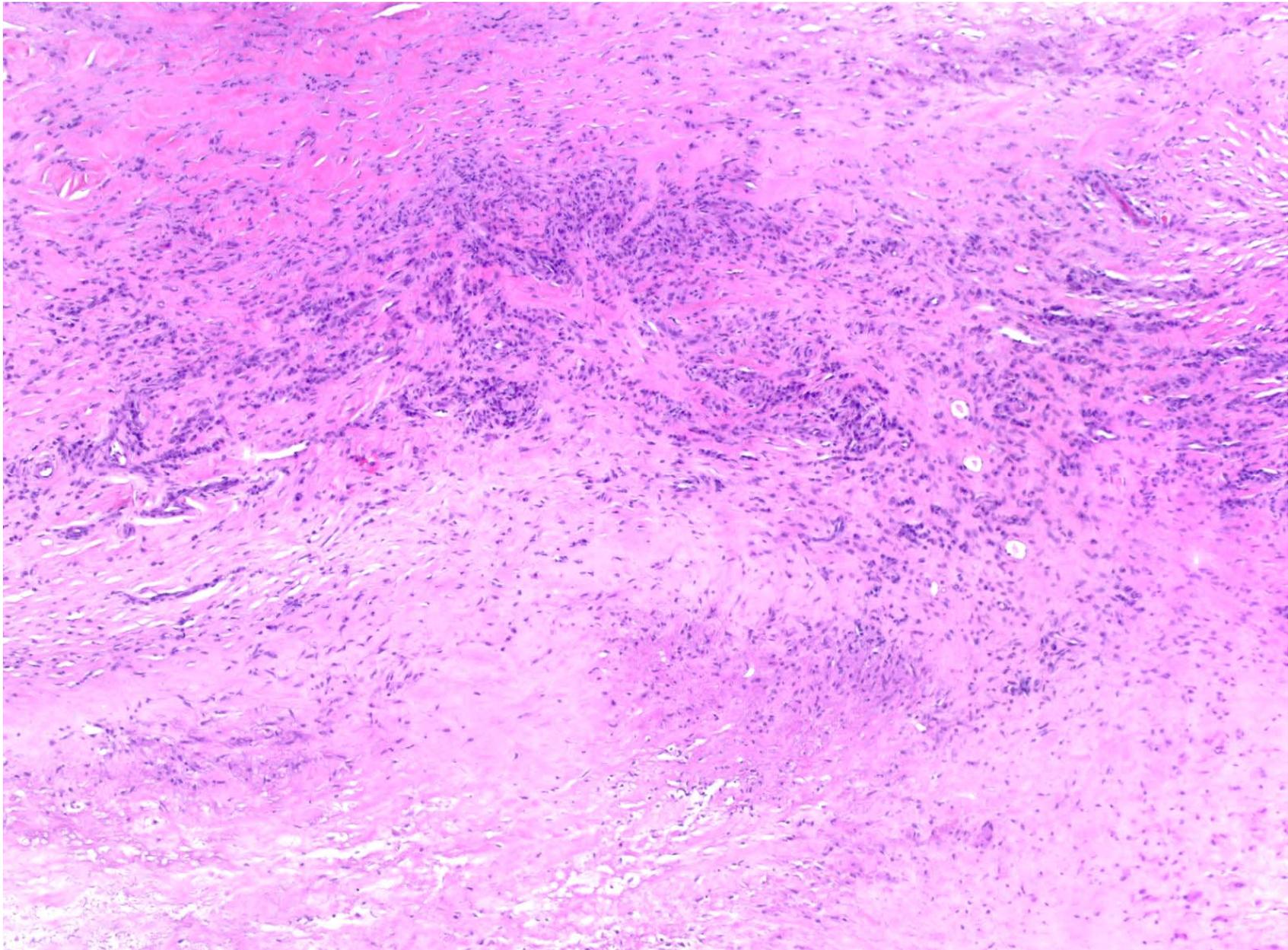
- Low power examination is critical to seeing the palisading pattern
- Palisade not always well developed
- Infiltrate usually does not involve the entire dermis
- Interstitial pattern common; may be subtle
- Plasma cells not a typical feature of granuloma annulare
- Certain drug eruptions may have a GA-like pattern; interface change argues for a drug eruption
- In GA-like eruption on actinically damaged skin, think about actinic granuloma and look for solar elastotic collagen fiber phagocytosis by multinucleated cells

Necrobiosis lipoidica: key microscopic features

- Diffuse dermal involvement
- Tiered pattern of inflammatory infiltrate alternating between necrobiotic collagen
- Lymphoid aggregates
- Plasma cells







Necrobiosis lipoidica: differential diagnosis

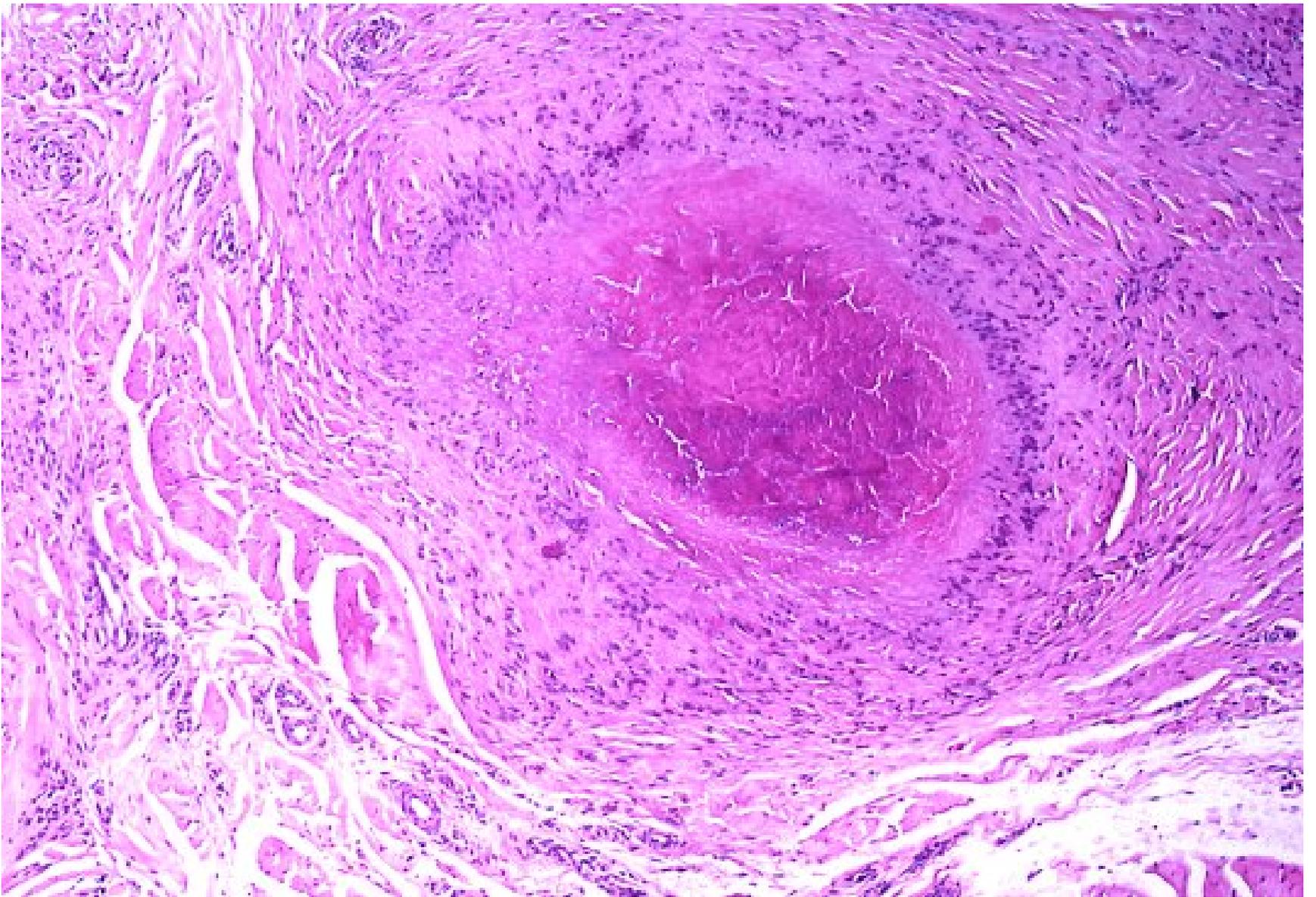
- Granuloma annulare (regional and not diffusely involvement of the dermis, no tiered pattern, no plasma cells)
- Sarcoidosis (no altered collagen-no necrobiosis, no tiered pattern)
- Necrobiotic xanthogranuloma (more diffuse infiltrate with less of a tiered pattern, conspicuous foamy macrophages and cholesterol clefts)

Necrobiosis lipoidica: practical tips

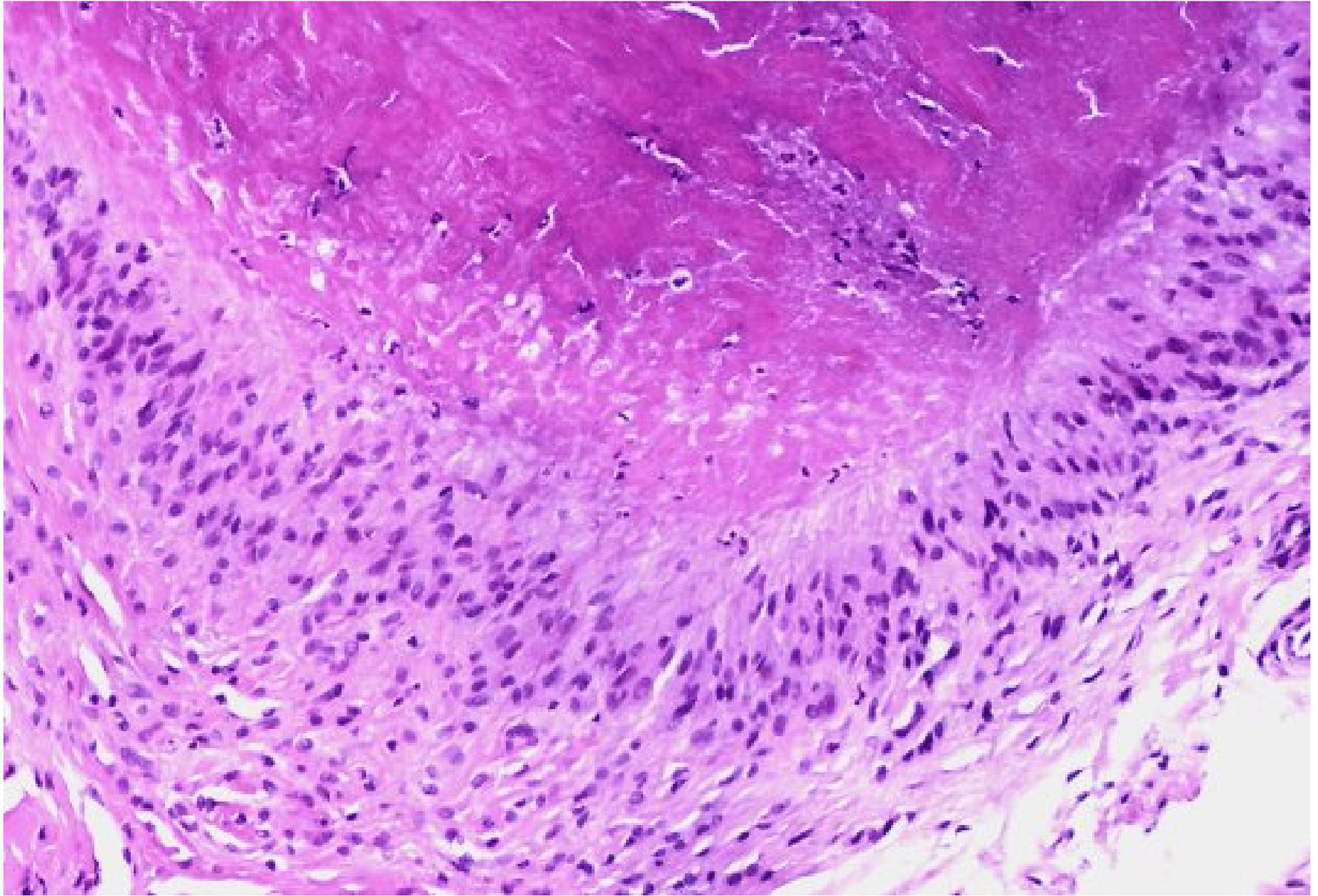
- Low power examination is the key to recognizing the tiered pattern
- The derm is diffusely involved
- Plasma cells favor necrobiosis lipoidica over granuloma annulare
- In some cases the differential between granuloma annulare and necrobiosis lipoidica is not clear. In these cases a descriptive diagnosis of “granulomatous dermatitis, see comment” is helpful.

Rheumatoid nodule: key microscopic features

- Palisading granuloma of histiocytes surrounding acellular fibrin
- No abundant mucin in granuloma
- Granulomas often lack significant surrounding lymphocytic cuff



Rheumatoid nodule



Rheumatoid nodule

Rheumatoid nodule: differential diagnosis

- *Deep granuloma annulare* (abundant mucin favors deep granuloma annulare!)
- *Epithelioid sarcoma*
- *Necrobiosis lipoidica*

Rheumatoid nodule: practical tips

- Usually over bony prominences
- Is not present in superficial dermis
- Central portion of granulomas contain brightly eosinophilic fibrin
- Usually associated with rheumatoid arthritis
- If no known history of rheumatoid arthritis, consider descriptive diagnosis

Vasculitis and thrombotic disorders

Practical approach to vasculitis

- Determine if vasculitis or vasculopathy is present or absent
- Primary or secondary vascular injury (is often not possible)
- Size of vessel and type (large-medium-small)
- Composition of the infiltrate (neutrophilic/leucocytoclastic, eosinophilic, lymphocytic, histiocytic/granulomatous)
- Evaluation of infection
- Serologic and immunopathologic evaluation (evaluation for ANCA, ANA, rheumatoid factor, cryoglobulins; IF for detection if immune complexes)
- Clinical context (cutaneous involvement only, extent of systemic involvement)

vasculitis

- **Primary**
- **Secondary:** vasculitic changes may merely be secondary from nonvasculitic causes like drugs, herpes virus infection, trauma, bullous pemphigoid or PLEVA.

vasculitis

- **Large- and Medium-sized vessels:** giant cell arteritis (temporal arteritis)
- **Medium-size vessels:** Kawasaki disease, Takayasu arteritis, infections, Buerger's disease, polyarteritis nodosa, rheumatoid vasculitis, giant cell (temporal) arteritis
- **Small-size vessels:** neutrophilic small-vessel vasculitis (especially the postcapillary venules) (infections, immunologic, drug-induced, paraneoplastic, idiopathic)

Vasculitis

Vasculitis-composition of the infiltrate

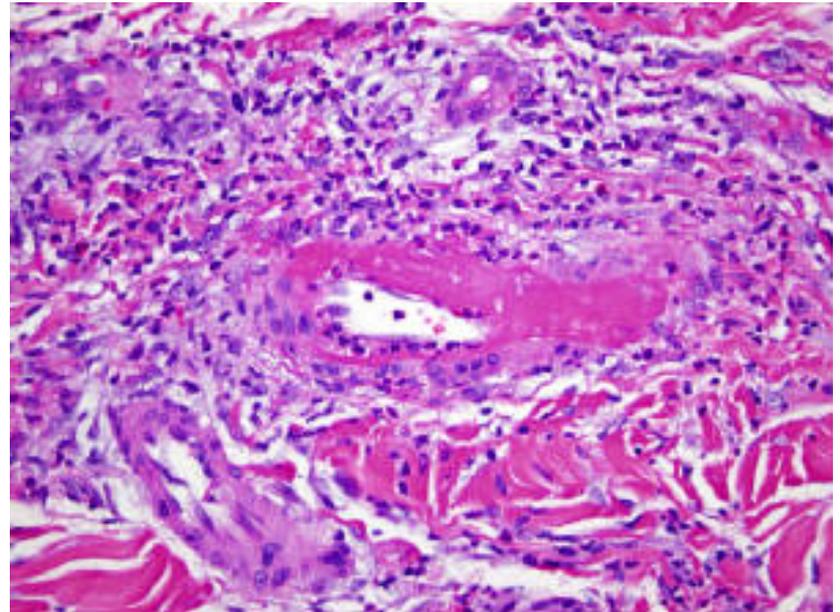
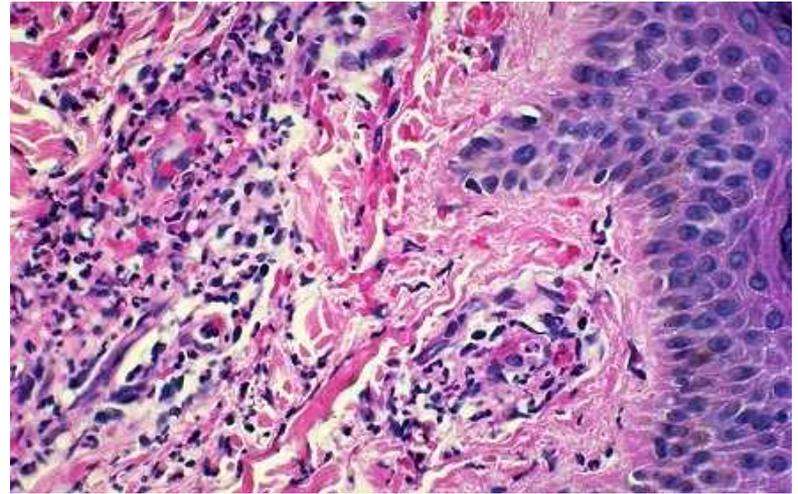
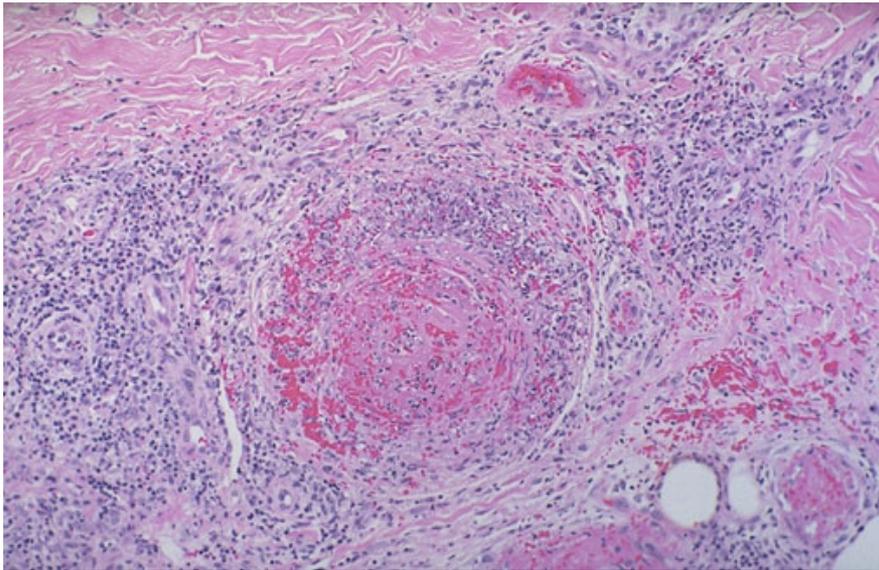
- leukocytoclastic (neutrophilic) vasculitis** (Henoch-Schönlein purpura, urticarial vasculitis, mixed cryoglobulinemia, Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa)
- lymphocytic vasculitis (true vasculitis?)** (pigmented purpuric dermatosis/M. Schamberg, perniones)
- eosinophilic vasculitis** (Churg-Strauss syndrome, urticarial vasculitis)
- granulomatous/histiocytic vasculitis** (Wegener's vasculitis-true granulomatous vasculitis is extremely rare!)

Vasculopathy-thrombotic disorders

- Processes that occlude vessels resulting in ischemic damage, but are not associated with significant inflammation.
- Coumadin necrosis, atrophie blanche (livedoid vasculopathy), antiphospholipid antibody syndrome, cholesterol emboli, calciphylaxis

Leucocytoclastic vasculitis: key microscopic features

- Perivascular infiltrate of neutrophils
- Fragmented nuclear debris (leukocytoclasia)
- Extravasation of erythrocytes
- Fibrin deposition in vessel walls
- Variable fibrinoid necrosis of blood vessels

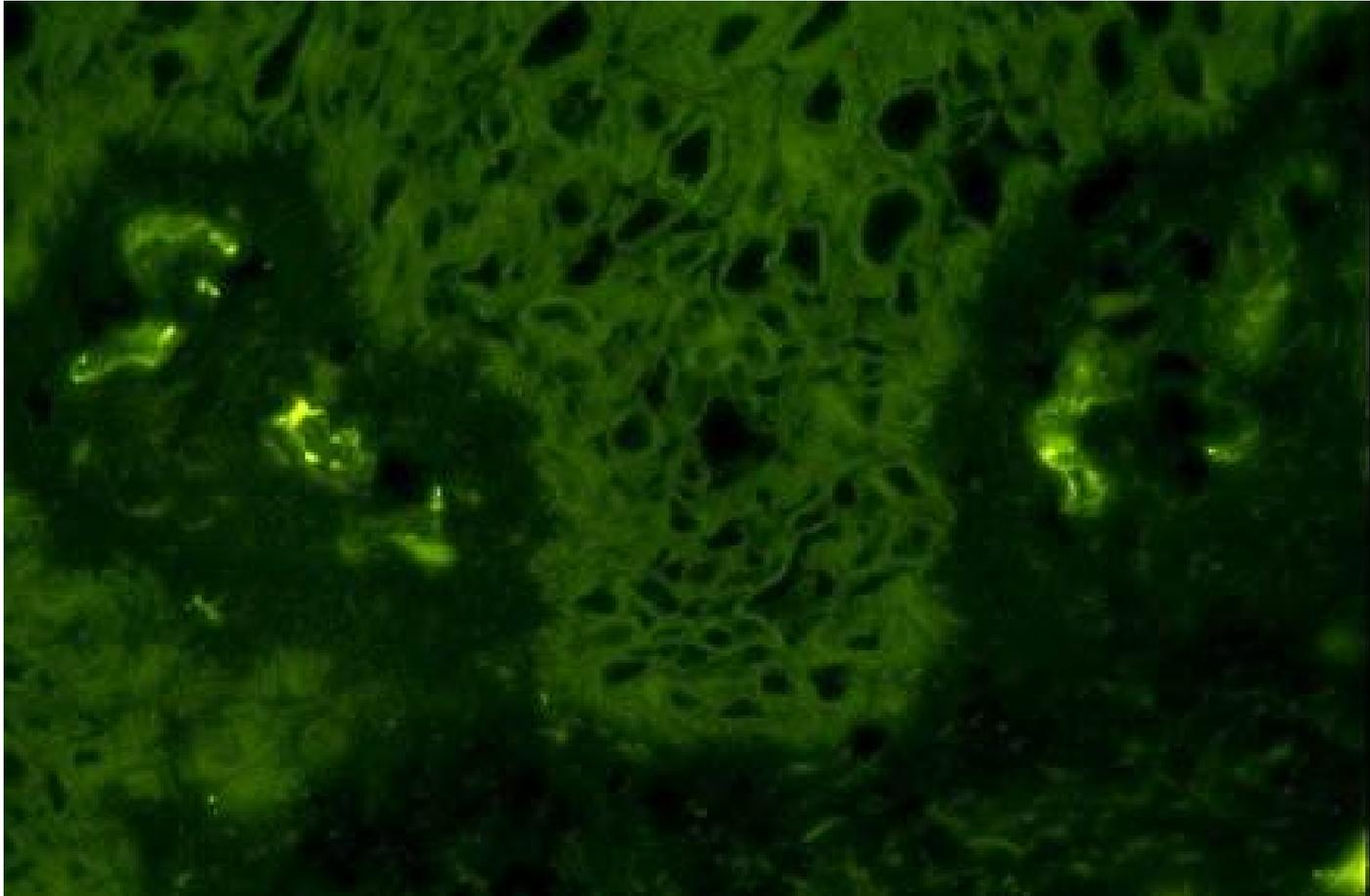


Leucocytoclastic vasculitis: practical tips

- Fully developed features not always present
- Early cases may show perivascular neutrophils, leucocytoclasia, and hemorrhage without significant fibrin deposition or vessel necrosis
- If epidermis is ulcerated, consider secondary vasculitis (also in Wegener's granulomatosis)

Henoch-Schönlein purpura: key microscopic features

- Leukocytoclastic vasculitis
- Perivascular IgA deposits on direct immunofluorescence



Perivascular IgA deposits

Henoch-Schönlein purpura: practical tips

- Correlation with clinical history is critical (palpable purpura in addition to various combinations of arthritis, gastrointestinal involvement and nephritis)
- More common in children but adult cases are also seen
- DIF requisite for definitive diagnosis

Urticarial vasculitis: key microscopic features

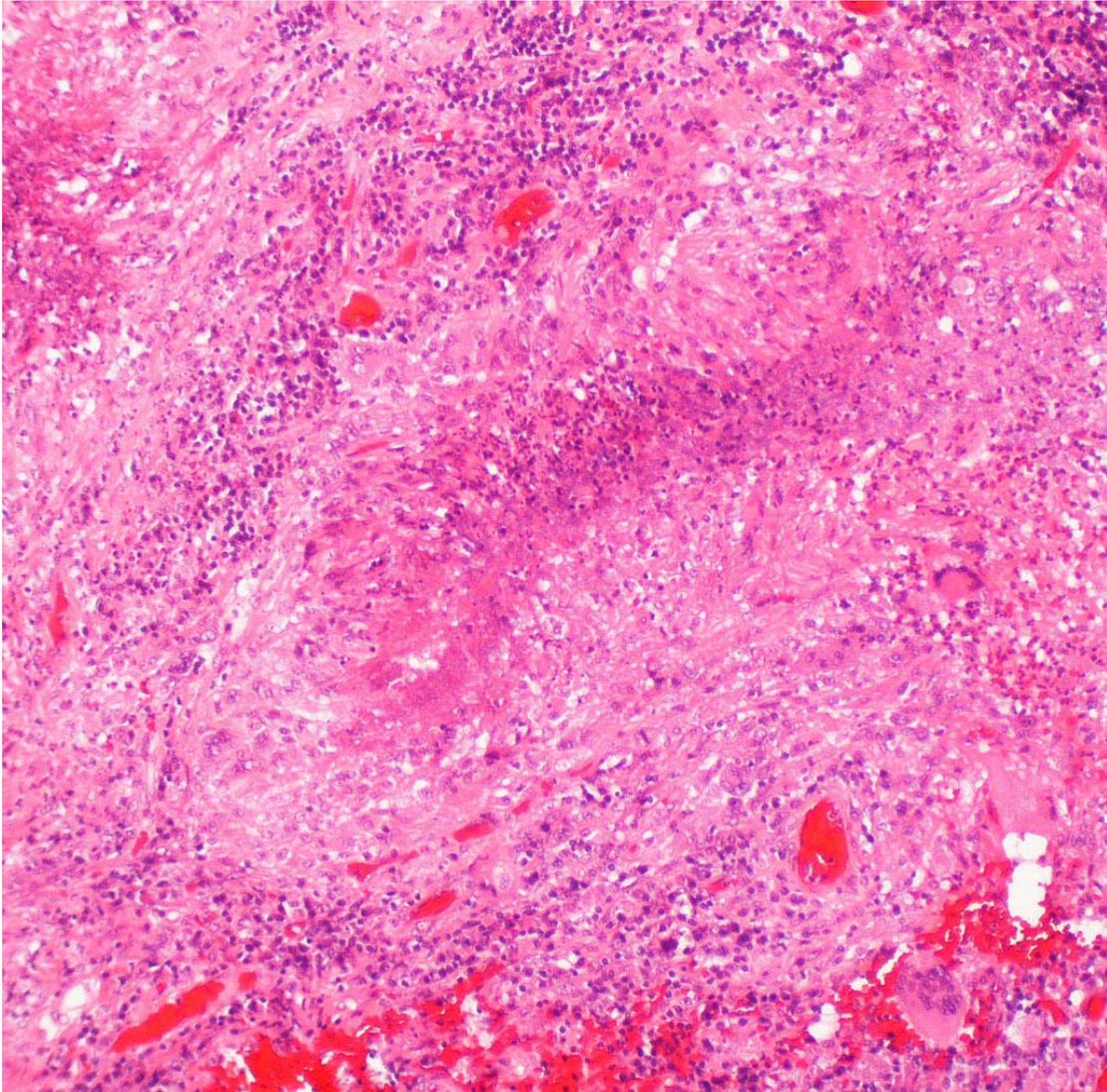
- Subtle leukocytoclastic vasculitis
- Usually mild perivascular neutrophils with leukocytoclasia
- Evidence of vascular damage, typically focal
- Eosinophils are frequently present
- Differential diagnosis: urticaria

Urticarial vasculitis: practical tips

- Deeper levels are often required to make diagnosis
- Lesions are present as urticarial plaques
- Criteria less stringent: neutrophilic infiltrate with any leukocytoclasia sufficient to suggest diagnosis. Knowledge of the clinical presentation of the lesions is necessary in these cases

Wegener's vasculitis: key microscopic features

- Leukocytoclastic vasculitis involving superficial and deep dermis
- Pyoderma gangrenosum like ulcers may be present
- Palisading granulomatous inflammation
- True granulomatous vasculitis is rare
- Differential diagnosis (because the superficial and deep involvement): mixed cryoglobulinemia, Churg-Strauss syndrome and microscopic polyangiitis



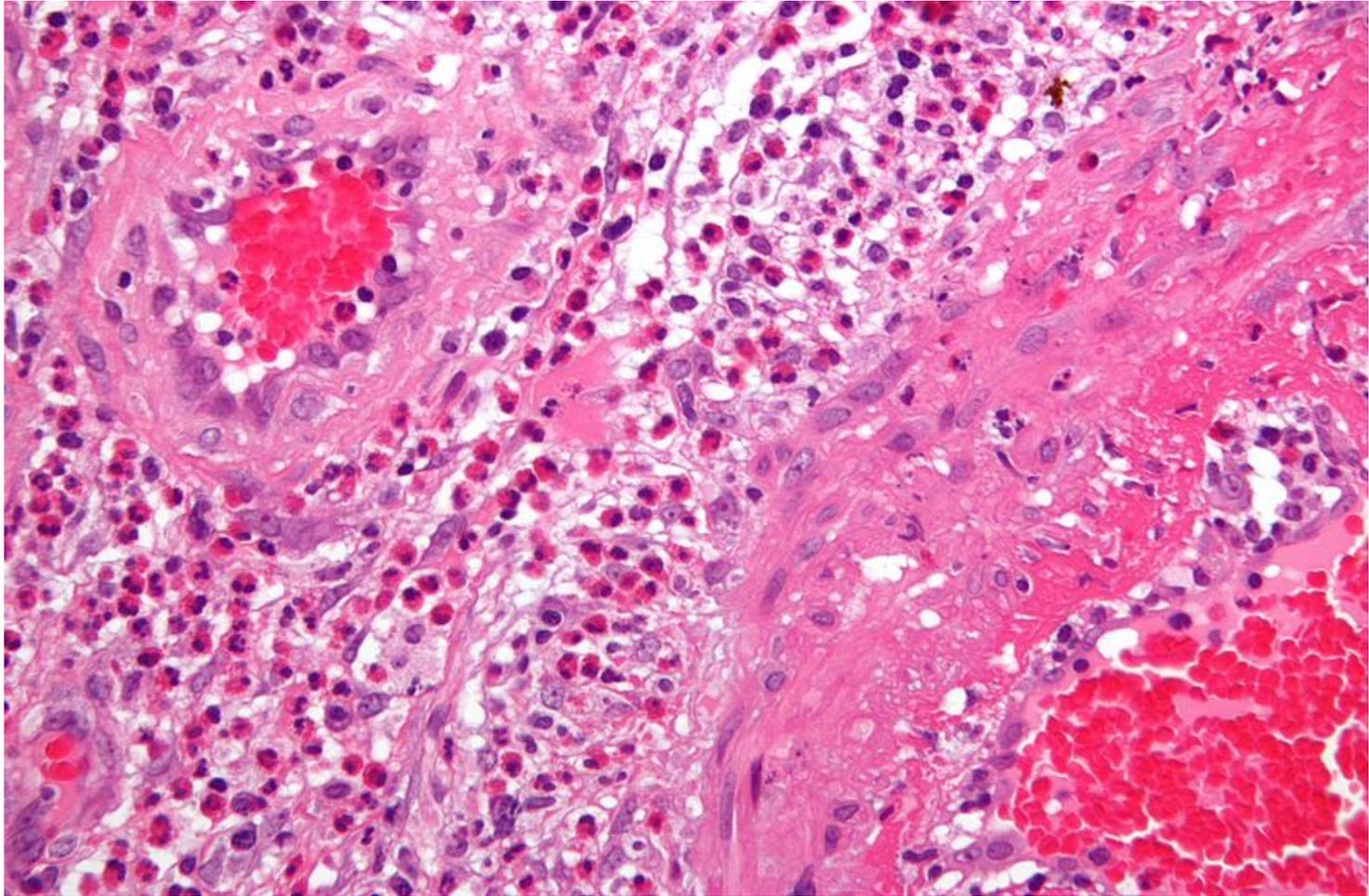
Granulomatous vasculitis (Wegener's vasculitis)

Wegener's vasculitis: practical tips

- Histologic findings are variable
- May present with only one of the features (usually leukocytoclastic vasculitis)
- Correlation with clinical presentation and serology (c-ANCA) critical!!

Churg-Strauss Syndrome: key microscopic features

- Eosinophil-rich neutrophilic leukocytoclastic vasculitis
- Interstitial eosinophils
- Variable flame figures
- Differential diagnosis: urticarial vasculitis (perivascular infiltrate is less dense and deep), Well's syndrome (no vasculitis), other dermal hypersensitivity reactions like arthropod bite reaction and drug eruption (lacking vasculitis)



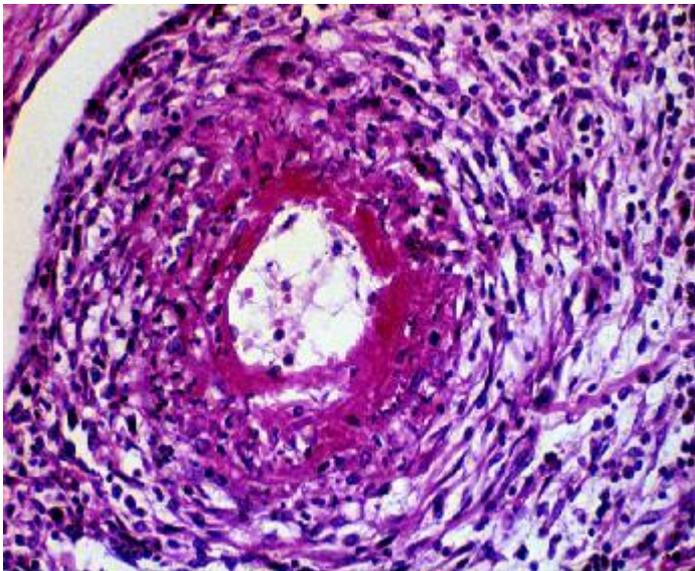
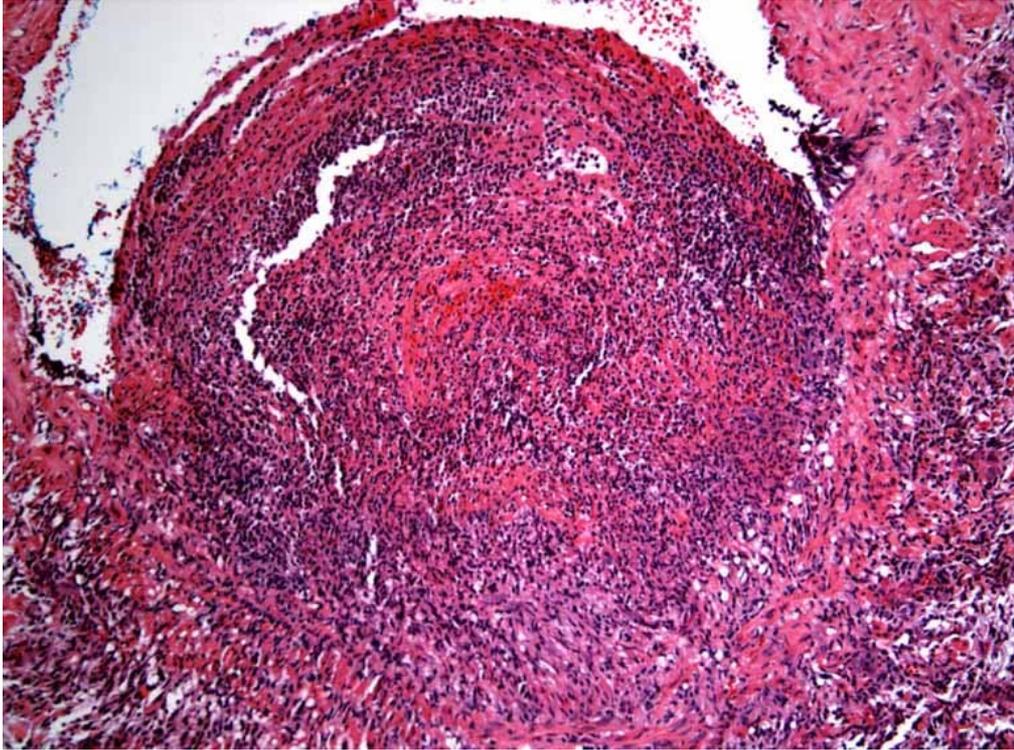
“eosinophilic vasculitis”

Churg-Strauss Syndrome: practical tips

- If a leukocytoclastic vasculitis has significant numbers of eosinophils, consider Churg-Strauss syndrome
- Correlation with history is critical (combination of asthma, other allergic symptoms e.g. allergic rhinitis, peripheral and tissue eosinophilia, systemic vasculitis)

Cutaneous polyarteritis nodosa: key microscopic features

- Affected vessels are in deep dermis/subcutis
- Medium-sized muscular arteries are involved by leukocytoclastic vasculitis
- Differential diagnosis: erythema induratum (nodular vasculitis) (but associated lobular panniculitis!)



Cutaneous polyarteritis nodosa: practical tips

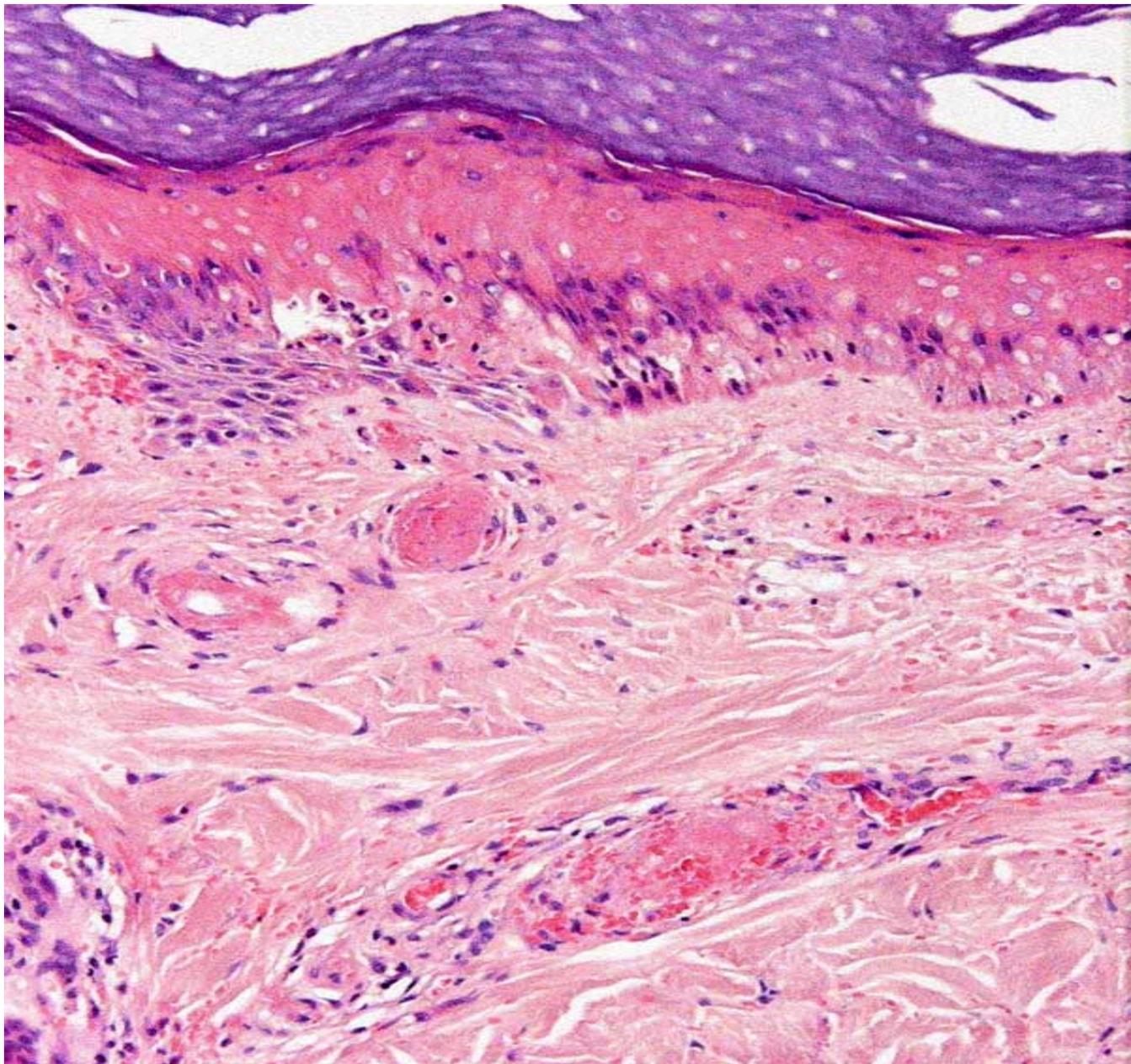
- Diagnostic features can be focal
- Deeper levels may be necessary
- No associated diffuse lobular panniculitis

Thrombotic disorders

- Hypercoagulable states: Coumadin necrosis, atrophie blanche (livedoid vasculopathy), antiphospholipid antibody syndrome and monoclonal cryoglobulinemia)
- Cholesterol emboli
- Calciphylaxis

Hypercoagulable states: key microscopic features

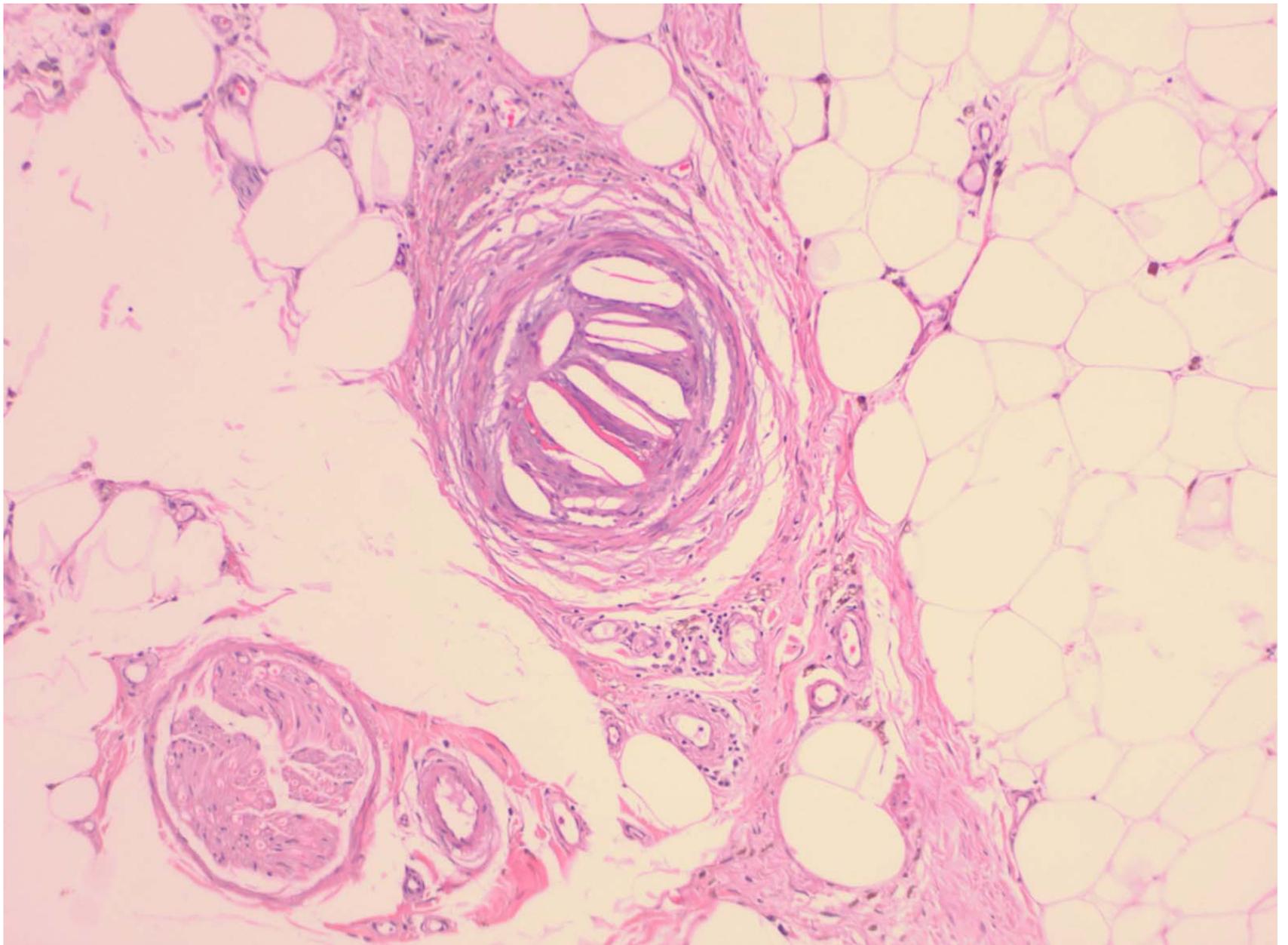
- Thrombi in venules and arterioles
- Non-inflammatory
- Clinical correlation in all these cases is **CRUCIAL.**
 - Coumadin necrosis (occurs within days of initiation of anticoagulant Coumadin therapy)
 - Atrophie Blanche (usually presents in elderly women, most common on distal lower extremities)
 - Antiphospholipid antibody syndrome (young adult women, history of spontaneous abortion or connective tissue disease)



Livedoid vasculopathy
(atrophie blanche)

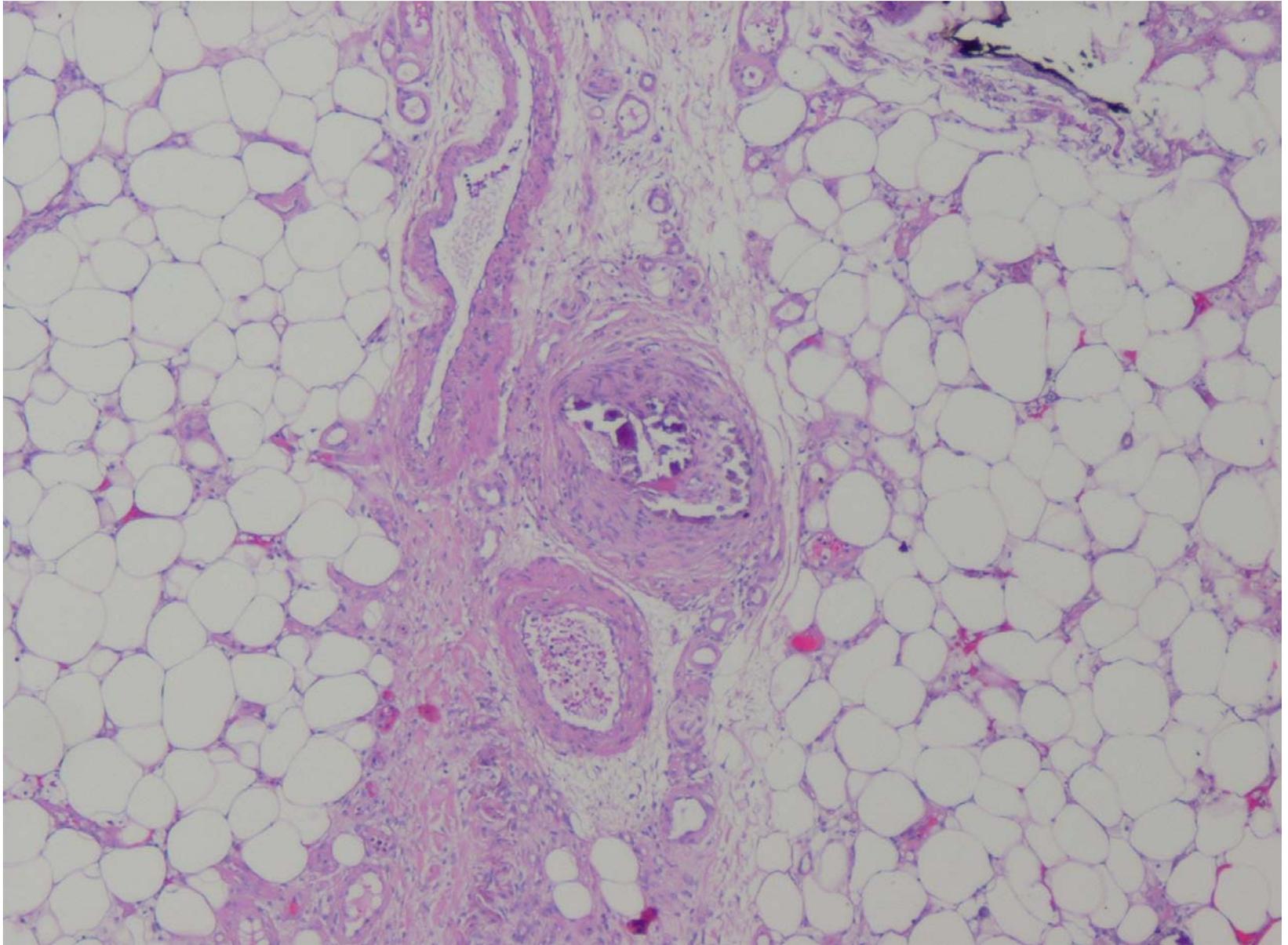
Cholesterol emboli

- Vascular thrombus in deep dermis or subcutis
- Cholesterol clefts are required for the diagnosis
- Multiple levels are often needed
- Occurs on distal extremities
- History of prior vascular procedure is common



calciophylaxis

- Calcification of small to medium-sized arteries
- Associated fat necrosis is common and often extensive
- It is important that a sufficiently large and deep biopsy is obtained as the involved vessels are usually in the subcutis. Superficial biopsies may not be diagnostic.
- Clinical history of renal failure
- Mortality rates approach 60%!!



panniculitis

panniculitis

- **Heterogenous** group of inflammatory disorders involving the subcutaneous adipose tissue
- Diagnosis remains **a challenge** to clinicians and pathologists for several reasons!
 - clinical monotony is common among the diseases
 - there are often sampling issues (inadequate superficial biopsies)
 - panniculitides are dynamic processes demonstrating different histologic features at different stages of development

stepwise approach when evaluating an inflammatory process in the subcutis

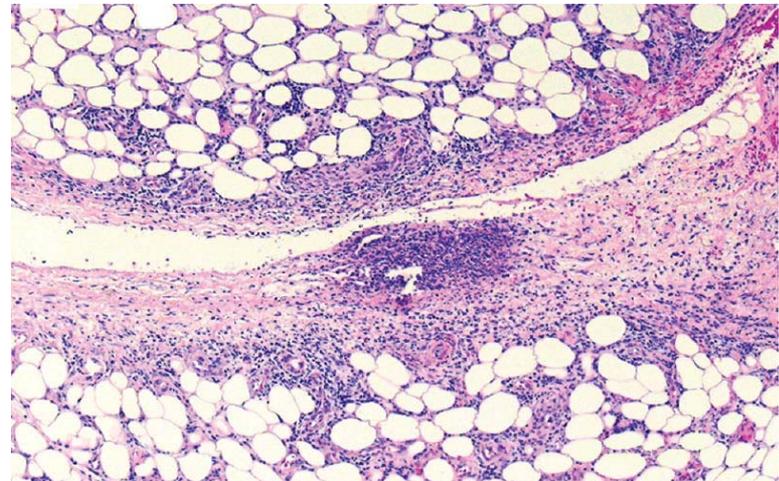
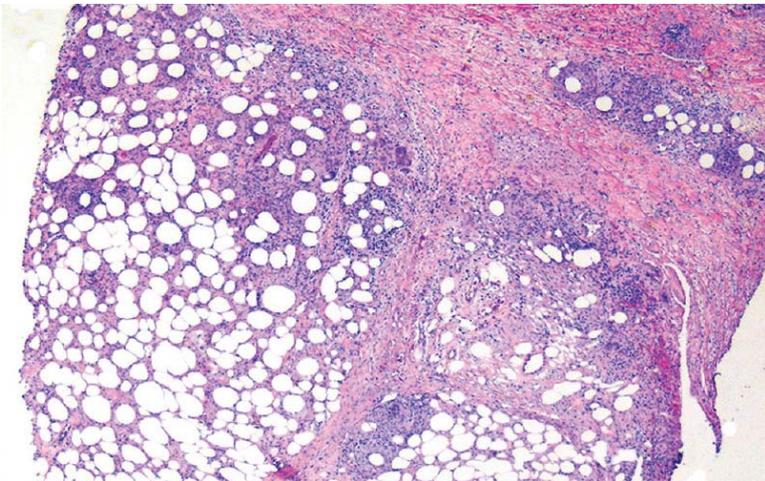
- Determine the predominant location of the inflammatory cell infiltrate: **septal vs lobular** at scanning magnification
- Note the **composition of the inflammatory infiltrate** (neutrophilic, eosinophilic, granulomatous or mixed)
- Examine blood vessels to determine whether there is **vascular inflammation** (vasculitis)
- *Note type of fat necrosis* (lipophagic, enzymatic, hyaline, membranous or ischemic)

panniculitis

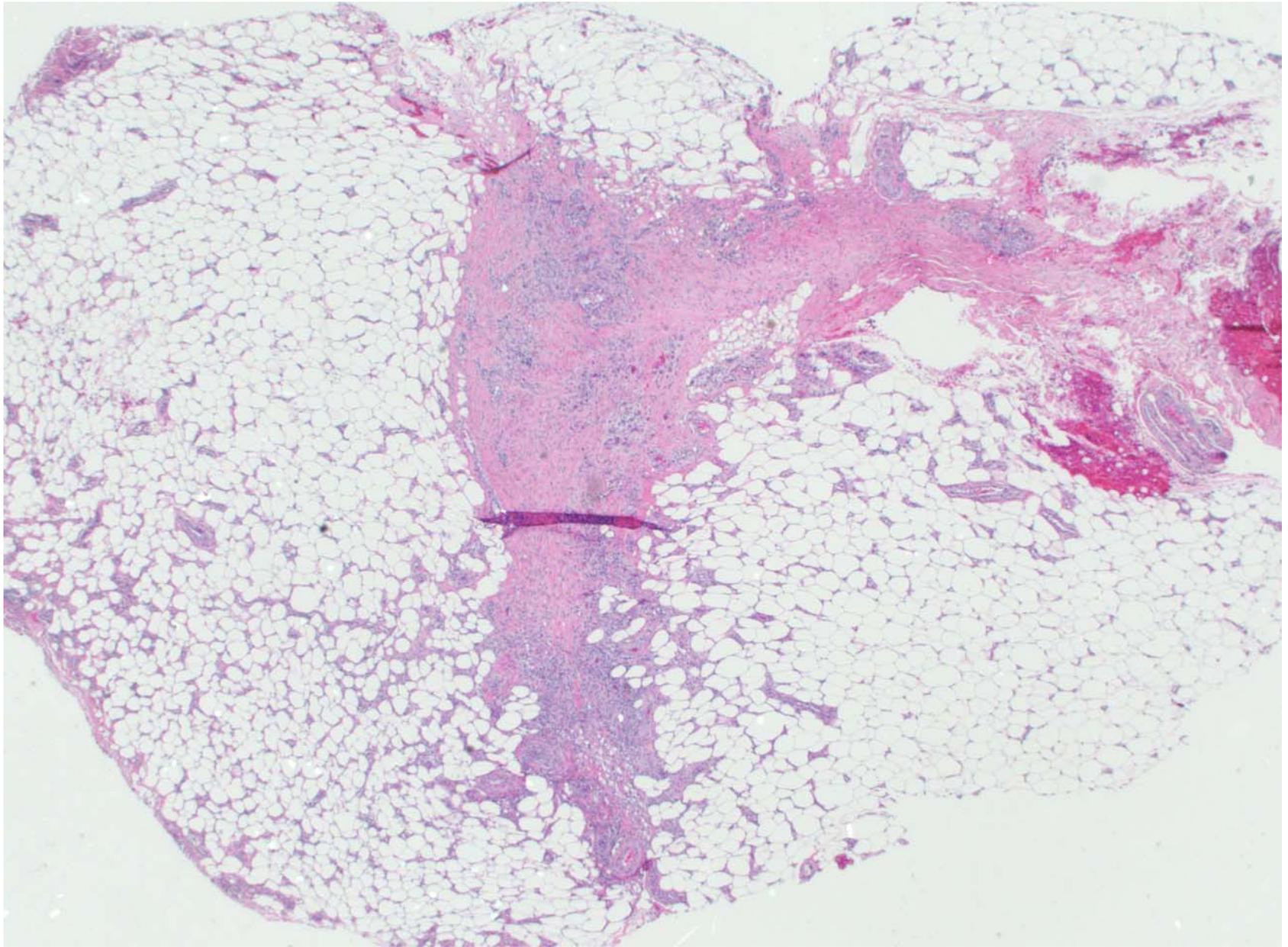
- **Predominant septal**
 - erythema nodosum (prototype)
- **Predominant lobular**
 - erythema nodosum (erythema induratum)
(prototype)
 - lupus panniculitis
 - artifactual panniculitis
- **Mixed septal and lobular**
 - lipodermatosclerosis (sclerosing panniculitis)
(relatively **NON**inflammatory)

Erythema nodosum: key microscopic features

- Prototype septal panniculitis
- Early lesions have more inflammation (neutrophils) and less fibrosis
- Later lesions demonstrate septal thickening, lymphocytes, histiocytes, eosinophils, and multinucleated giant cells
- Miescher's radial granulomas: aggregates of small histiocytes around central cleft
- No vasculitis



Erythema nodosum: septal panniculitis



Erythema nodosum: differential diagnosis

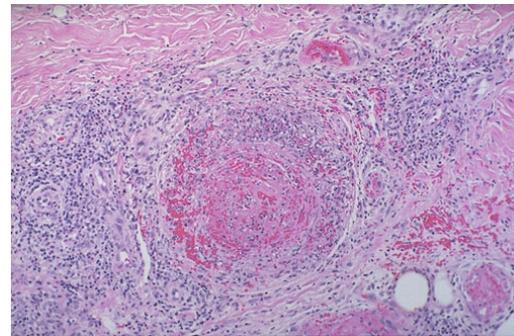
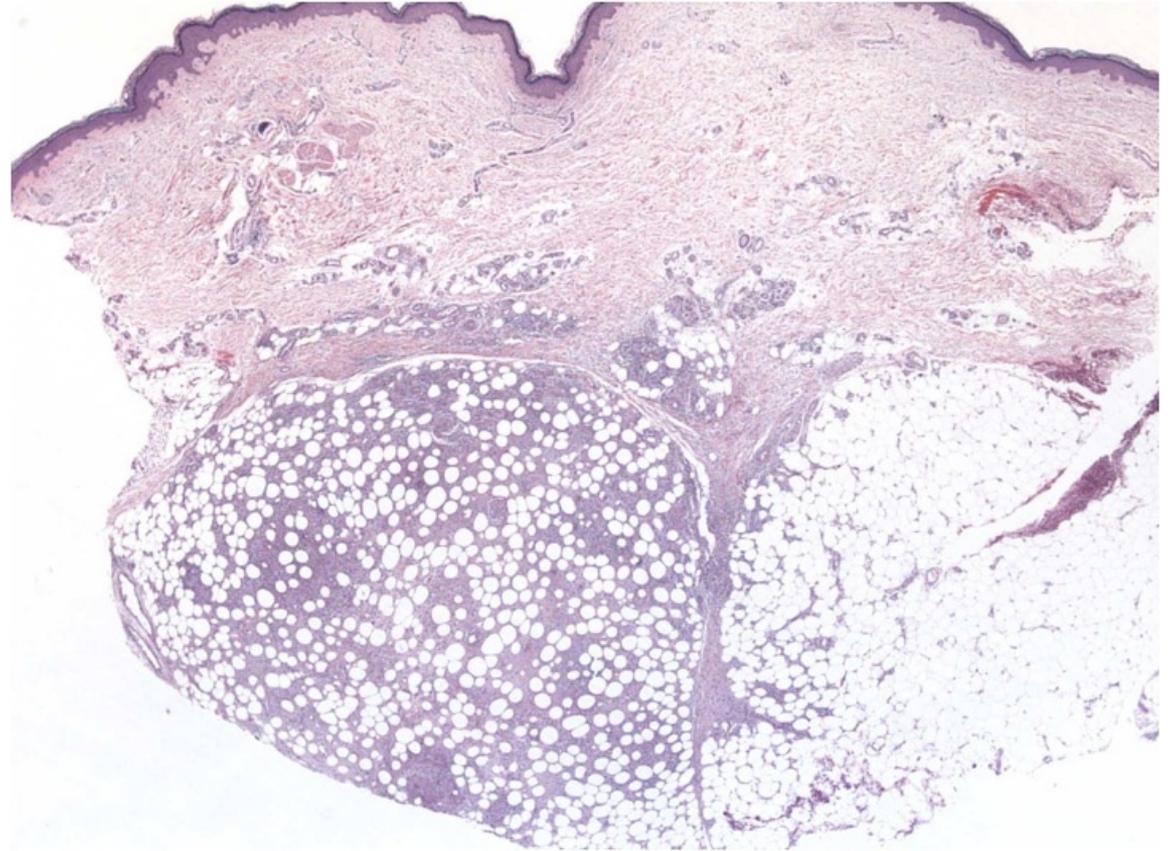
- *Infectious panniculitis* (especially in early lesions, when neutrophils may be prominent)
- *Sarcoidosis* (in well-developed lesions) (well defined, lobular-based naked granulomas with minimal or no septal involvement)
- *Nodular vasculitis* (erythema induratum) (predominantly lobular, presence of vasculitis)

Erythema nodosum: practical tips

- Evaluation of all panniculitides requires an adequate biopsy (preferably a deep wedge) for optimal visualization of the inflammatory pattern and involvement of blood vessels
- Low power examination is crucial for dividing the inflammatory process into septal or lobular patterns
- Erythema nodosum is the prototypic example of a septal panniculitis
- Remember erythema nodosum accounts for the >80% of all cases of panniculitis

Erythema induratum: key microscopic features

- Acute vasculitis in septae affecting artery and/or veins
- Adjacent lobular panniculitis with granulomas and fat necrosis
- Septae may be widened in older lesions



Erythema induratum: lobular panniculitis, vasculitis

Erythema induratum: differential diagnosis

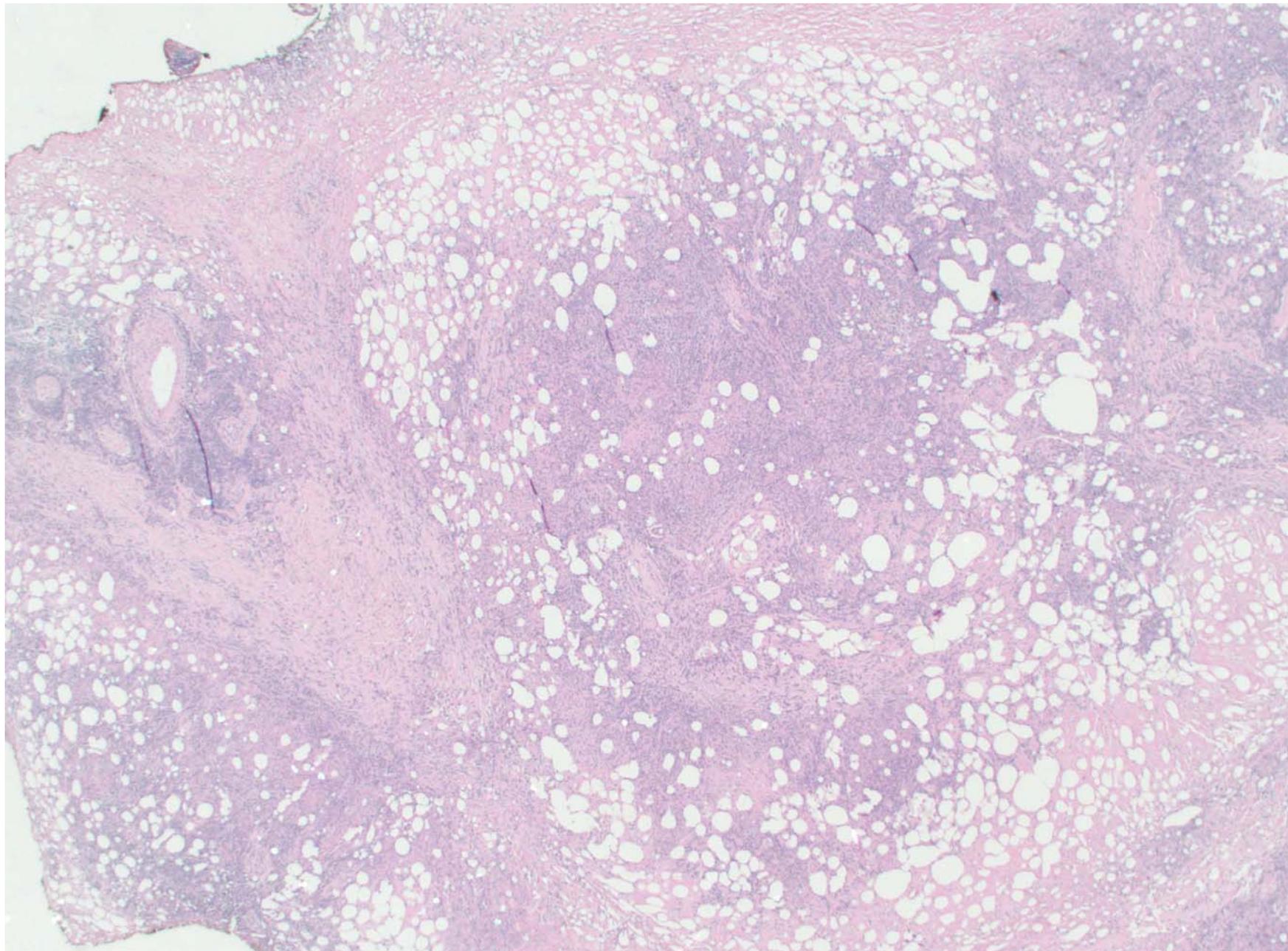
- *Erythema nodosum (late stage)* (no vasculitis, septal panniculitis)
- *Polyarteritis nodosa* (the inflammation of fat lobules is more restricted to the immediate area around damaged vessels rather than the more diffuse pattern of erythema induratum)
- *Infectious panniculitis* (especially if areas of neutrophilic inflammation, vasculitis is not a feature)

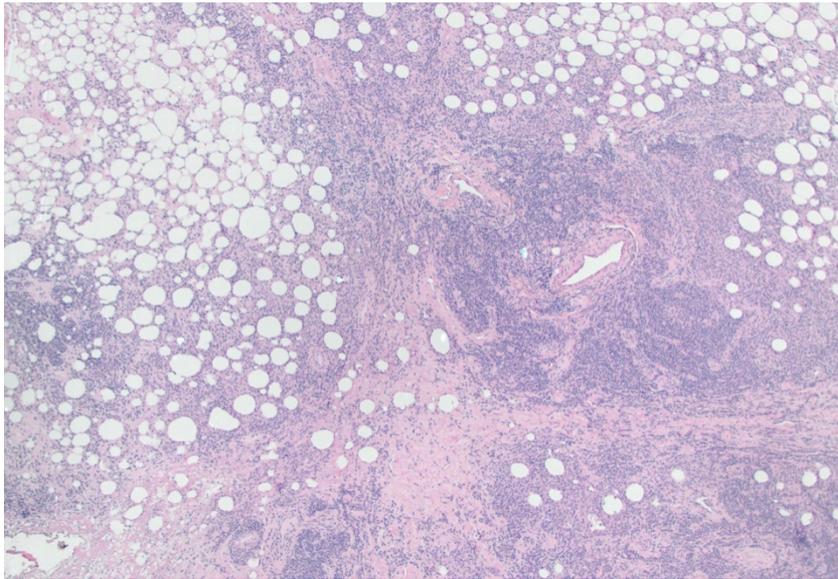
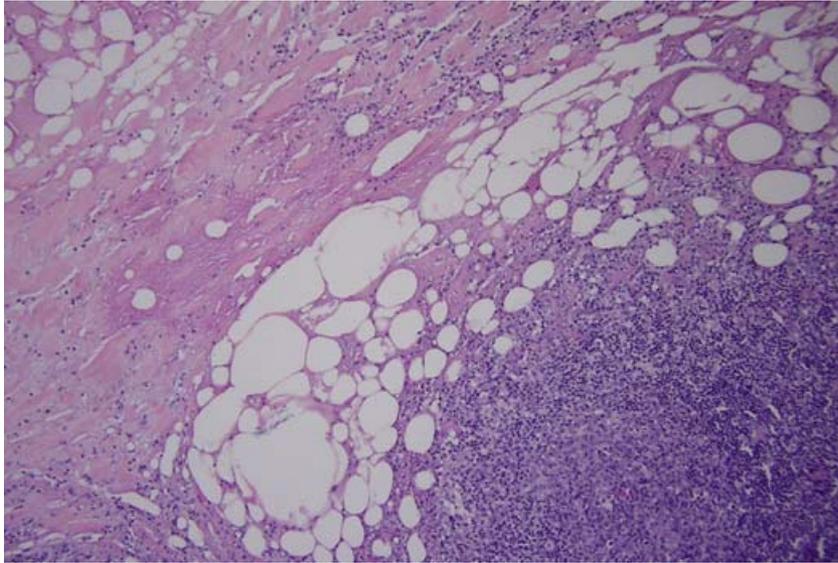
Erythema induratum: practical tips

- Low power examination crucial
- Inflammatory process involves the entire lobule (vs polyarteritis nodosa in which inflammation is more restricted around vessels)
- Look for evidence of vascular damage
- Most common on calves

Lupus panniculitis: key microscopic features

- The most important histologic features are lobular lymphoplasmacytic inflammation accompanied by hyaline necrosis and nuclear dust
- Lymphoid follicles in the subcutaneous fat are characteristic
- Lymphocytic vasculitis may be seen





Lupus panniculitis: differential diagnosis

- Subcutaneous morphea (no hyaline fat necrosis, no germinal center formation)
- **Subcutaneous panniculitic-like T-cell lymphoma**=the most challenging and important differential diagnosis
 - rare mature T-cell lymphoma
 - hyaline fat necrosis, mucin deposition, lymphoid follicle formation and interface change favor lupus panniculitis
 - immunophenotypic and gene rearrangement studies may be needed
 - borderline cases should be followed clinically

Lupus panniculitis: practical tips

- Consider lupus panniculitis in cases of panniculitis presenting in the upper half of the body
- Unlike other forms of LE, ANA serology is typically negative to low titer positive
- The presence of histopathologic features of discoid LE in the overlying epidermis and dermis are helpful clues to the diagnosis when present (mucin deposition, interface change,...)

infections

infections

- Discuss some examples of infectious entities that are relatively commonly encountered in dermatopathology specimens
- As a rule, many of the infectious entities do not neatly fall into a reaction pattern, they will be described according to the general class of infection!

infections

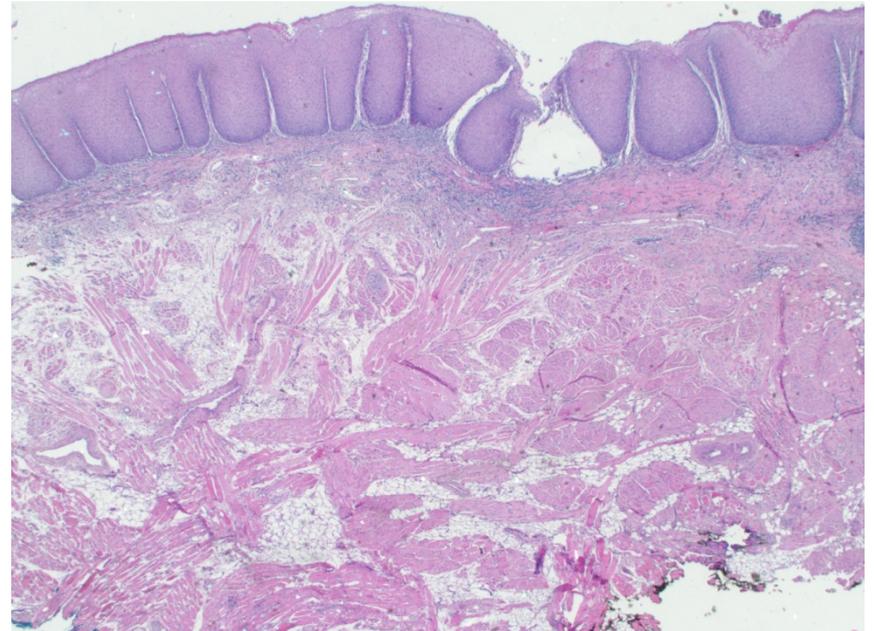
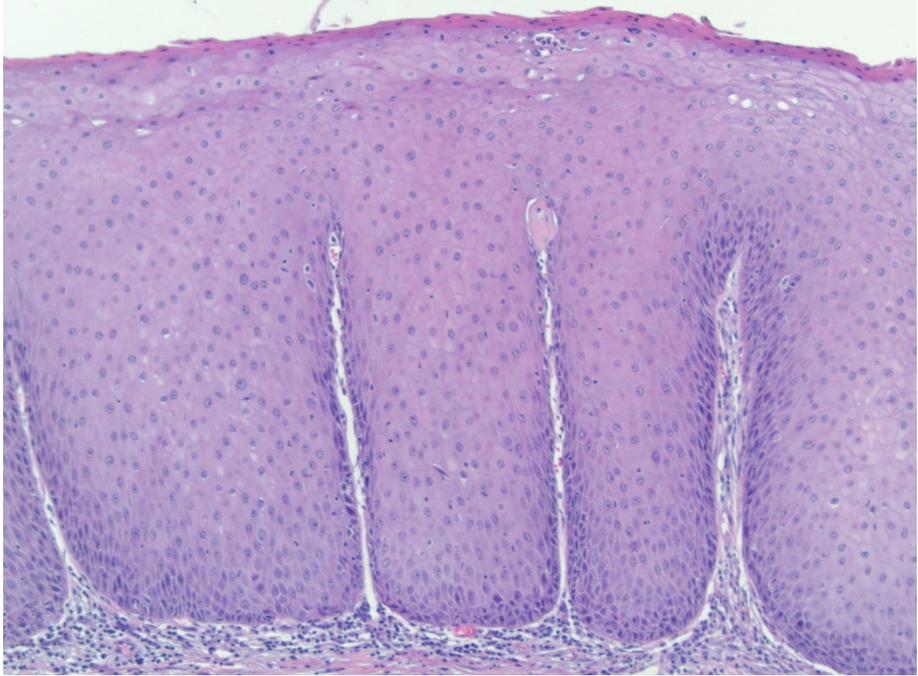
- A large collection of other common but also more rare infectious entities of the skin will be extensively discussed by Prof. Dr. E. Van Marck, UZA (FORPATH workshop infectious pathology 12/14 March 2012)

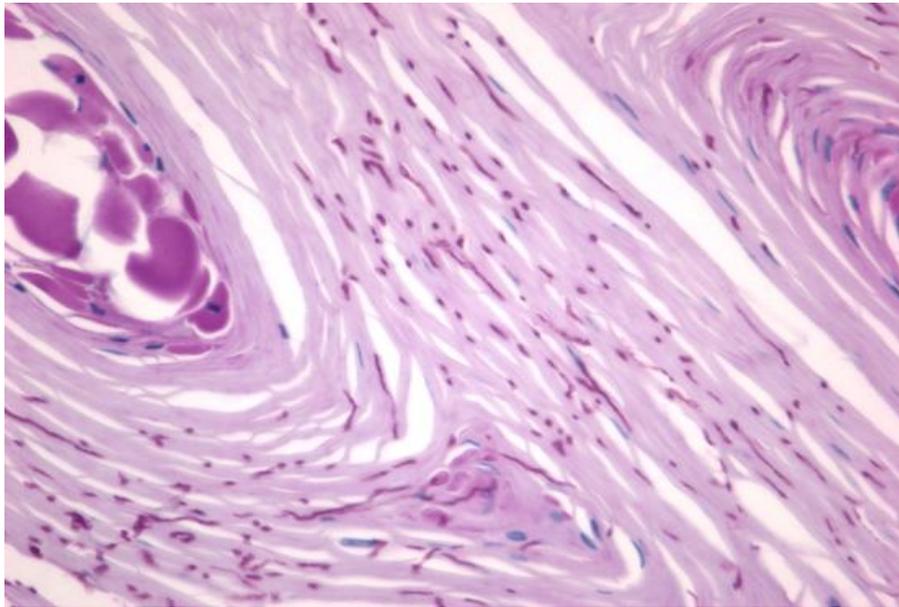
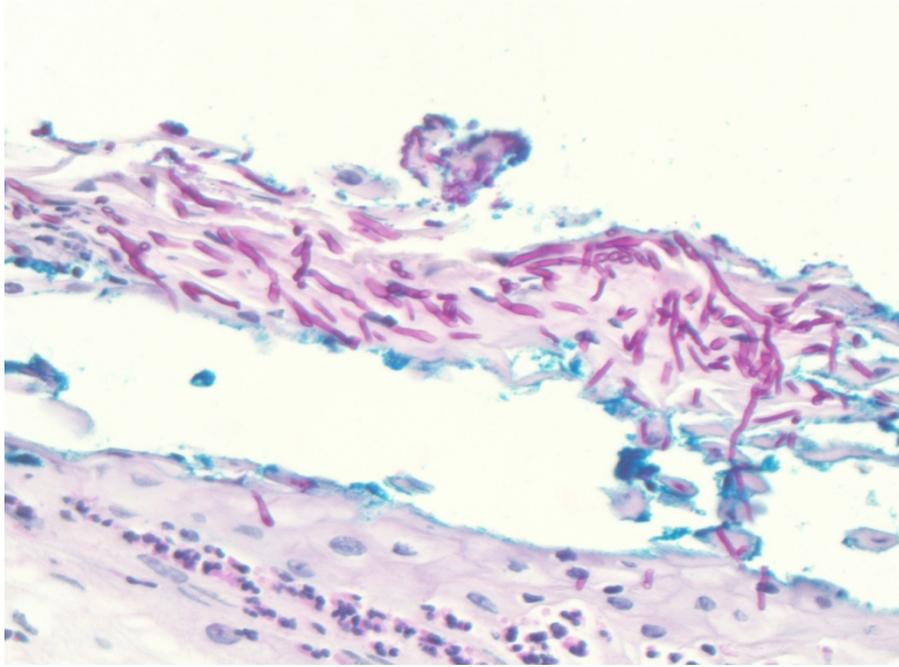
Fungal infections

- **Dermatophyte infection**
(Dermatophytosis or Tinea)
- **Candidiasis**
 - (Blastomycosis)
 - (Cryptococcosis)
 - (Coccidioidomycosis)
 - (Sporotrichosis)
 - (Mucormycosis)
 - (Aspergillosis)
 - (Zygomycosis)

Dermatophytosis/Tinea

- Neutrophils in stratum corneum
- Acanthosis, sometimes psoriasiform
- Superficial perivascular infiltrate usually contains eosinophils
- Fungal hyphae are difficult to see on routine H&E stained sections, it is often necessary to perform special stains (PAS, Grocott stains)





Dermatophytosis/Tinea: differential diagnosis

- *Spongiotic dermatitis (eczematous dermatitis)*: if neutrophils are present in the stratum corneum, it is prudent to consider fungal stains)
- *Psoriasis*: consider fungal stains especially if the dermal infiltrate contains eosinophils!
- *Erythema annulare centrifugum*

Dermatophytosis/Tinea: differential diagnosis

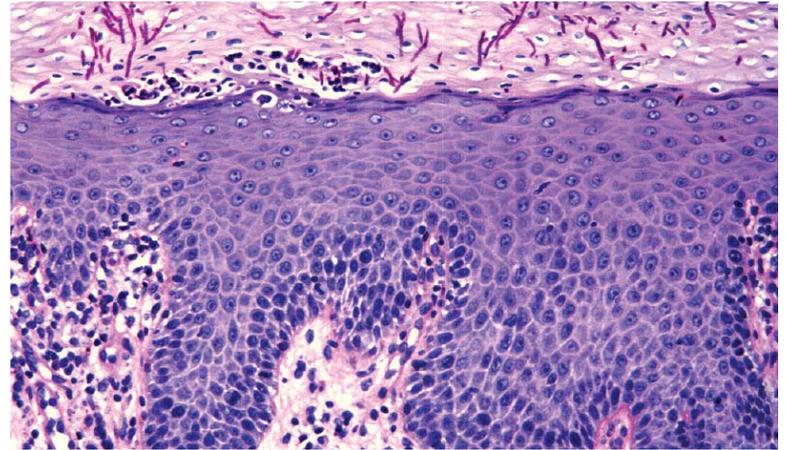
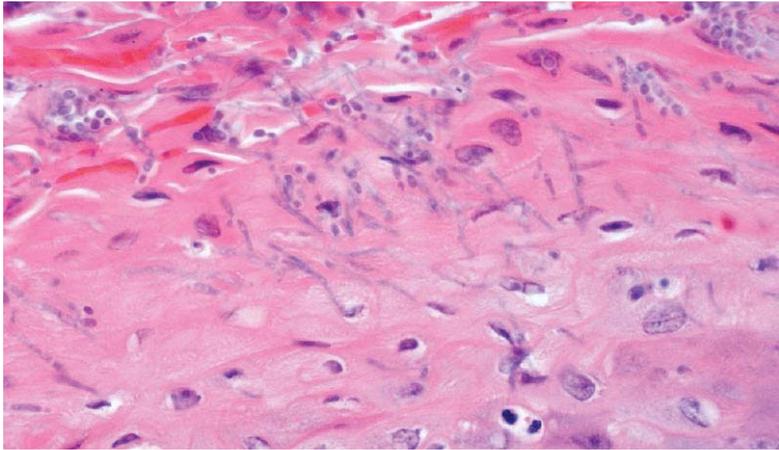
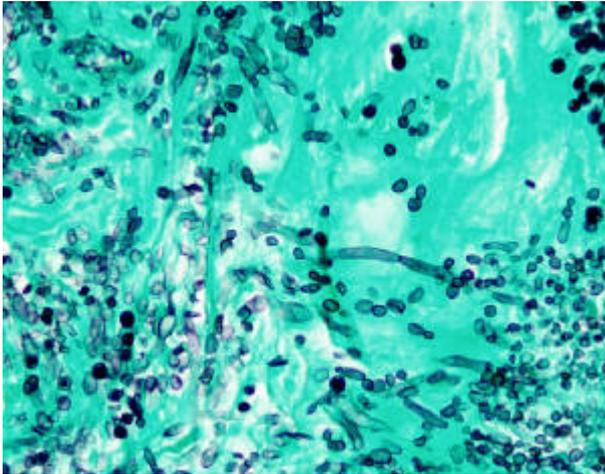
- Candidiasis (usually in intertriginous areas, yeasts cells as well as pseudohyphae)
- Pityrosporum folliculitis (normally commensal organism, look similar but there are typically abundant yeasts forms in the affected follicle)
- Bacterial folliculitis

Dermatophytosis/Tinea: practical tips

- It is important to keep a high index of suspicion for dermatophytosis
- If neutrophils are in the stratum corneum, consider special stains for fungi
- “sandwich sign” in which there is normal stratum corneum overlying an area of parakeratosis/compact hyperkeratosis.
- If lesion is clinically annular, consider special stains for fungi
- Always suspect dermatophyte infection when there is a history of a poor response to topical steroids even in the absence of characteristic histologic features

Candidiasis: key microscopic features

- Neutrophilic pustules
- Spongiosis
- Yeast and pseudohyphae in stratum corneum/superficial epidermis
- Mixed dermal infiltrate with eosinophils



Candida

Candidiasis: differential diagnosis

- *Dermatophyte infection* (different clinical distribution, do not have the same light purple color on H&E stained sections, lack yeast) (same treatment with antifungals)
- *!inverse psoriasis* (form of psoriasis that present in intertriginous zones and may resemble candidiasis) (lacks yeast or pseudohyphae and does not have eosinophils in the dermal infiltrate)

Candidiasis: differential diagnosis

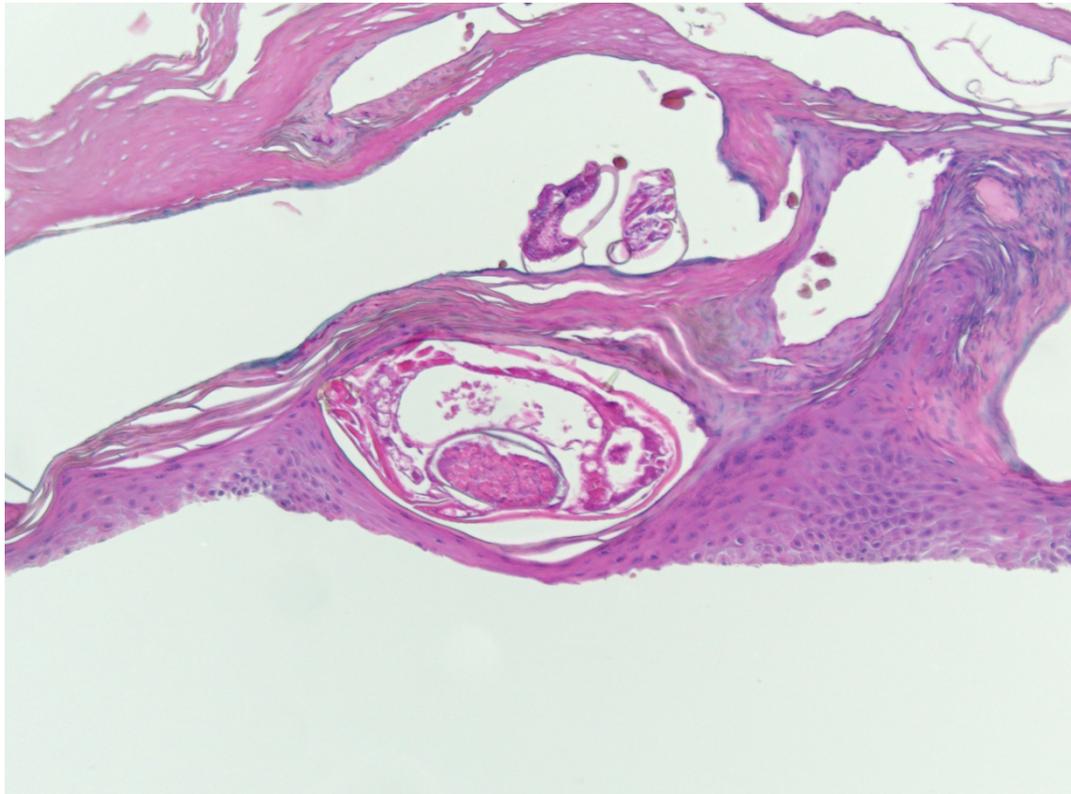
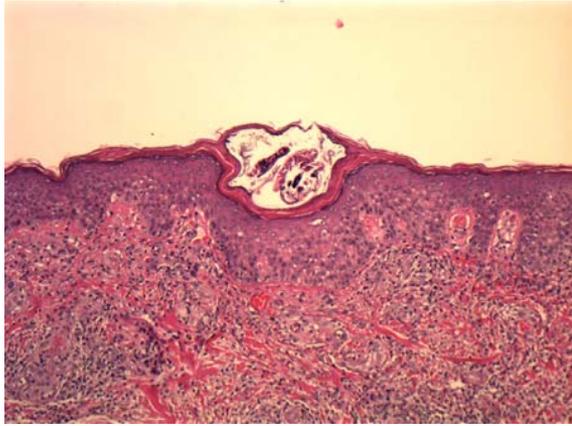
- Contact dermatitis (form of eczematous dermatitis frequently presents in the axillae like candidiasis) (spongiotic dermatitis lacking fungal organisms and may have Langerhans cell microabcesses in the epidermis)
- AGEP (clinical distribution is different, no fungal organisms)
- Scabies (can clinically present in intertriginous zones, especially the groin) (recognition of the mite and absence of fungal organisms)

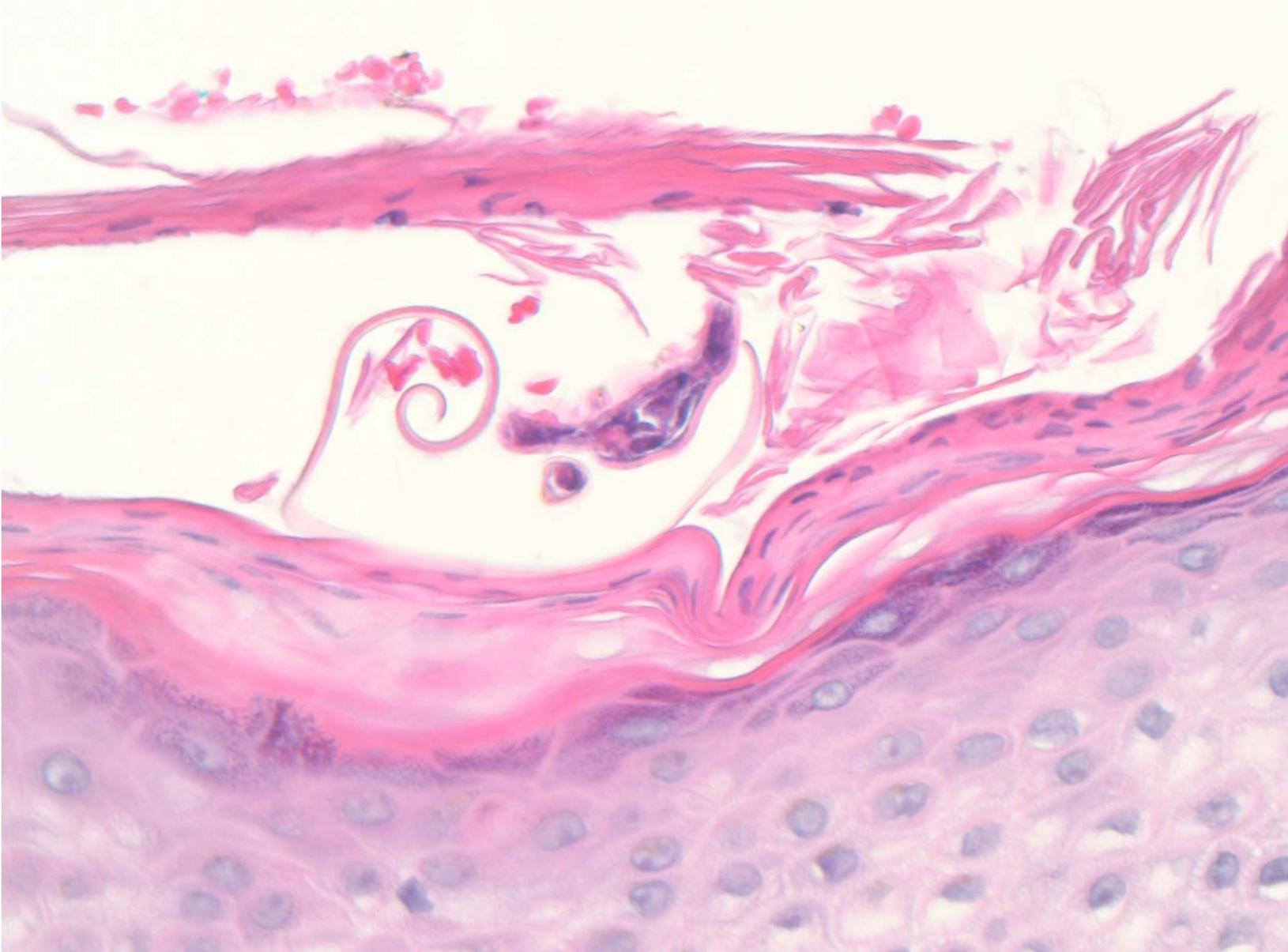
Candidiasis: practical tips

- Pseudohyphae may greatly outnumber yeast forms
- Light purple color of organisms on H&E stain is a clue
- Occurs in skin folds (e.g. groin, axilla)

Scabies: key microscopic features

- Evidence of mites in stratum corneum
- Mixed dermal infiltrate with numerous eosinophils
- Obtain multiple deeper levels if initial slides are negative
- Evidence of infestation may be subtle: look for “pink pigtails”





Scabies: differential diagnosis

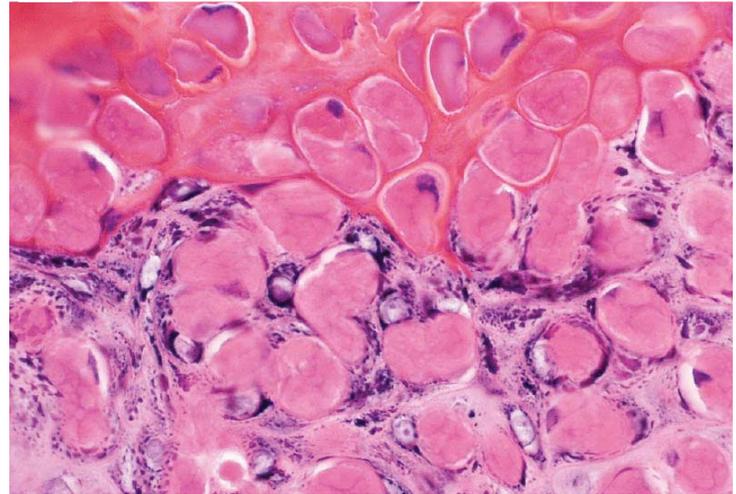
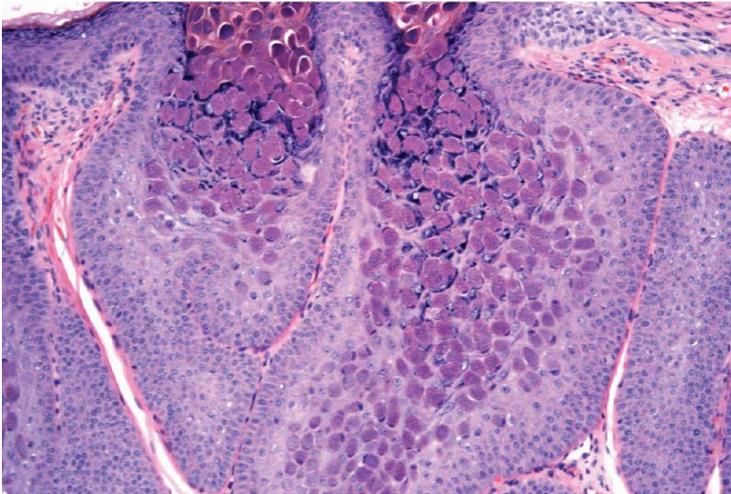
- The dermal infiltrate can be confused with dermal hypersensitivity reactions (urticaria, drug eruptions,...) if there is no histological evidence of scabies infestation.
- Clinical correlation!!

Viral infections

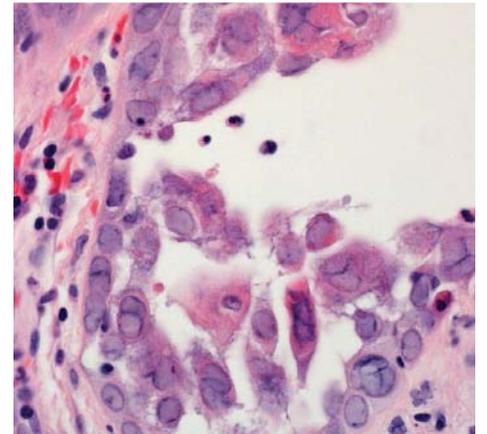
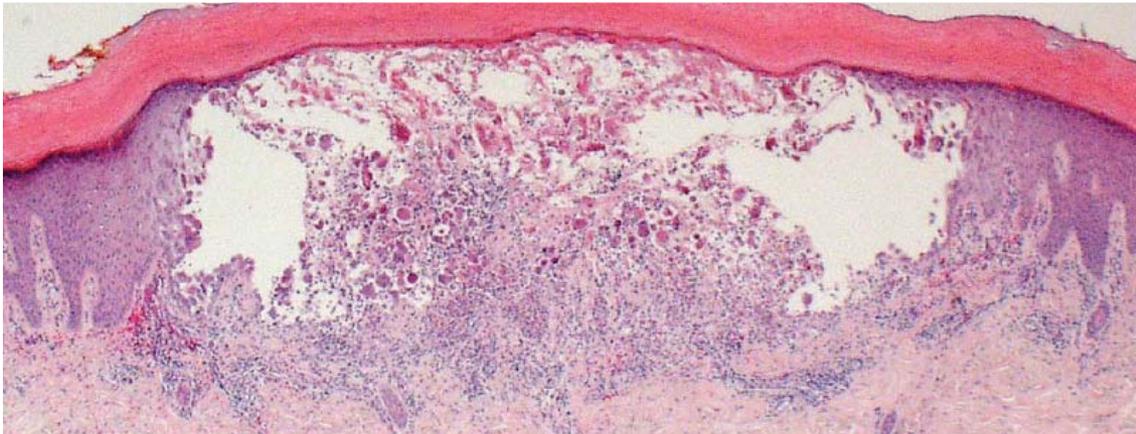
- **Molluscum contagiosum** (endophytic proliferation of epidermis, intracytoplasmic eosinophilic viral inclusions)
- **Herpesvirus infections**
- **Human papilloma virus infections** (verruca vulgaris, verruca plantaris, verruca plana, condyloma acuminatum)

Herpes virus infections: practical tips

- Look for evidence of viral infection (multinucleated keratinocytes, intranuclear viral inclusions) in necrotic keratinocytes
- Follicular involvement is common: examine follicles when epidermis is ulcerated!!



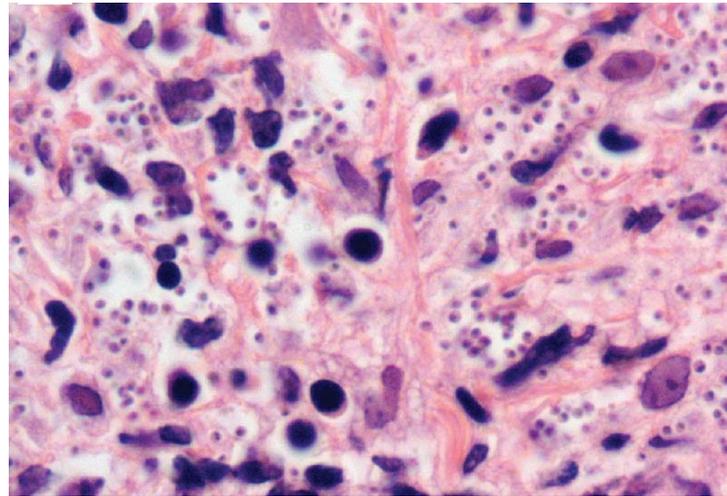
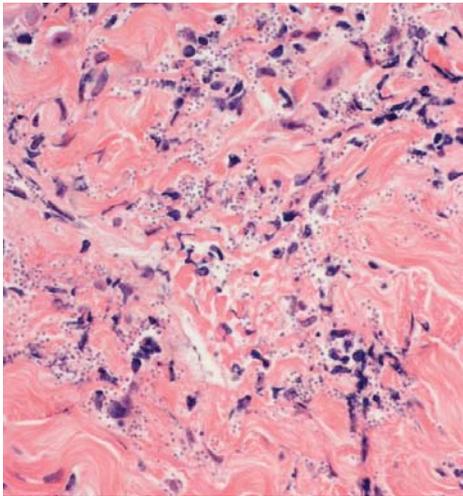
Molluscum contagiosum



Herpes simplex

Parasitic infection

- **(leishmania)**



Leishmaniasis

Bullous dermatitis

Bullous dermatitis: approach/definition

- Primary
- Secondary (i.e. blisters secondary to contact dermatitis)

Bullous dermatitis: approach/definition

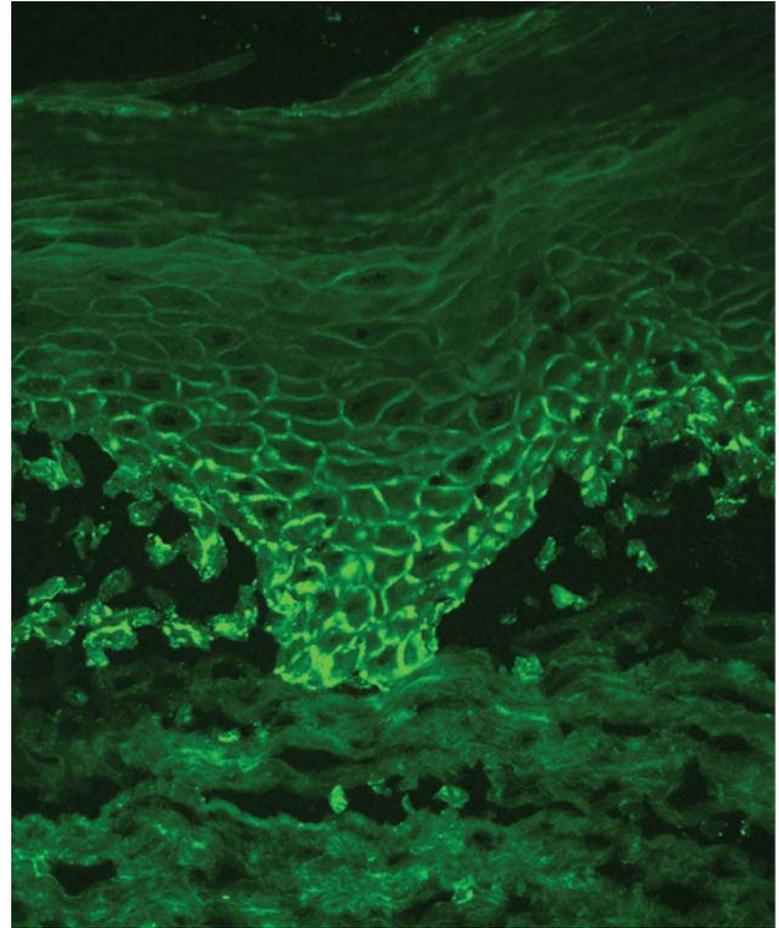
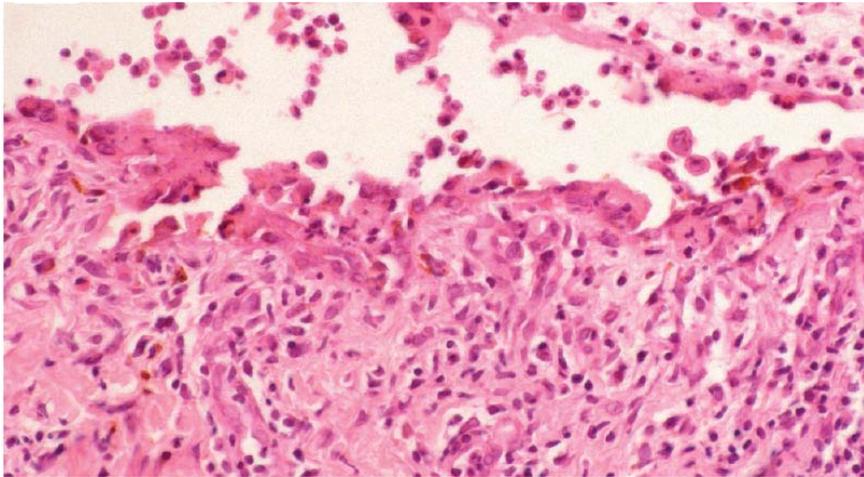
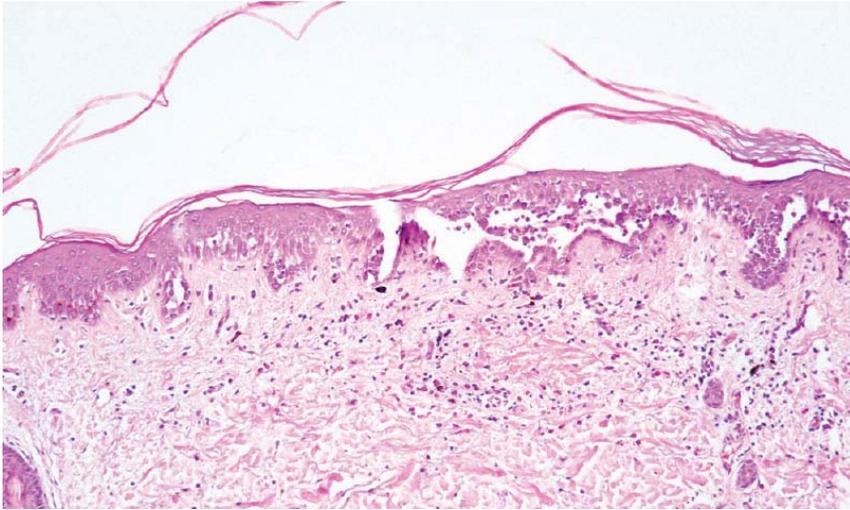
- **Intraepidermal** blister (*intraepidermal vesicular dermatitis*): formation of an intraepidermal blister via ***acantholysis***. The basal layer remains attached to the basement membrane
- **Subepidermal** blister (*subepidermal vesicular dermatitis*): the entire epidermis is separated from the underlying dermis

Intraepidermal vesicular dermatitis

- Pemphigus vulgaris
- Transient acantholytic dermatosis (Grover's disease)

Pemphigus vulgaris: key microscopic features

- Suprabasilar blister with acantholysis which extends into the follicular epithelium
- Basal layer spared (“tombstone”)
- Rarely, eosinophilic spongiosis observed
- DIF: IgG and possibly C3 deposited in the intercellular regions of the epidermis



Pemphigus vulgaris: intra-epidermal positivity voor IgG

Pemphigus vulgaris: differentiaal diagnose

- **Pemphigus foliaceus** (more superficial intraepidermal blister formation occurring at the stratum corneum or granular layer)
- **Drug-induced pemphigus** (a clear association with a drug is needed for diagnosis)
- **Paraneoplastic pemphigus**
- **IgA pemphigus** (subcorneal or intraepidermal neutrophilic pustules, with minimal or no acantholysis, DIF intraepidermal intercellular IgA)
- **Familial benign pemphigus (Hailey-Hailey disease)**
- **Focal acantholytic dyskeratosis (Grover's disease)** (involves smaller more discrete foci of epithelium, DIF negative)
- **Darier's disease** (typical dyskeratotic cells-corps ronds-grain, DIF negative)
- **Herpesvirus infection** (HSV immunostains useful in difficult cases, DIF negative)
- **Acantholytic variants of actinic keratosis** (parakeratosis, crowding and atypia of the basilar keratinocytes, different clinical presentation)

Acantholytic dyskeratosis

- The pattern of focal acantholytic dyskeratosis may be seen as an incidental finding in otherwise benign keratoses!

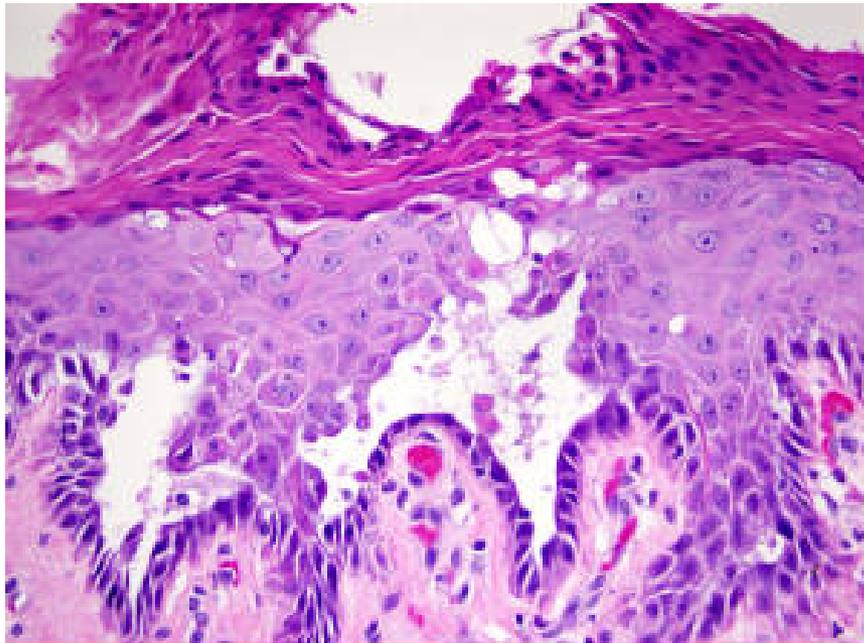
Pemphigus vulgaris: practical tips

- The clinical and histologic/direct immunofluorescence findings are usually distinctive
- Not all histologic features are necessarily seen in a given biopsy!
- If presenting in intertriginous areas consider Hailey-Hailey disease
- Other acantholytic disorders to be considered include Darier's disease and Grover's disease

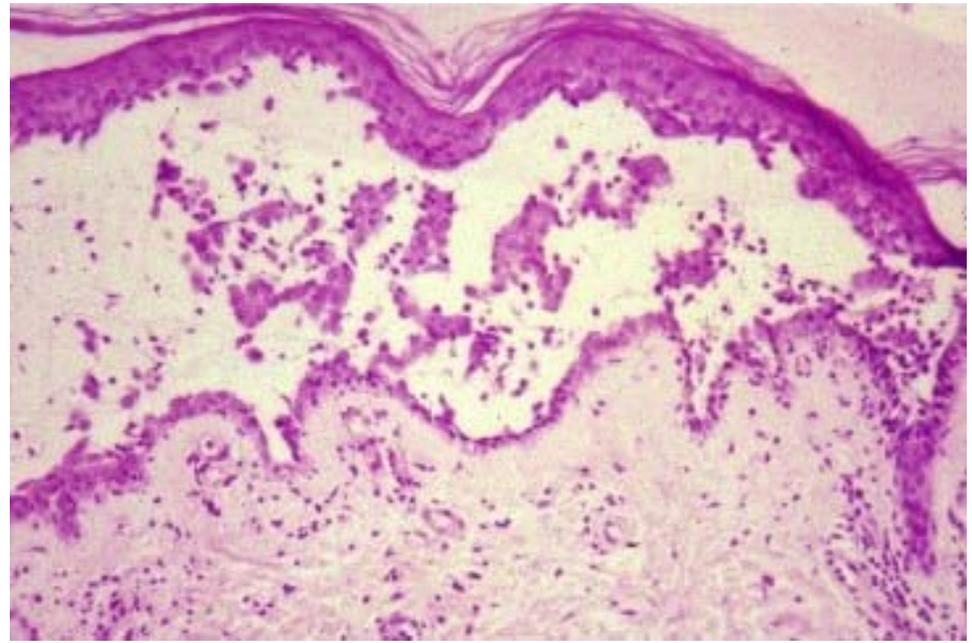
Intraepidermal vesicular dermatitis

A. Suprabasal keratinocyte separation

- scant inflammatory cells: transient acantholytic dermatosis (Grover)
- lymphocytes and plasmacells: acantholytic solar keratosis
- lymphocytes and eosinophils: pemphigus vulgaris



Grover

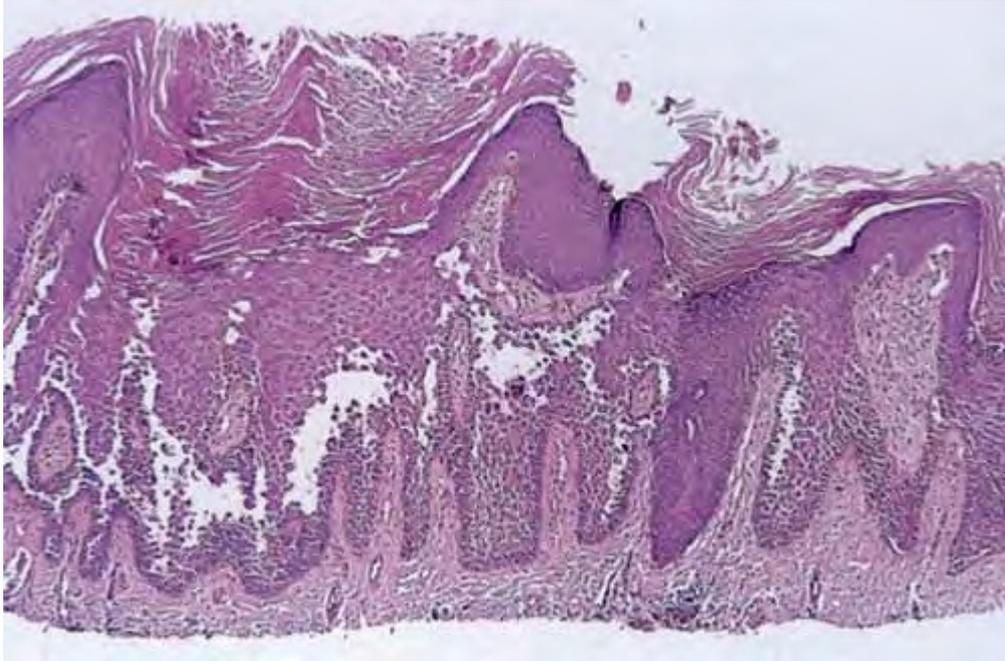


pemphigus

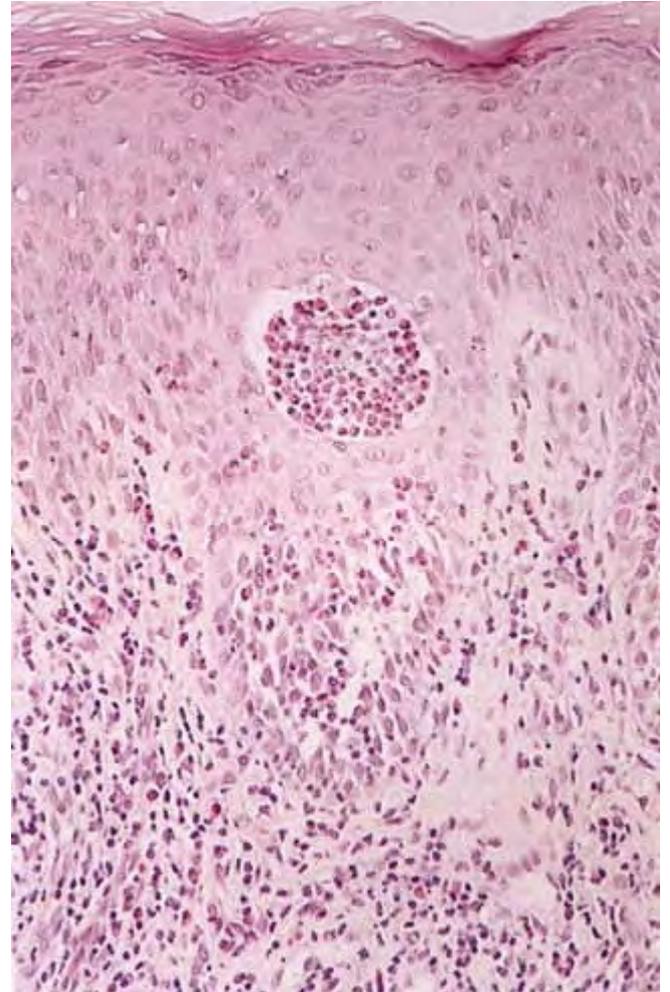
Intraepidermal vesicular dermatitis

B. Intraspinous acantholytic keratinocyte separation

- scant inflammatory cells: Hailey-Hailey disease
- lymphocytes predominant: herpes simplex, varicella-zoster
- lymphocytes and eosinophils: pemphigus vegetans
- mixed cell types: acantholytic solar keratosis



Hailey-Hailey disease



Pemphigus vegetans

Subepidermal vesicular dermatitis

- **With predominant eosinophils**

- bullous pemphigoid
- cicatricial pemphigoid
- pemphigoid (Herpes) gestationes

- **With predominantly neutrophils**

- dermatitis herpetiformis
- bullous lupus erythematosus
- linear IgA disease

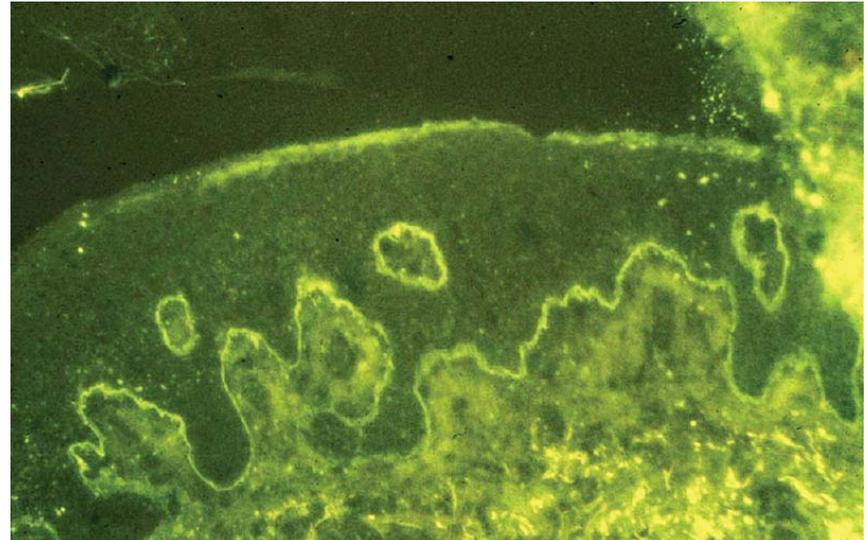
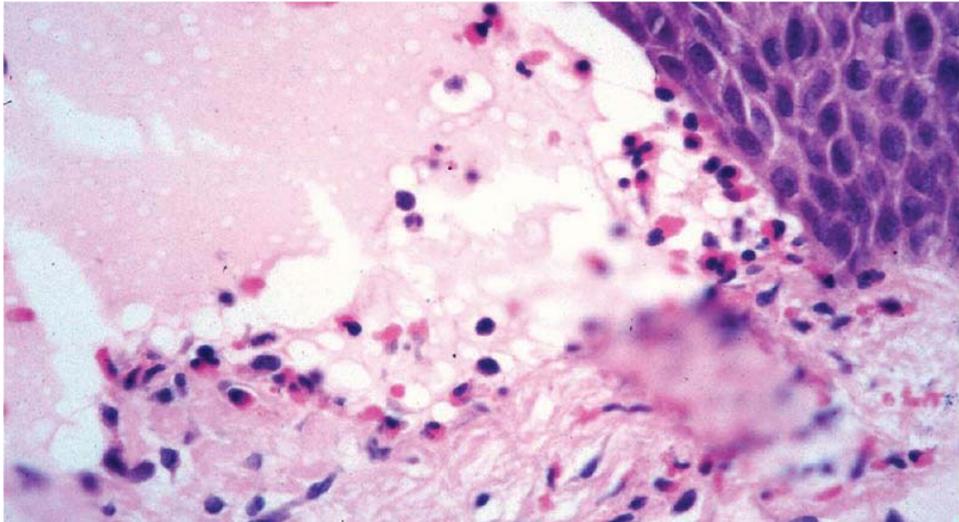
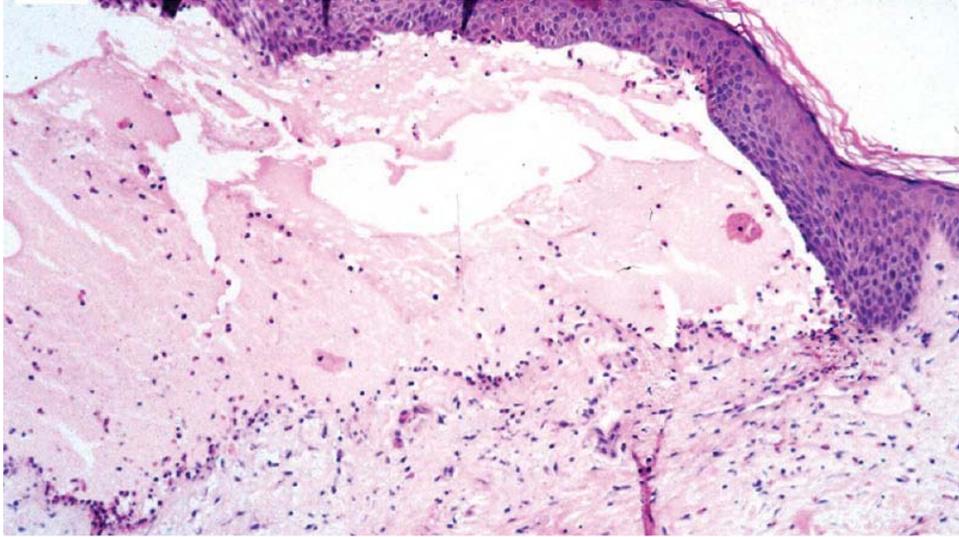
- **With little or no inflammation**

- epidermolysis bullosa acquisita (EBA)
- porphyria cutanea tarda
- pseudoporphyria

Subepidermal vesicular
dermatitis with predominant
eosinophils

Bullous pemphigoid: key microscopic features

- Subepidermal blister with eosinophils and other inflammatory in and around the blister
- Rarely the inflammatory process can be neutrophil-predominant or cell poor
- Dermal infiltrate is generally confined to the papillary dermis and is composed of lymphocytes, eosinophils and rarely neutrophils
- Prebullous phase of a bullous pemphigoid (urticarial form of bullous pemphigoid) shows eosinophilic spongiosis and eosinophils tagging the basal layer
- DIF: linear C3 (100%) and IgG (65-95%) at the dermoepidermal junction



Bullous pemphigoid:
Linear deposition of C3
at the dermoepidermal
junction

Bullous pemphigoid: differential diagnosis

- Arthropod bite reaction (deep infiltrate!)
- Pemphigoid (herpes) gestationis (histologically indistinguishable, clinical presentation of periumbilical plaques in second or third trimester of pregnancy)
- Cicatricial pemphigoid (resembles bullous pemphigoid, involves mucosa!)
- In case of a neutrophil-dominant BP case (rare!!): dermatitis herpetiformis, bullous LE and linear IgA disease
- In case of a cell-poor BP: Epidermolysis Bullosa Acquisita (EBA)

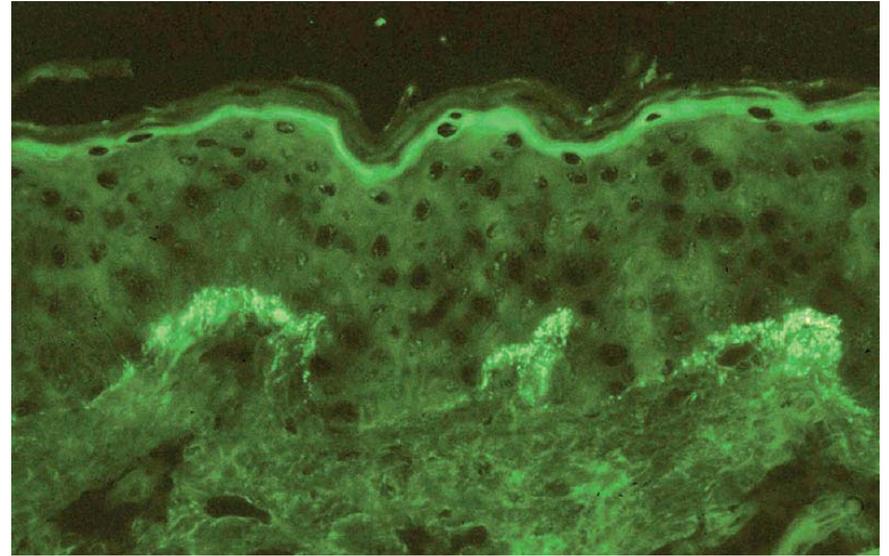
Bullous pemphigoid: practical tips

- For accurate DIF use perilesional skin
- False negative DIF results may be seen in biopsies from the lower extremities and especially lesional skin
- Always consider urticarial bullous pemphigoid when a biopsy from an elderly patient demonstrates eosinophilic spongiosis

Subepidermal vesicular
dermatitis with predominantly
neutrophils

Dermatitis herpetiformis: key microscopic features

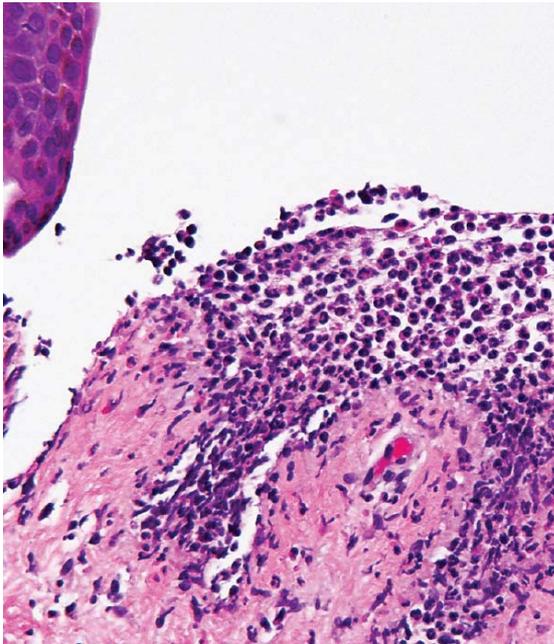
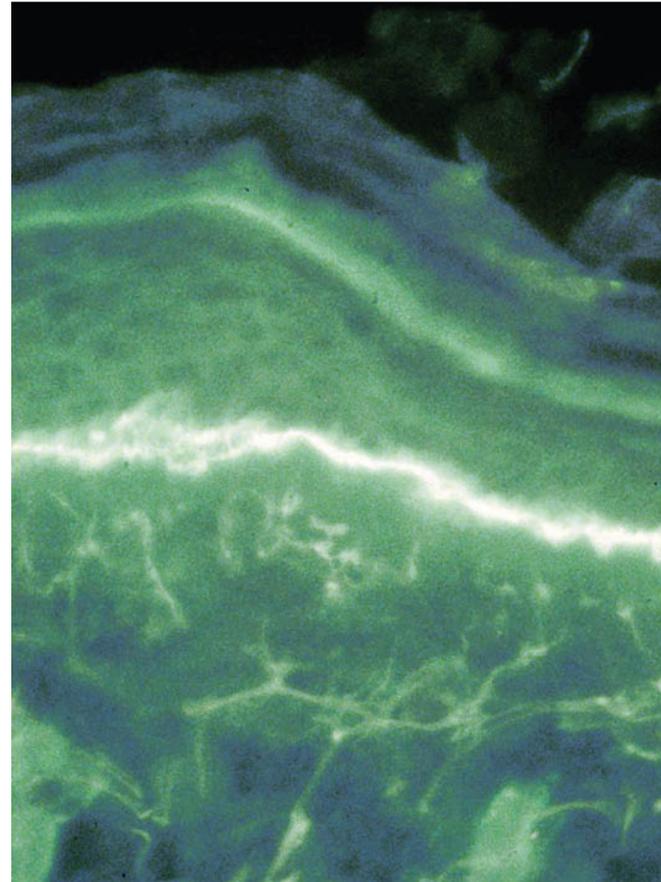
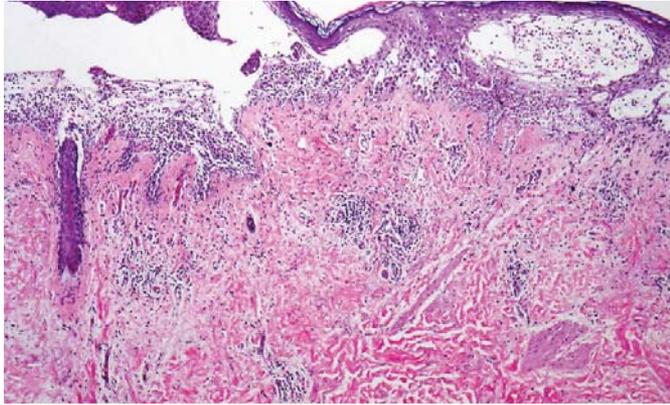
- Early lesions: neutrophils at the tips of dermal papillae (“papillary microabscesses”)
- Well-developed lesions: subepidermal vesiculation with neutrophils
- DIF demonstrates IgA deposited in a granular fashion along the basement membrane
- IgA deposits often more prominent at the dermal papillary tips



Dermatitis herpetiformis:
Granular deposition of IgA along the
basement membrane, more
prominent at the dermal papillary tips

Dermatitis herpetiformis: differential diagnosis

- Linear IgA disease (DIF linear deposition of IgA along the basement membrane zone)
- Bullous LE (neutrophils tend to extend more deeply and in around vessels, DIF: lupusband, other histologic features of LE like dermal mucin, leucocytoclastic vasculitis may be present, clinical presentation)
- Inflammatory-rich Epidermolysis Bullosa Acquisita (EBA) (DIF)



Linear IgA bullous disease:
Linear deposition of IgA at the dermoepidermal junction

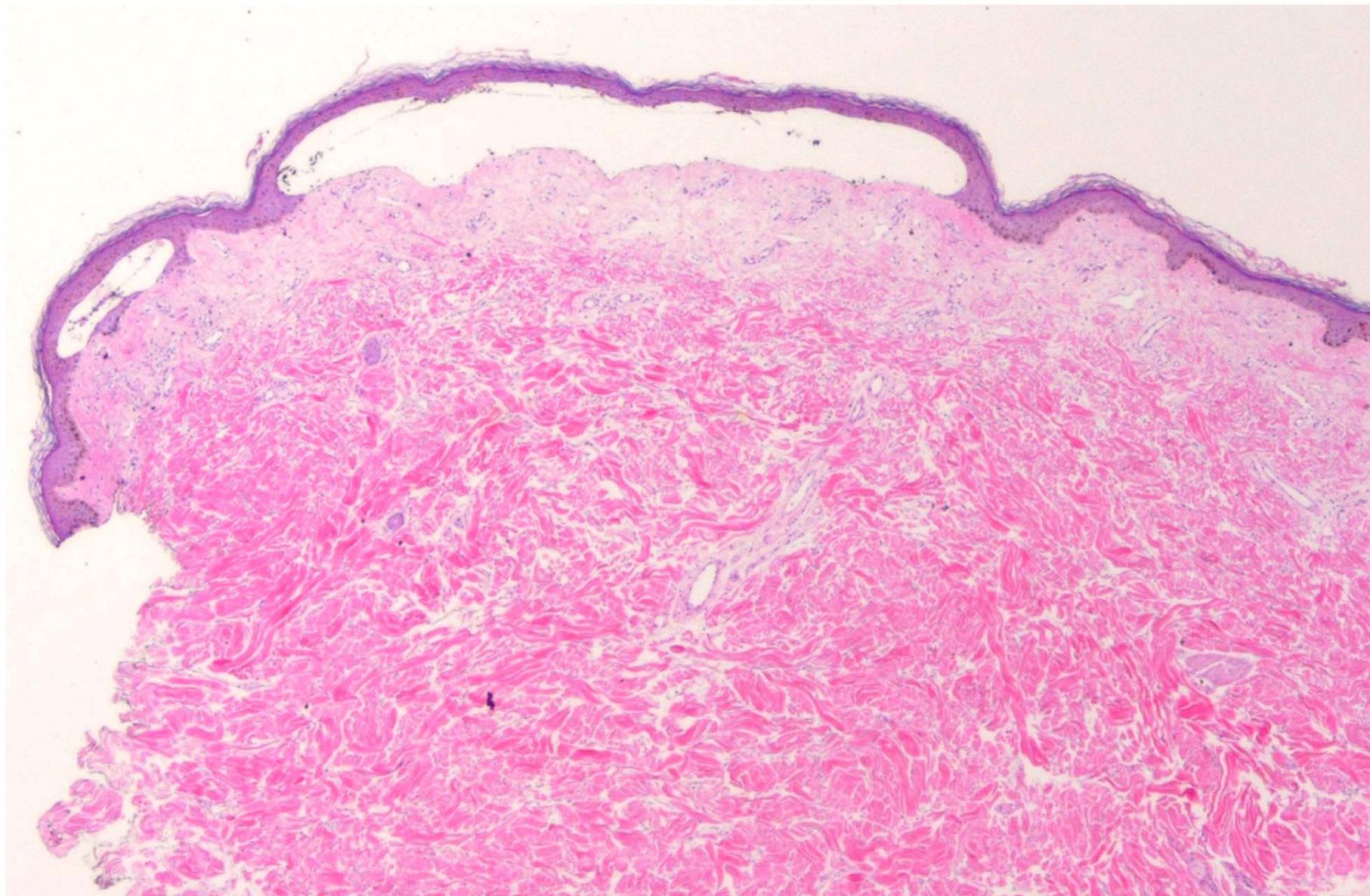
Dermatitis herpetiformis: practical tips

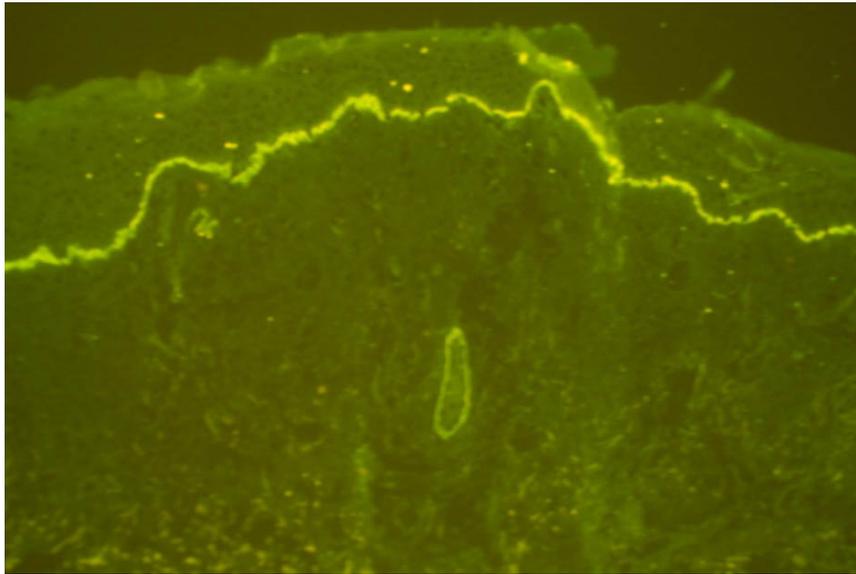
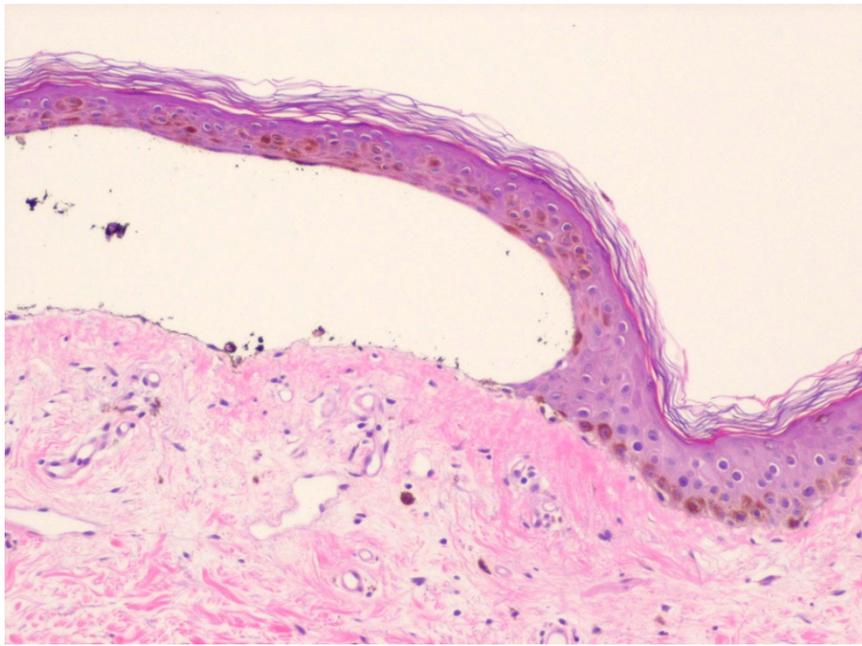
- Significant overlap with bullous LE, linear IgA and inflammatory-rich cases of epidermolysis bullosa acquisita
- In the absence of DIF, sign out descriptively
- Clinically, dermatitis herpetiformis and excoriated eczematous dermatitis can look alike. Histologically an eczematous dermatitis is a spongiotic dermatitis, not a blistering disease

Subepidermal vesicular
dermatitis with little or no
inflammation

Epidermolysis Bullosa Acquisita (EBA): key microscopic features

- The most common pattern is that of a subepidermal blister with fibrin and only a few inflammatory cells in the lumen (non-inflammatory pattern)
- Rare inflammatory-rich cases
- Older lesions may demonstrate dermal scarring and milia
- DIF: linear IgG and C3 at the dermal-epidermal junction (for differentiation with BP: salt skin with antibodies binding to the dermal side (vs. epidermal side for BP))





Linear C3 deposition at the dermoepidermal junction

Epidermolysis Bullosa Acquisita (EBA): differential diagnosis

- Cell-poor bullous pemphigoid (differentiated by the location of the autoantibody on salt-split skin DIF: in EBA the autoantibodies are on the floor of the salt-skin blister)
- Porphyria cutanea tarda (most common on dorsal hands, subepidermal blister with festooning of dermal papillae, thick-walled papillary dermal blood vessels highlighted by a PAS stain, caterpillar bodies adjacent to the epidermis in the roof of the blister)
- Pseudoporphyria (clinical associated with renal disease, with NSAIDs and diuretics, histology identical to porphyria cutanea tarda)

Epidermolysis Bullosa Acquisita (EBA): practical tips

- Noninflammatory subepidermal blister should prompt consideration
- Blisters tends to be on trauma prone areas
- No festooning of dermal papillae like in porphyria cutanea tarda

addendum

- “nothing lesions”
- Pathology involving sweat glands
- Pathology involving nerves

Miscellaneous dermatoses:
“nothing lesions”

“nothing lesions”

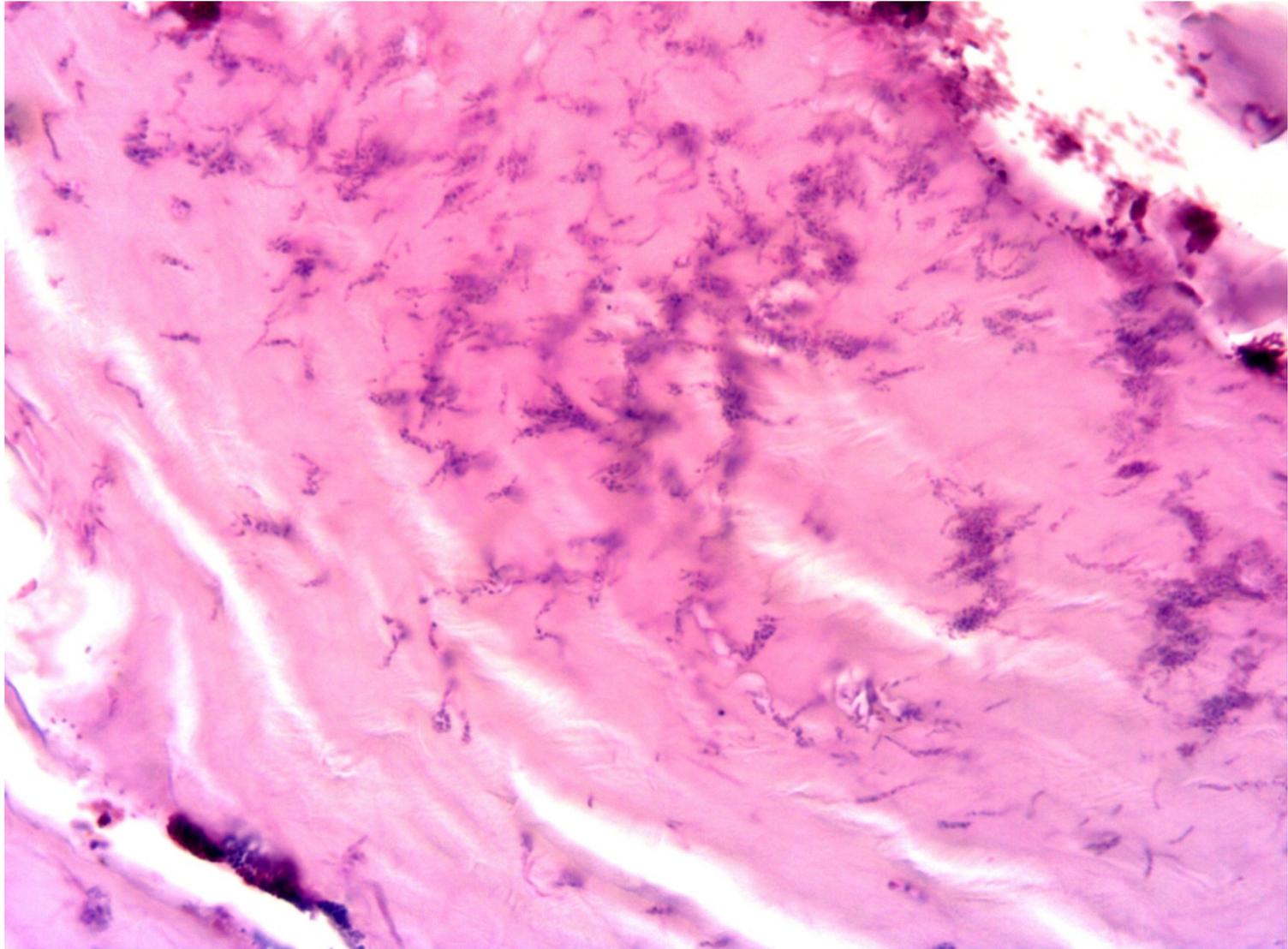
- Viewing the biopsy there are no obvious abnormalities noted at low magnification (“invisible lesions”)

Looking for the subtle changes (subtle clues):

- in the keratin layer (fungal infection)
- in the basal layer (melanocytes, melanin deposition, basal vacuolization)
- in the papillar dermis (vascular wall thickening, amyloid deposition, mast cell infiltrates)
- in dermis and adnexae (changes in collagen, elastic tissue, mucin deposition and alterations in adnexae)

“nothing lesions”

- *Tinea versicolor* (epidermis is normal, relatively noninflammatory, hyphae and yeast in stratum corneum, PAS stain!) (clinically presenting as pigment disorder)
- *Corynebacterial infection* (normal appearing axillary or acral skin, filamentous bacteria in stratum corneum, Gram or PAS stains helpful) (clinically common cause of interdigital foot infection-Erythrasma)



Corynebacterial infection

“nothing lesions”

- Post inflammatory pigment alteration (unremarkable epidermis, mild perivascular lymphocytic infiltrate with melanophages) (clinically hyperpigmented or hypopigmented)
- Vitiligo (absence of melanocytes on H&E Malan A immunostains ideal to prove reduction/absence of melanocytes)

“nothing lesions”

- Macular amyloidosis and lichen amyloidosis (homogenous dull pink papillary dermal deposits of amyloid, widened dermal papillae, melanophages)
- Dermatophyte infections (could be histologically quite subtle!)
- Cutaneous mastocytosis (especially urticaria pigmentosa and telangiectasia macularis eruptiva perstans-TMEP)

“nothing lesions”

- Morphea
- Dermal hypersensitivity reaction (urticaria or drug eruption) (the dermal infiltrate can be very sparse!)
- Pseudoxanthoma elasticum (distorted fragmented elastic fibers in the mid and deep reticular dermis, elastica van Gieson staining necessary!)

Pathology involving sweat glands

- **With lymphocytes:** Lupus erythematosus (interface), Lichen striatus (interface), perniones (chilblains) (perivascular dermatitis)
- **With eosinophils:** arthropod bite reaction (perivascular dermatitis)
- **With neutrophils:** neutrophilic eccrine hidradenitis
- **With plasma cells:** cheilitis glandularis

Pathology involving nerves

- Lymphocytic infiltrates: herpes zoster
- Mixed inflammatory infiltrates (e.g. plasma cells): Leprosy, Lyme disease (erythema chronicum migrans)

Pathology involving hair follicles

- Lymphocytes predominant: alopecia areata, lichen planopilaris
- Lymphocytes and eosinophils: eosinophilic pustular folliculitis
- Neutrophils prominent: acute bacterial folliculitis