Vesiculobullous disorders

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Update in Dermatopathology
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Icahn School of Medicine at Mount Sinai

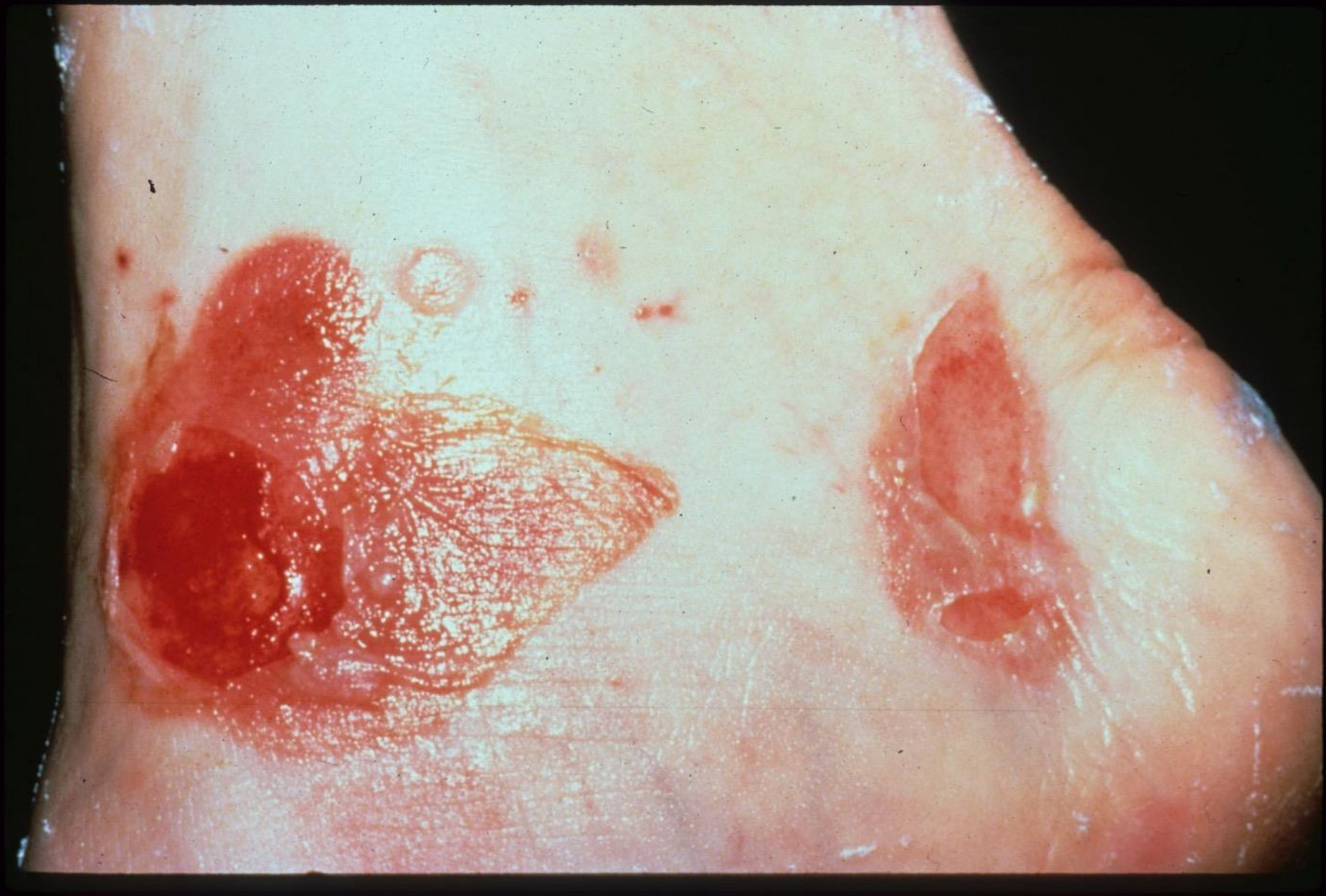
Classification

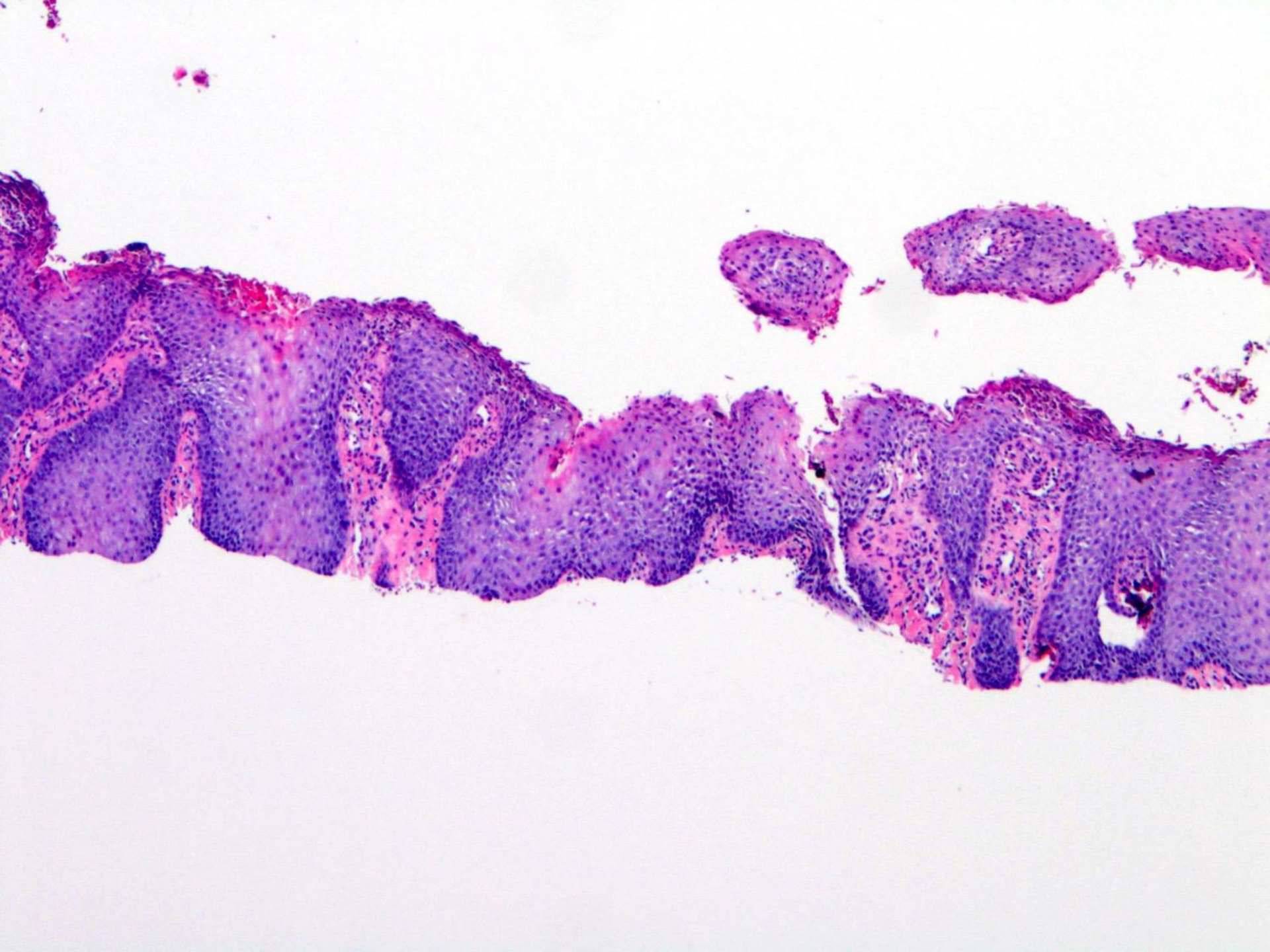
- Location of Split
  - Subcorneal, intraepidermal, subepidermal
- Mechanism
  - Acantholytic, spongiotic, ballooning degeneration
- Composition of infiltrate
  - Eosinophils, neutrophils, lymphocytes

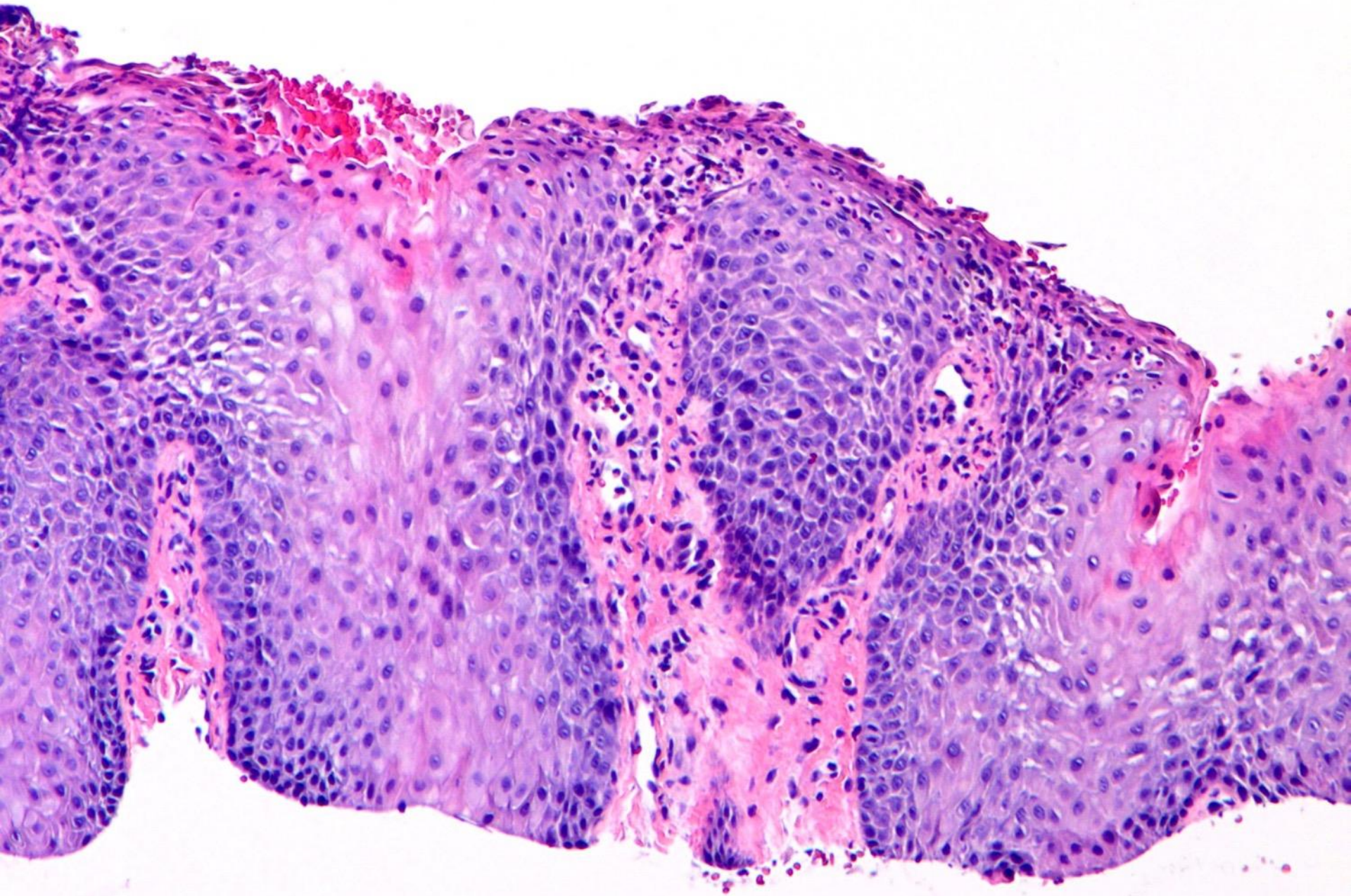
Group I: Subcorneal

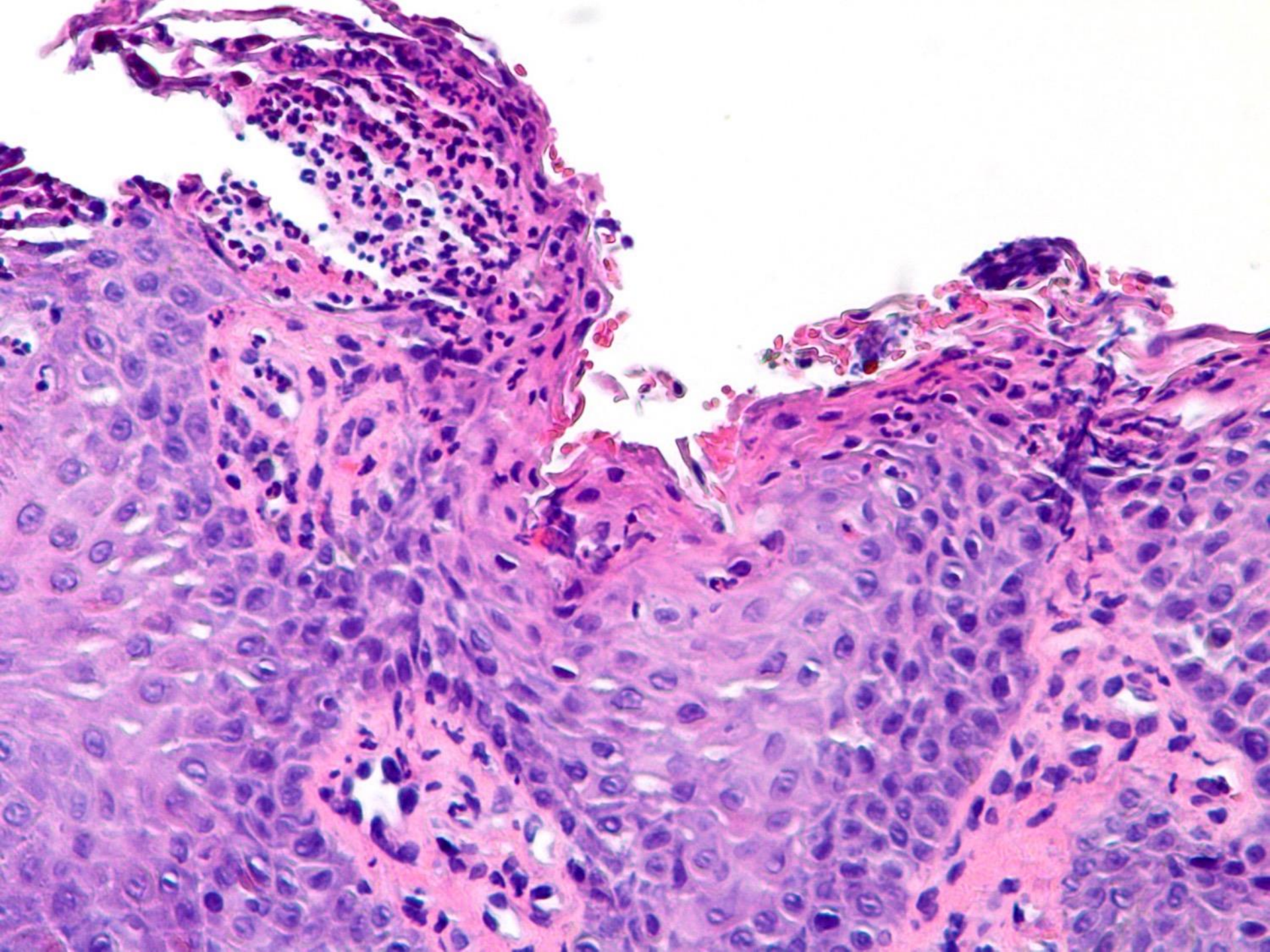
- Bullous impetigo
- Staphycoccal scalded skin
- Pempigus foliaceus

Subcorneal/intracorneal









Bullous impetigo

Clinical features

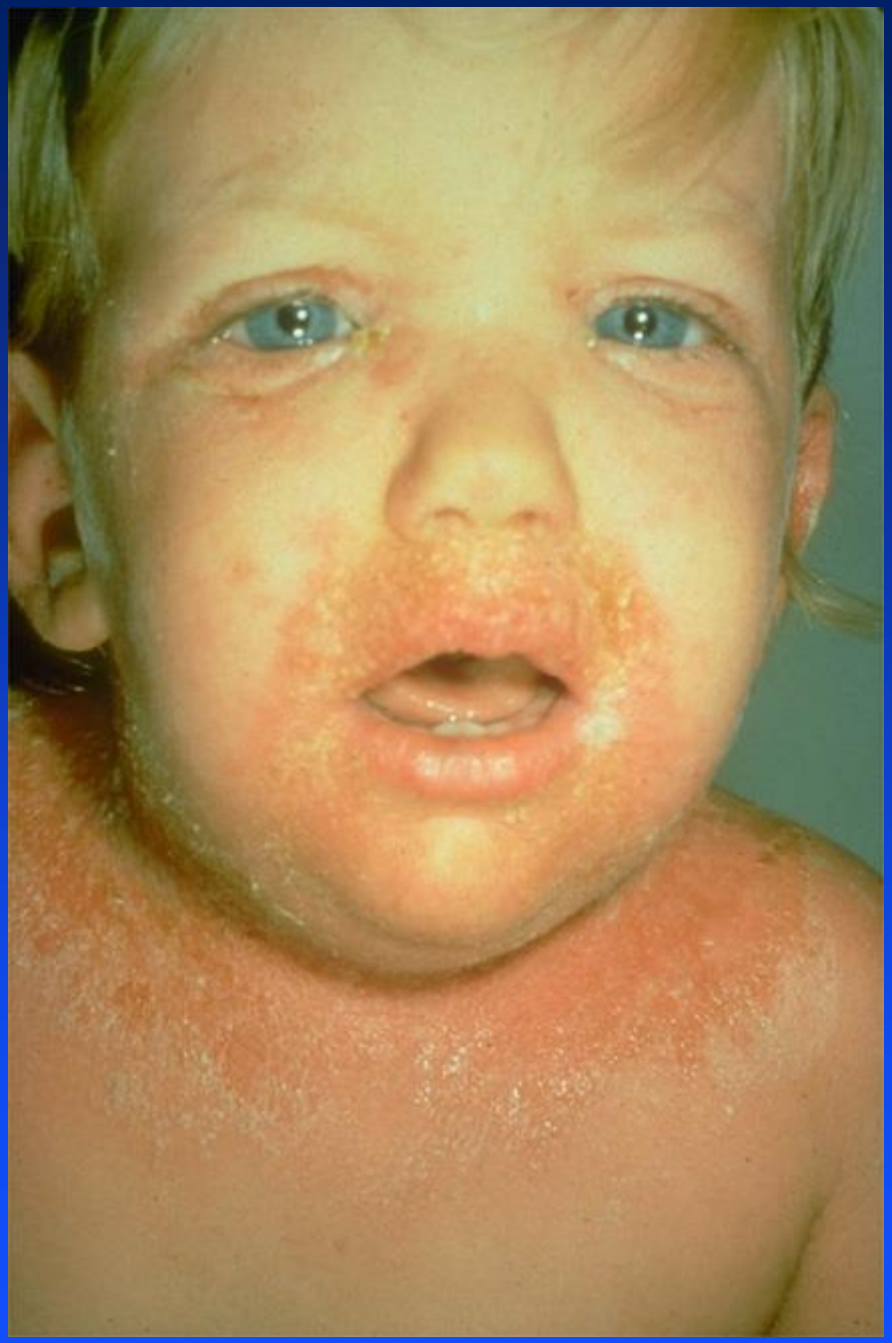
- Superficial pyoderma
- Often childhood
- Bullous type usually staph aureus associated with toxin
- Flaccid bullae that rupture

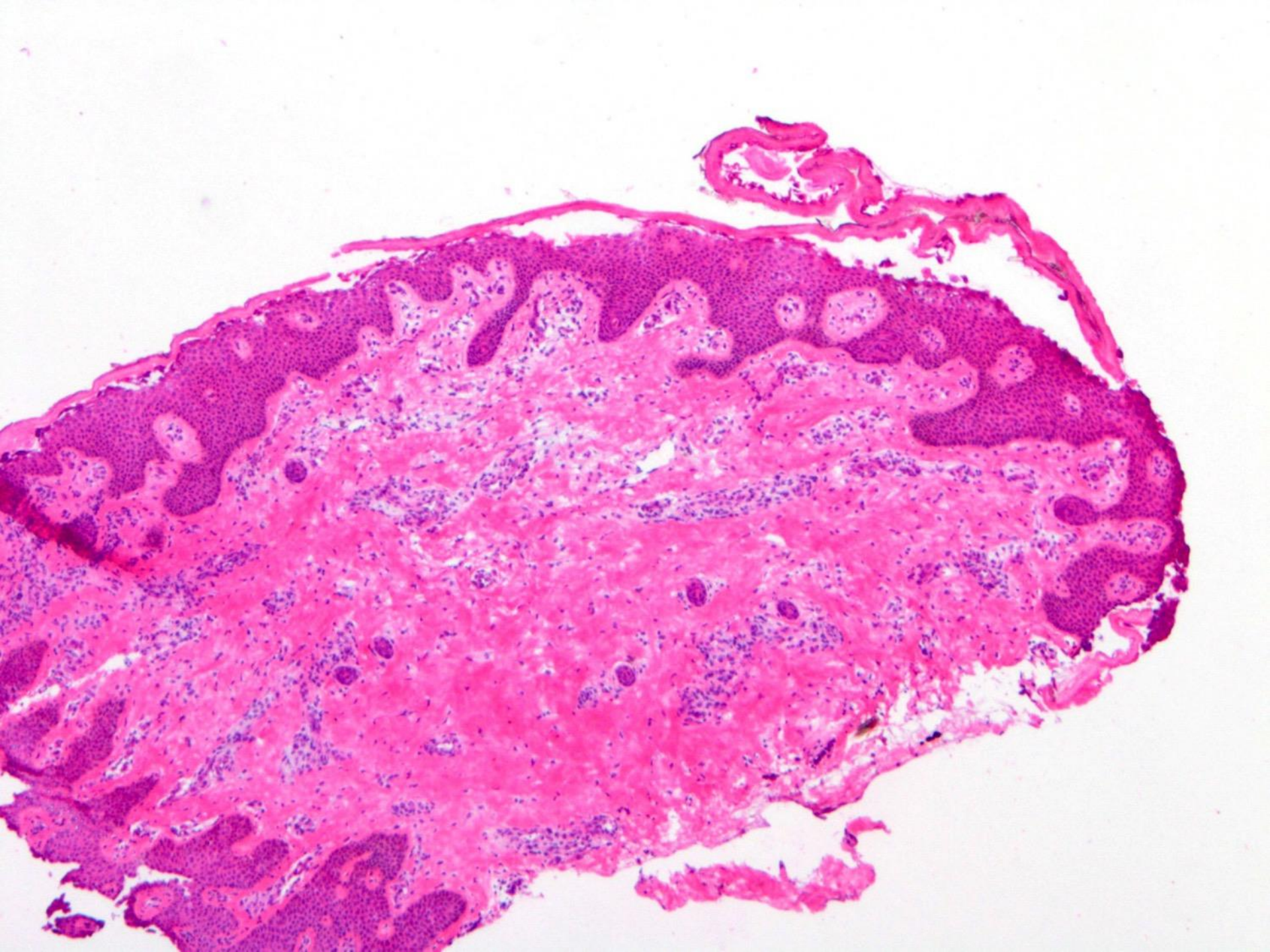
Pathology

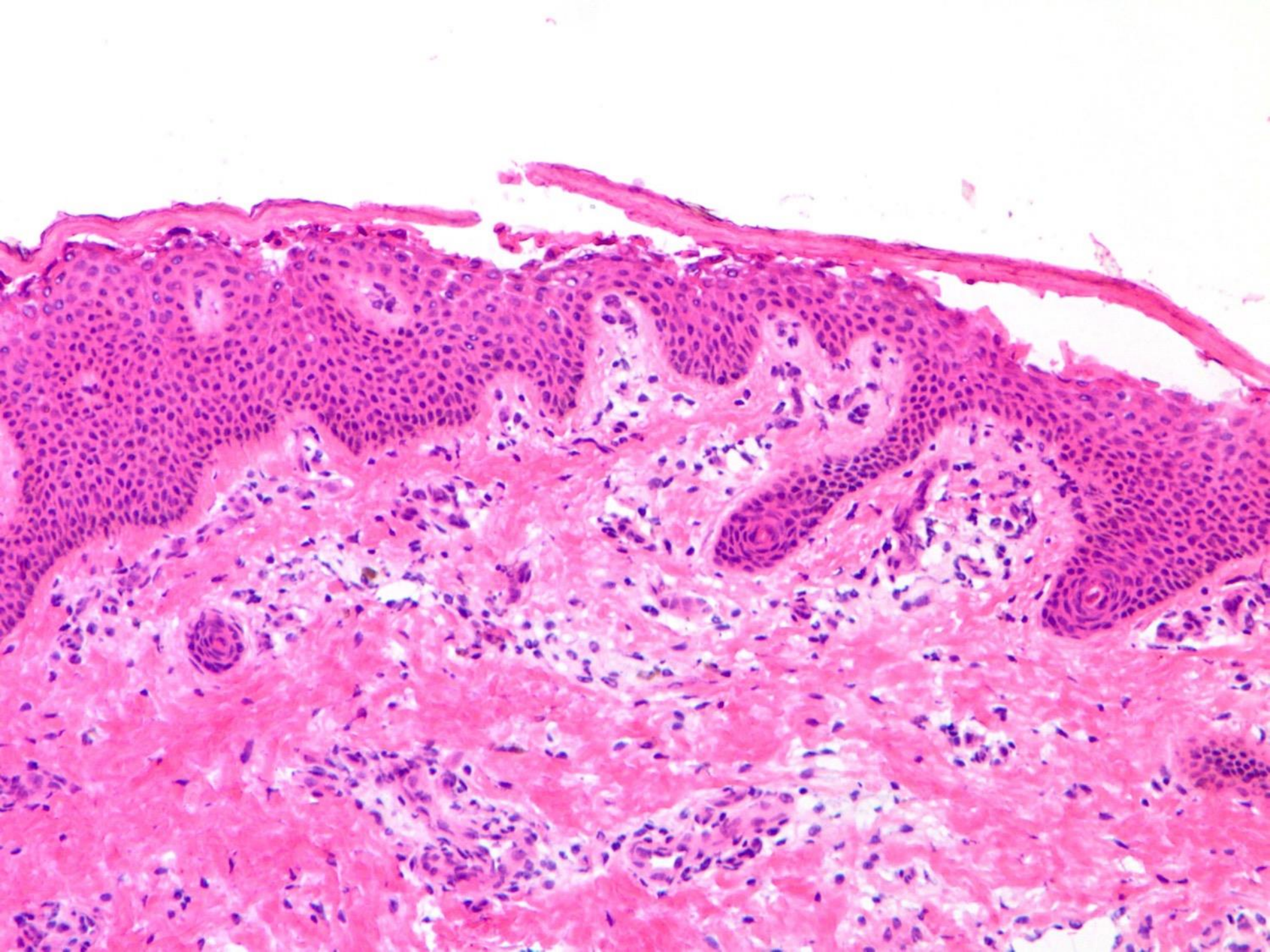
- Subcorneal split
- Acantholytic keratinocytes
- Neutrophils in cleft
- Gram positive cocci
- Mixed dermal infiltrate

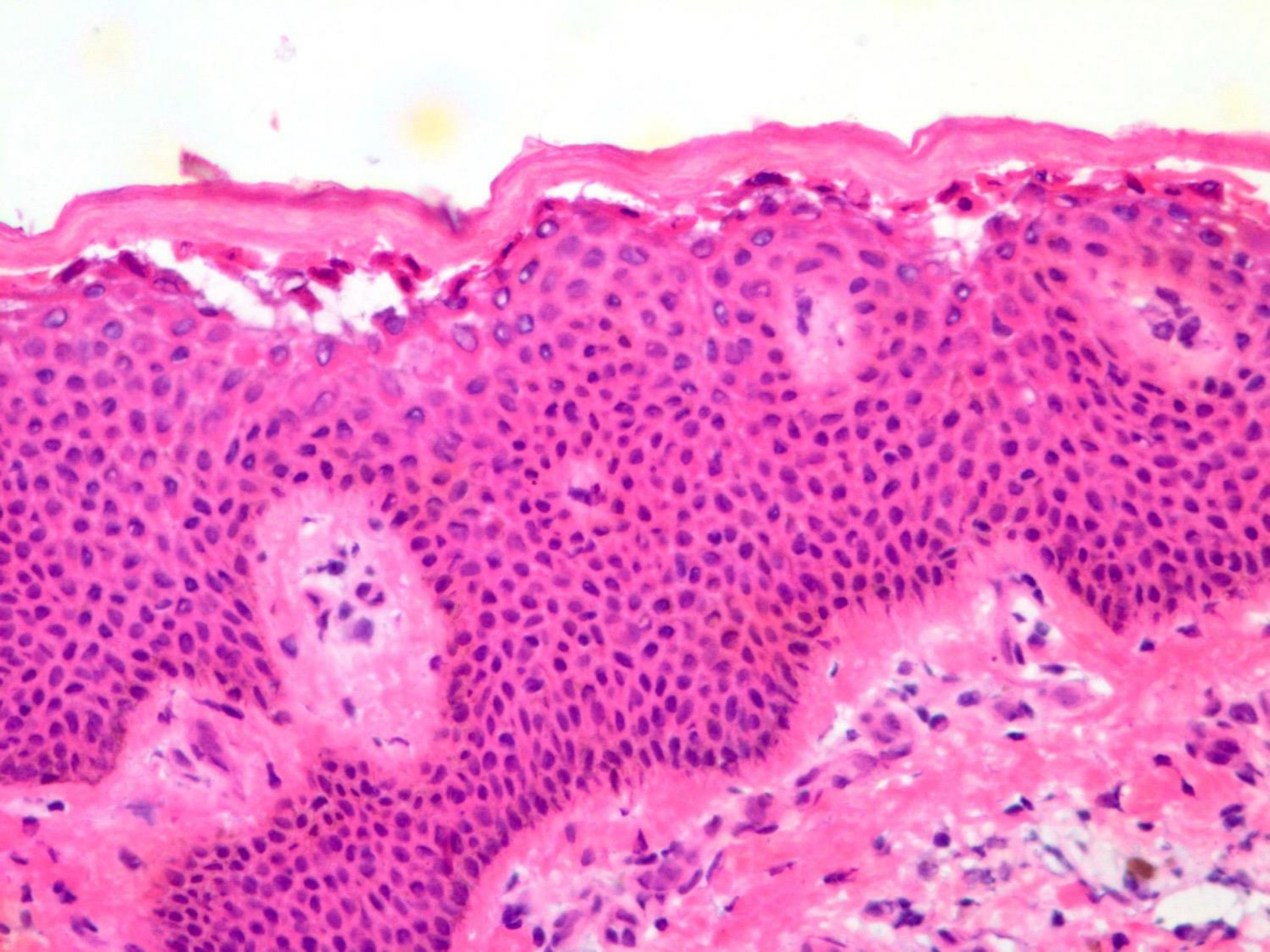
Differential diagnosis

- Pemphigus superficial type
- SSSS
- Subcorneal pustular dermatosis









Staph scalded skin syndrome

Clinical features

- Usually infants and young children; adults with immunosuppression
- Skin tenderness, scarlatiniform eruption
- Large areas of flaccid bullae easily ruptured
- Variant presentations

Pathology

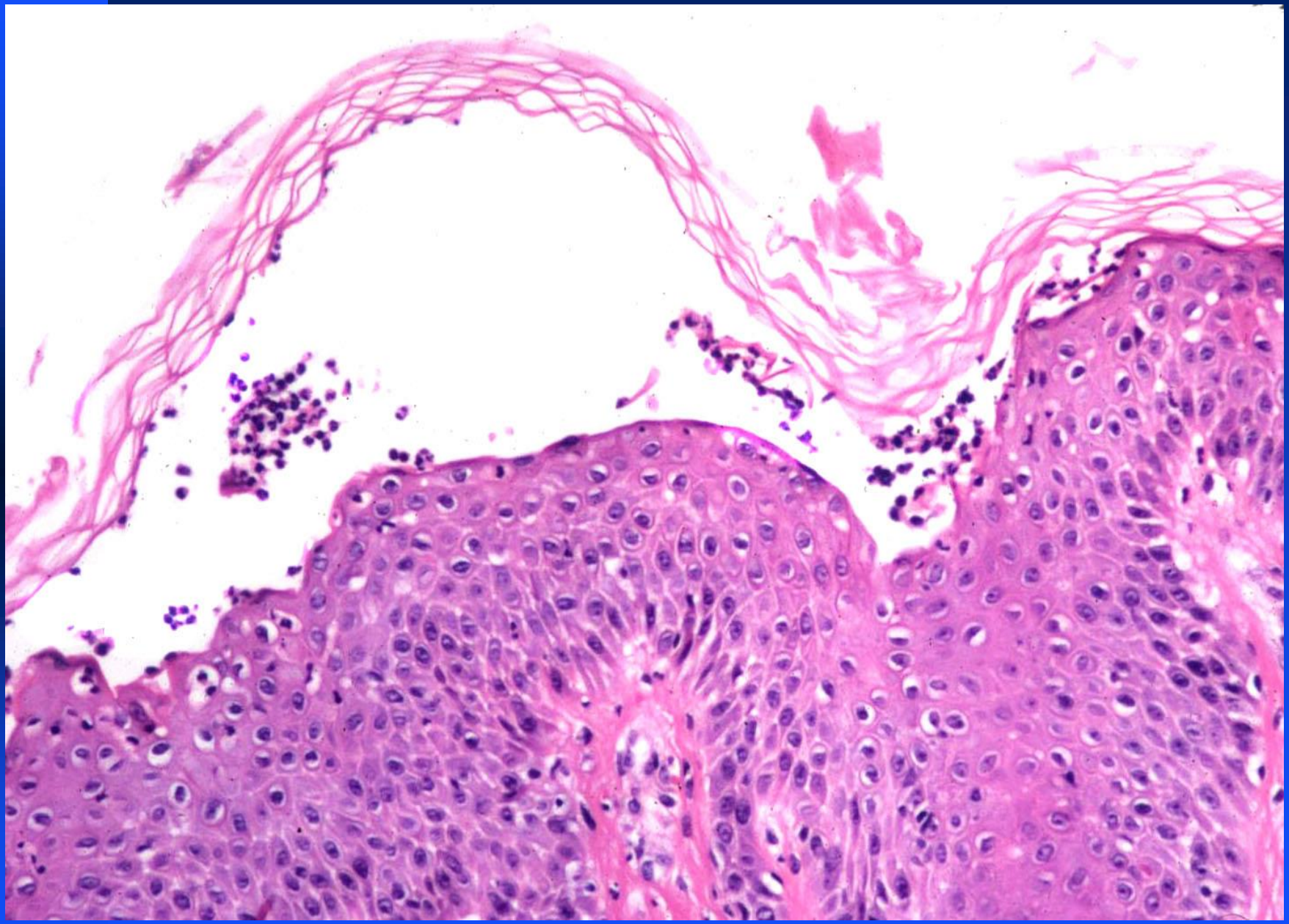
- Subcorneal split
- Acantholytic cells
- Focal keratinocytic necrosis
- Rare neutrophils

Mechanism

- Exfoliative toxin produced by ~ 5% of *Staphylococcus aureus*
- Two exfoliative toxins ETA and ETB
- Proteases that target the protein desmoglein-1 (DG-1)
- Spread hematogenously from a localized source - oral or nasal cavities, throat, or umbilicus

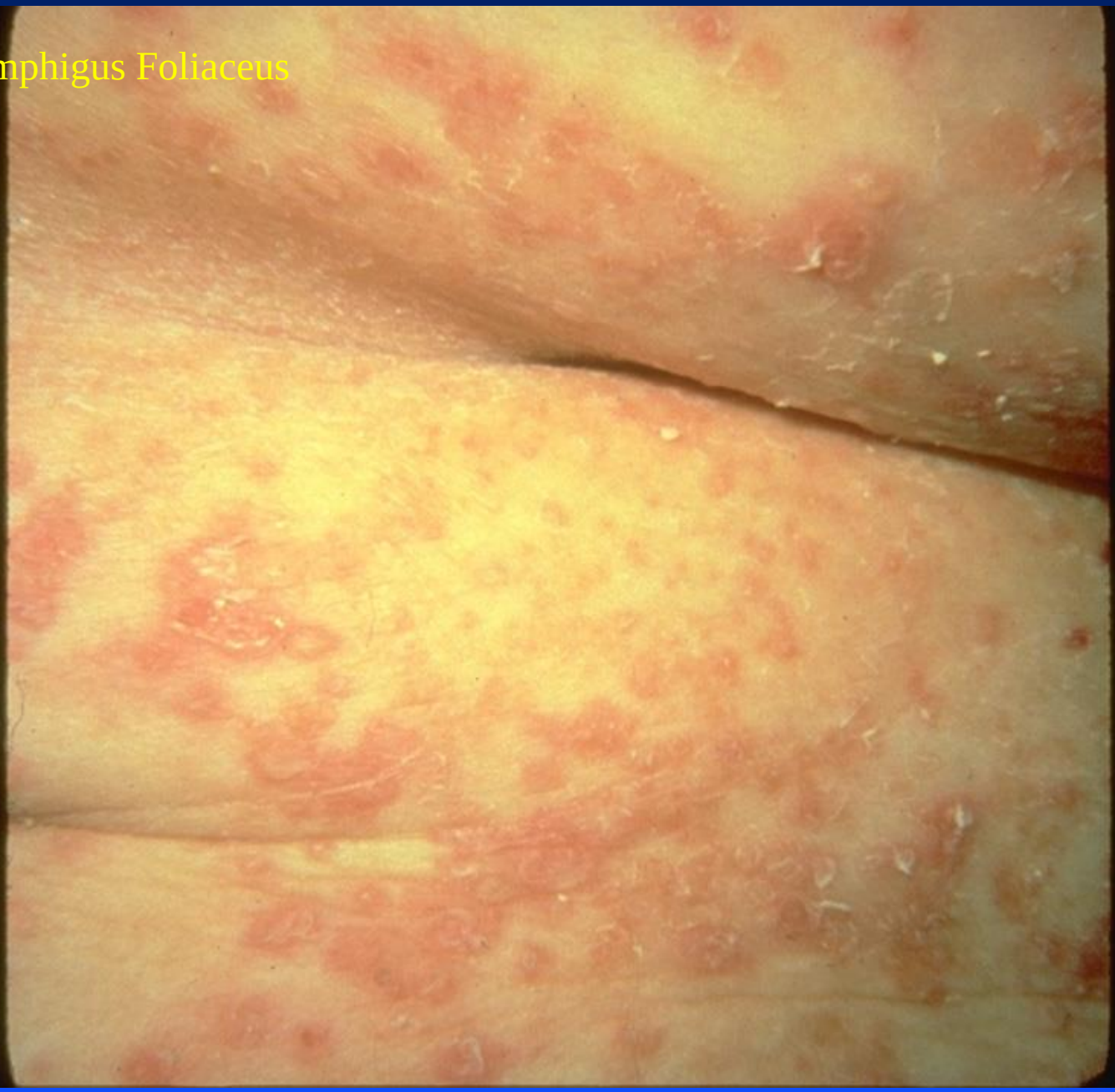
Differential diagnosis

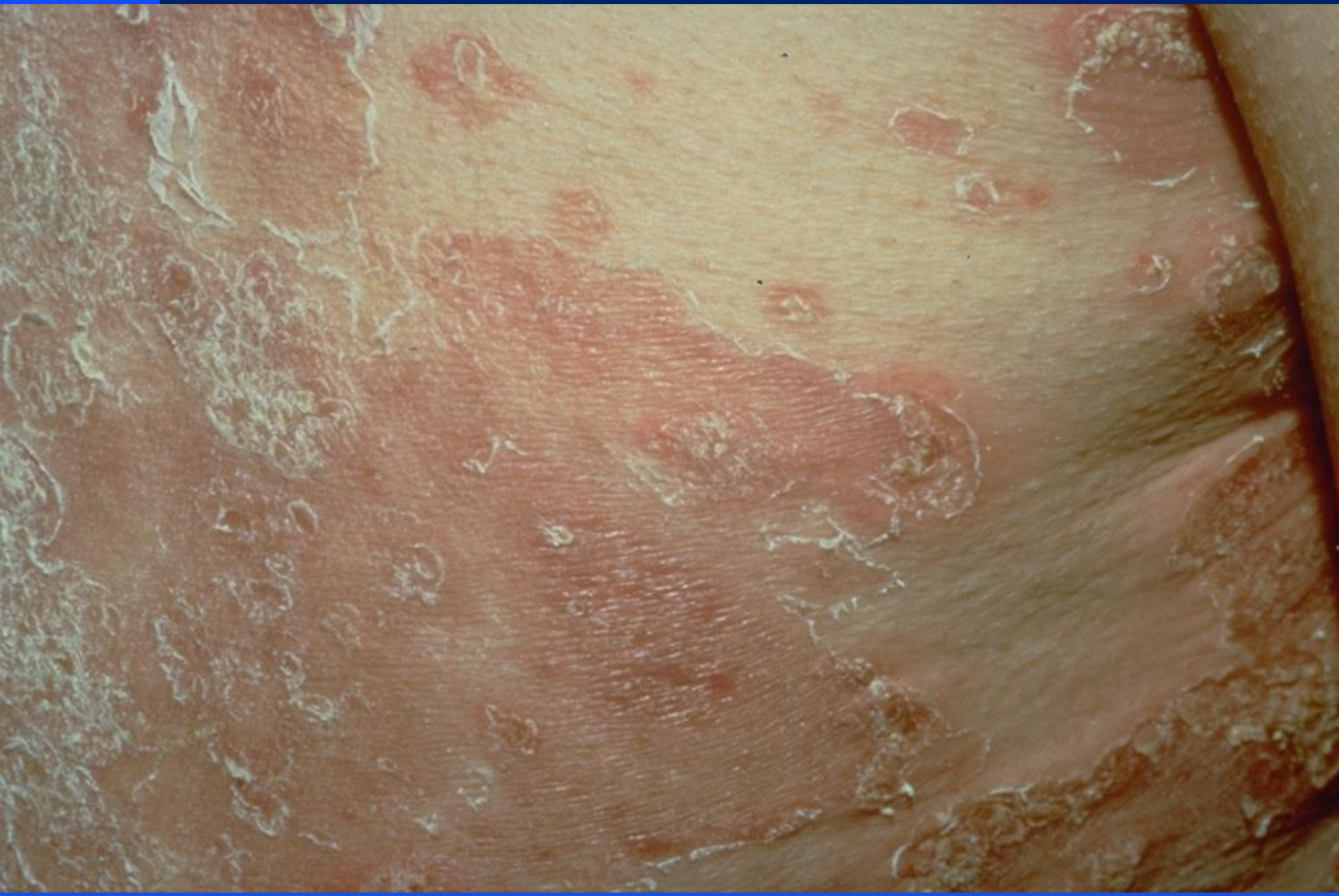
- Superficial pemphigus
- Bullous impetigo
- TEN

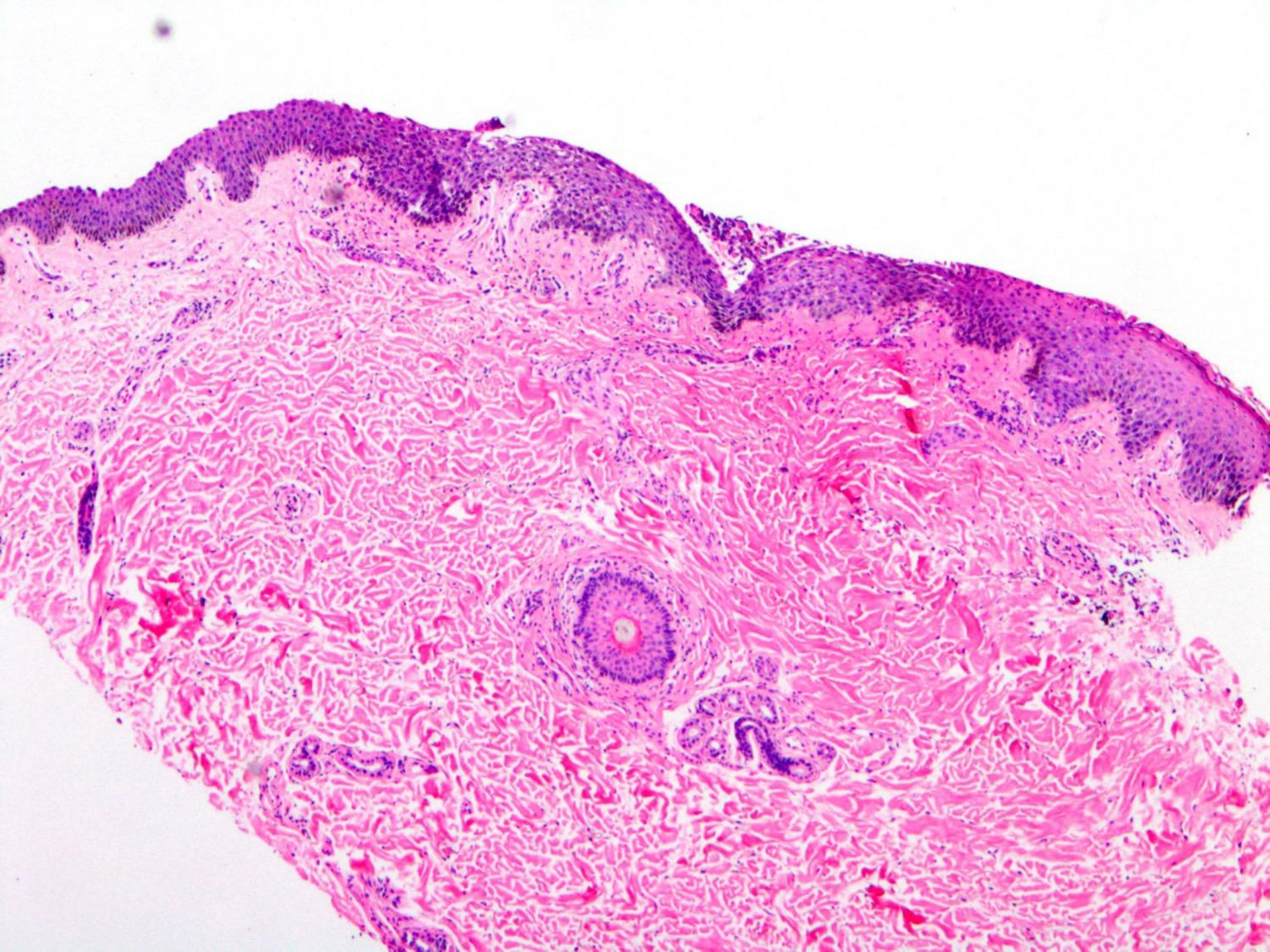


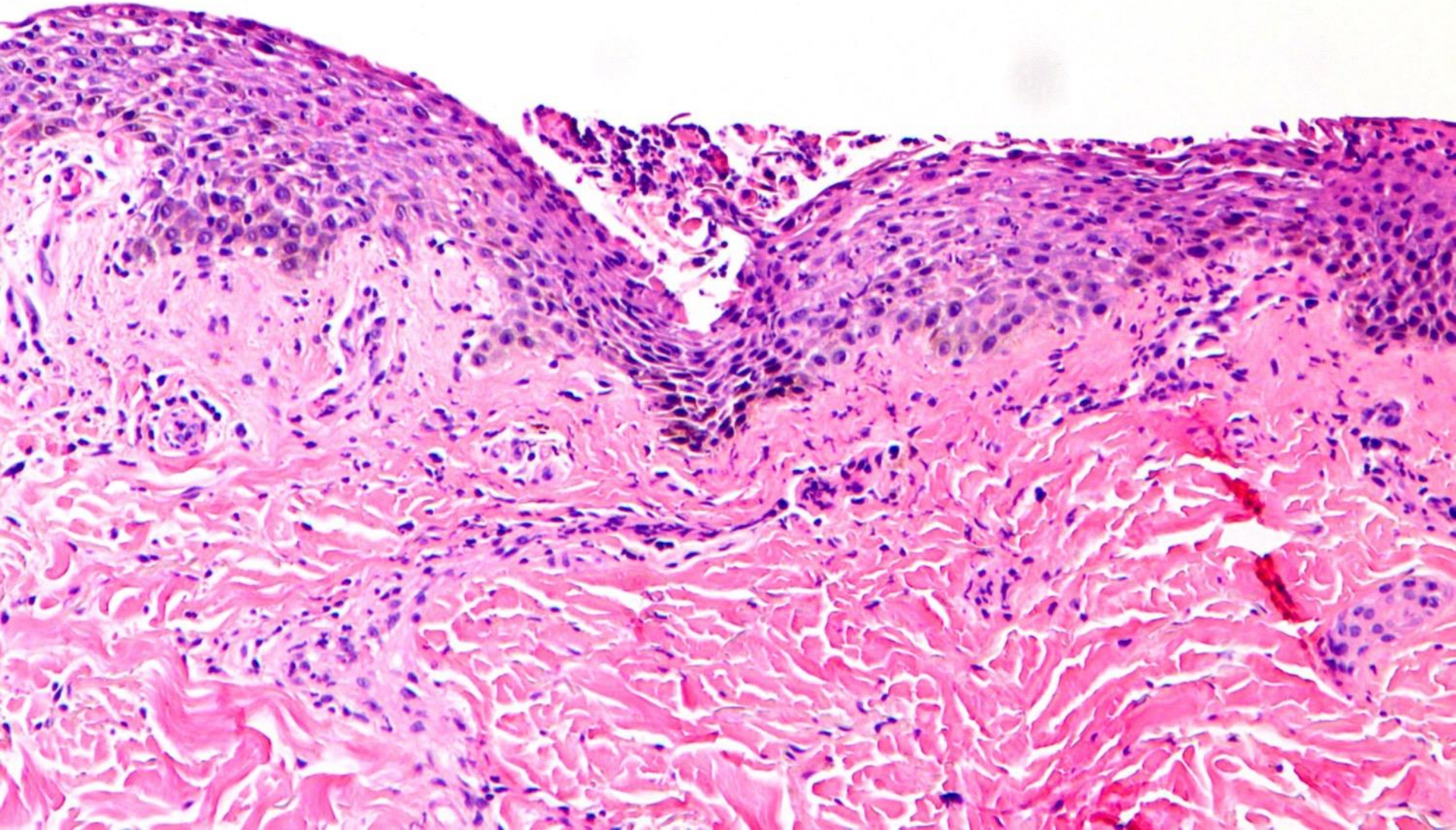
Bullous impetigo

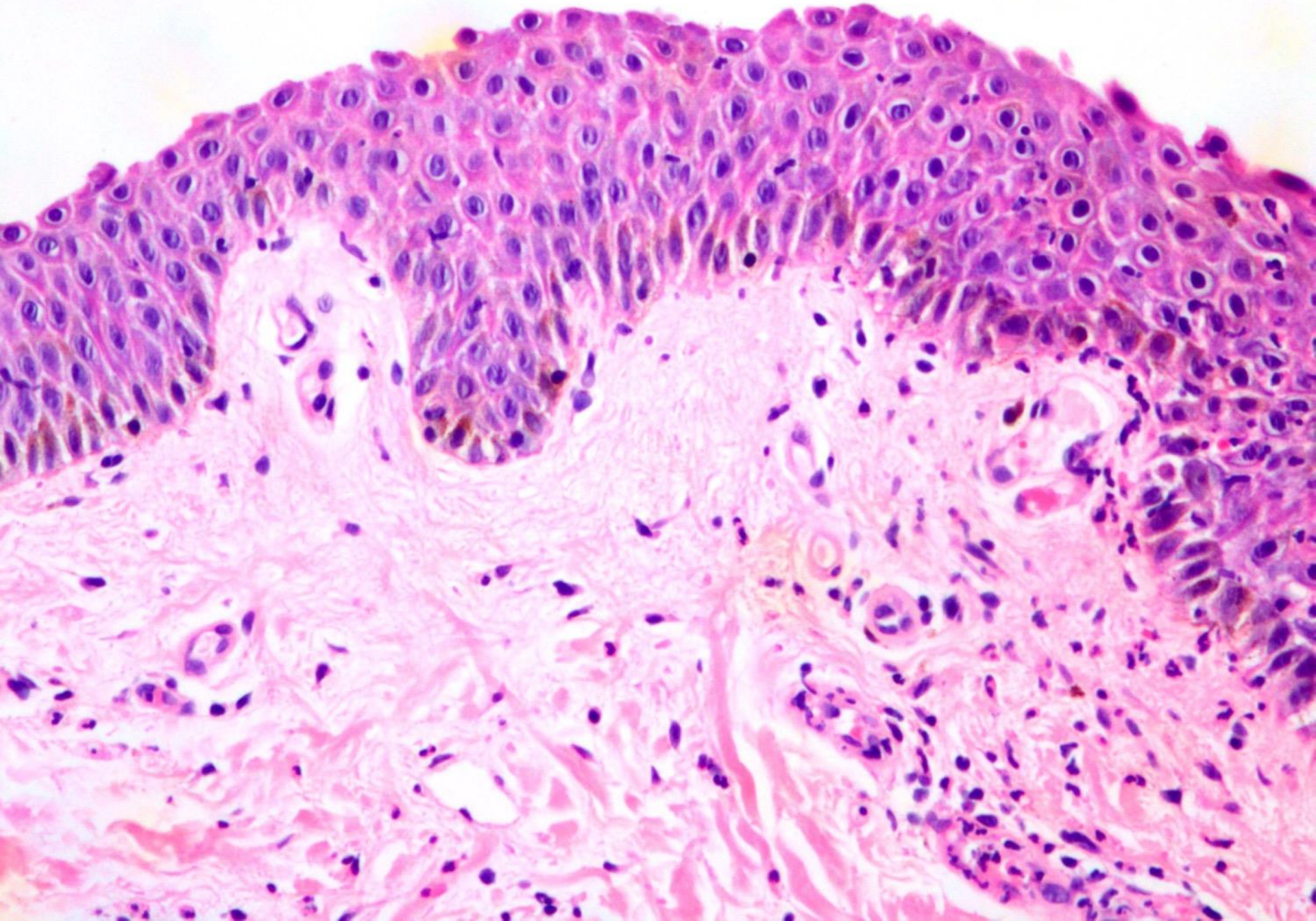
Pemphigus Foliaceus

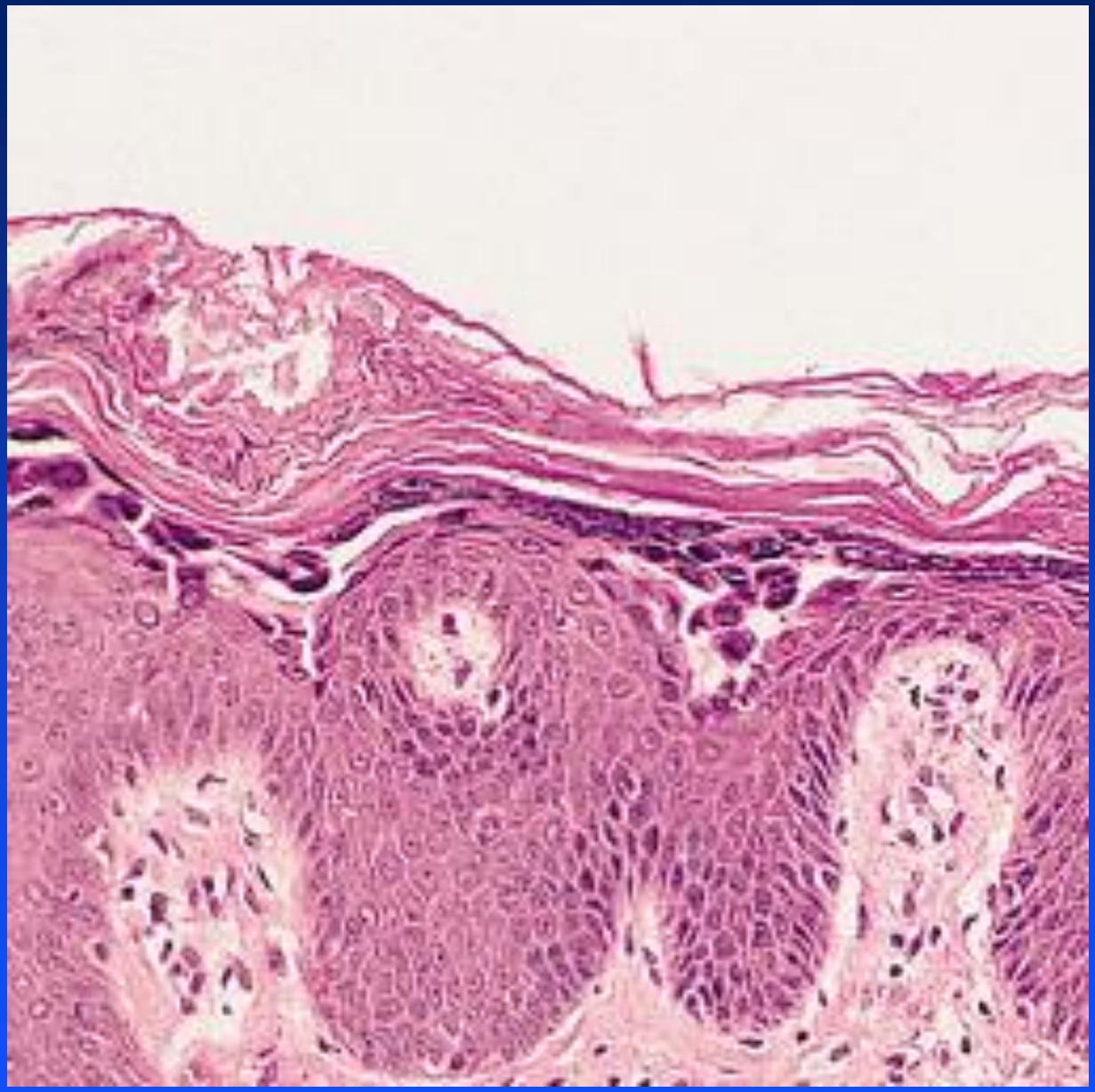












Pemphigus foliaceus

Clinical features

- Usually later in life but any age including children
- Flacced bullae, shallow erosions, crust and scale; “cornflakes”
- Can involve large areas, seborrheic distribution scalp, nose, face, and trunk
- Erythroderma
- No mucous membrane involvement

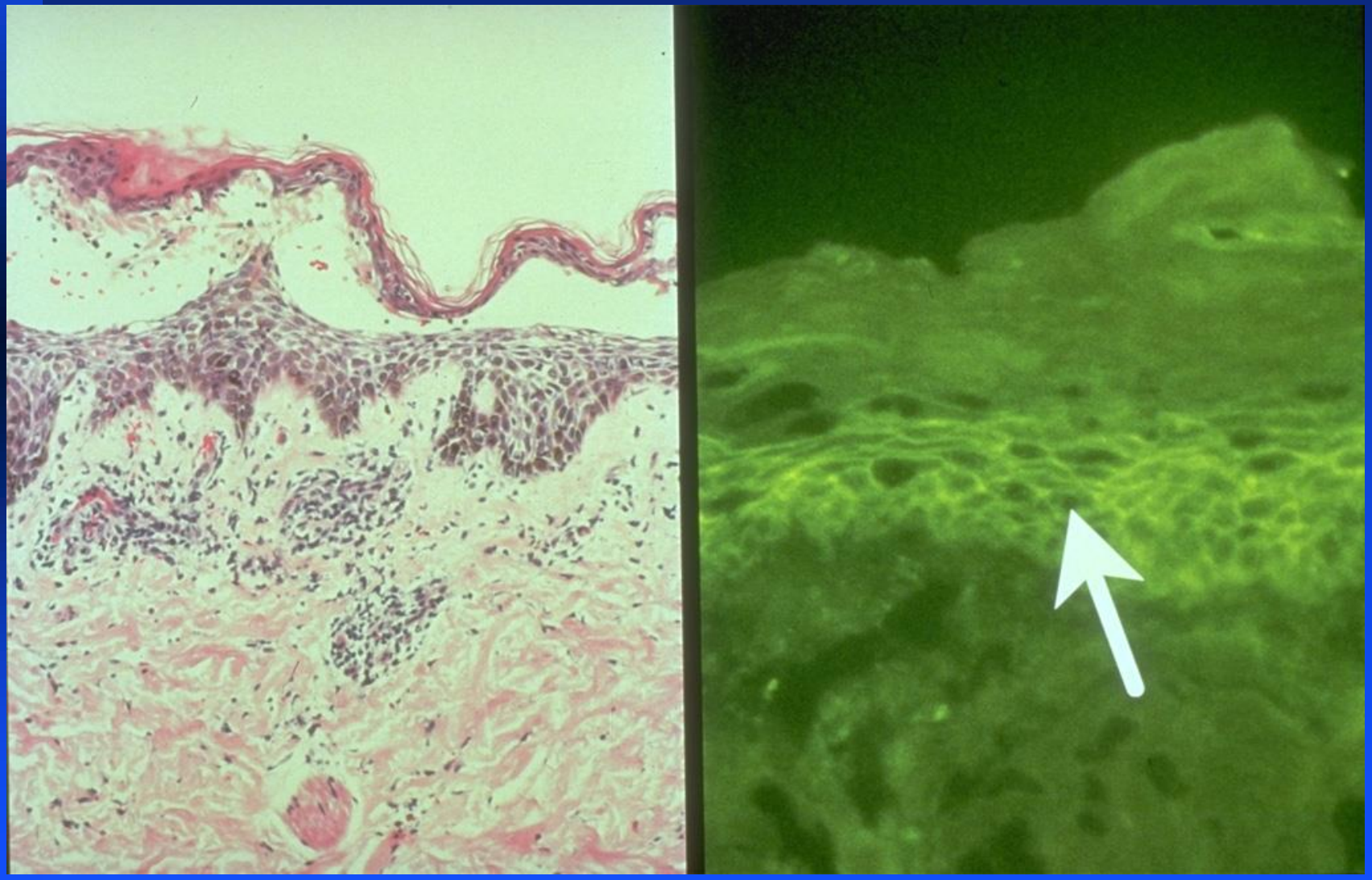
Pemphigus Foliaceus

- Histology
  - Subcorneal/granular layer split
  - Acantholysis with some fibrin, neutrophils
  - Initially can see eosinophilic spongiosis or neutrophilic spongiosis
  - Older lesions may have neutrophilic, subcorneal pustule or dyskeratotic cells- Darier like
  - Dermal mixed infiltrate with eos

Pemphigus Foliaceus

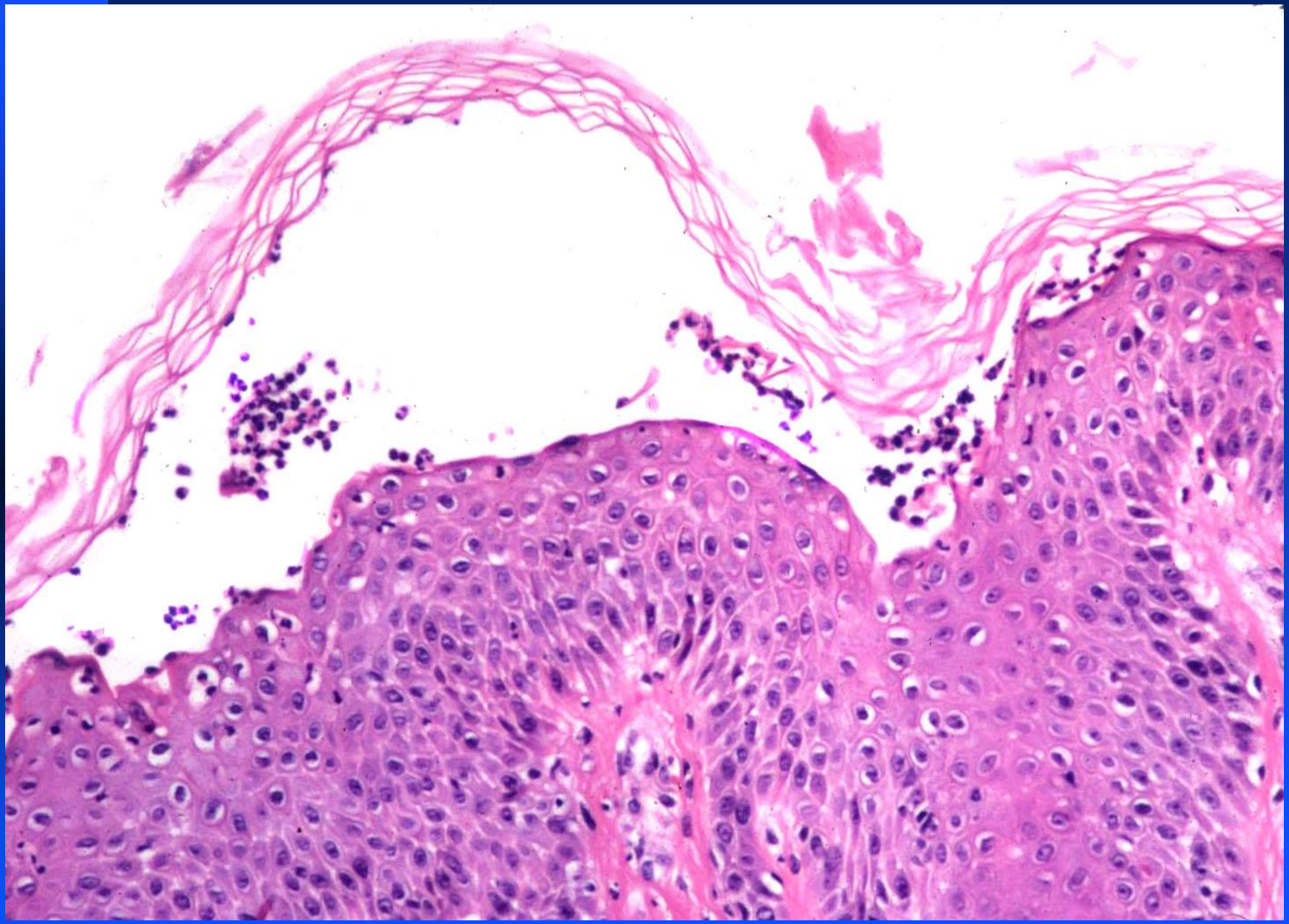
- Immunofluorescence
  - Direct- IgG, C3: full thickness all skin, intercellular cell surface staining, 75%(+)
  - Sometimes localized to upper epidermis
  - Indirect- 80-90%(+) guinea pig
  - IgG4
- Can diagnose by ELISA
- Target Antigen
  - Desmoglein 1 160kd- same ag as is targeted by exfoliative toxin A of SSSS

Pemphigus Foliaceus



Differential diagnosis

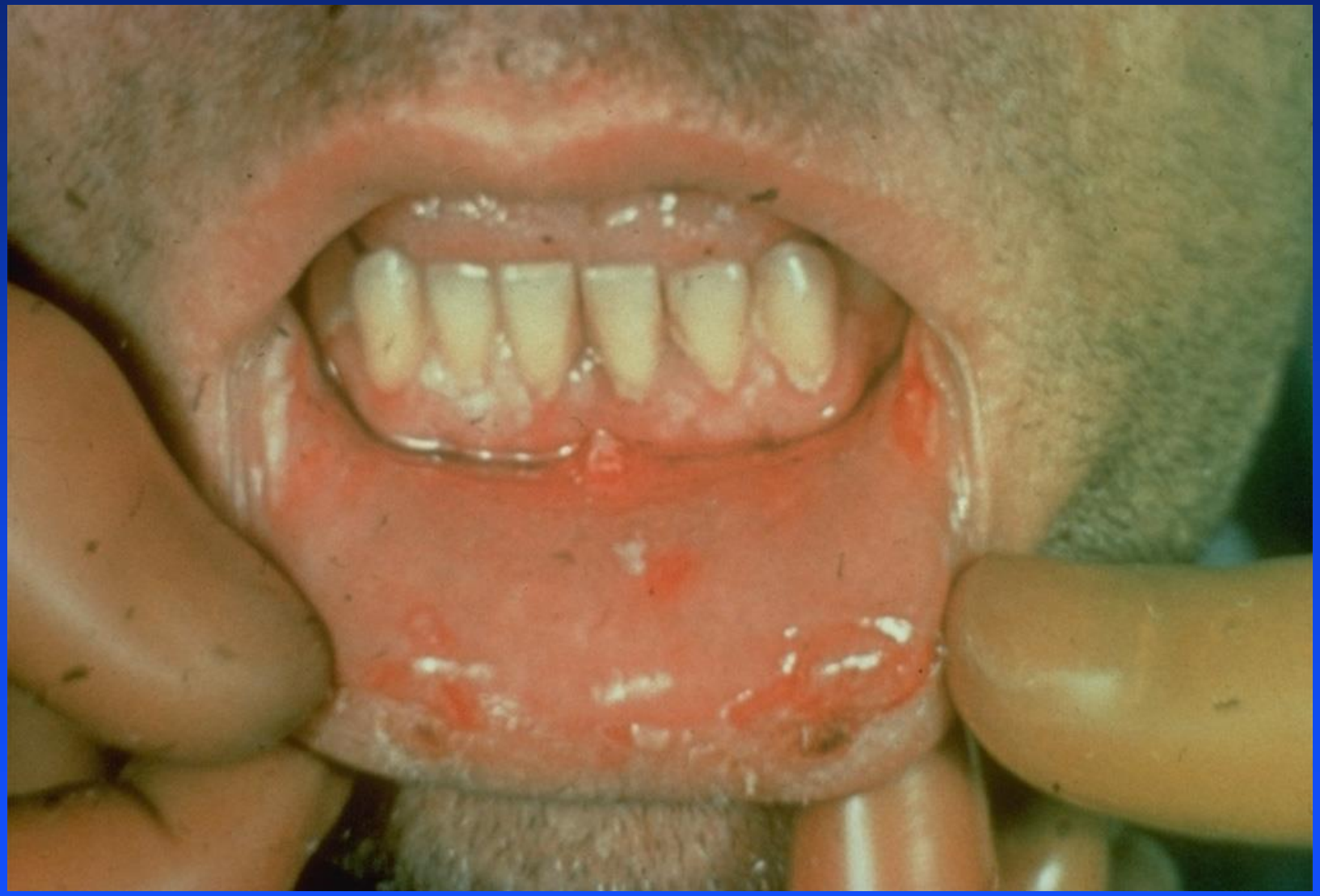
- Bullous impetigo
- Staph scalded skin syndrome
- Subcorneal pustular dermatosis



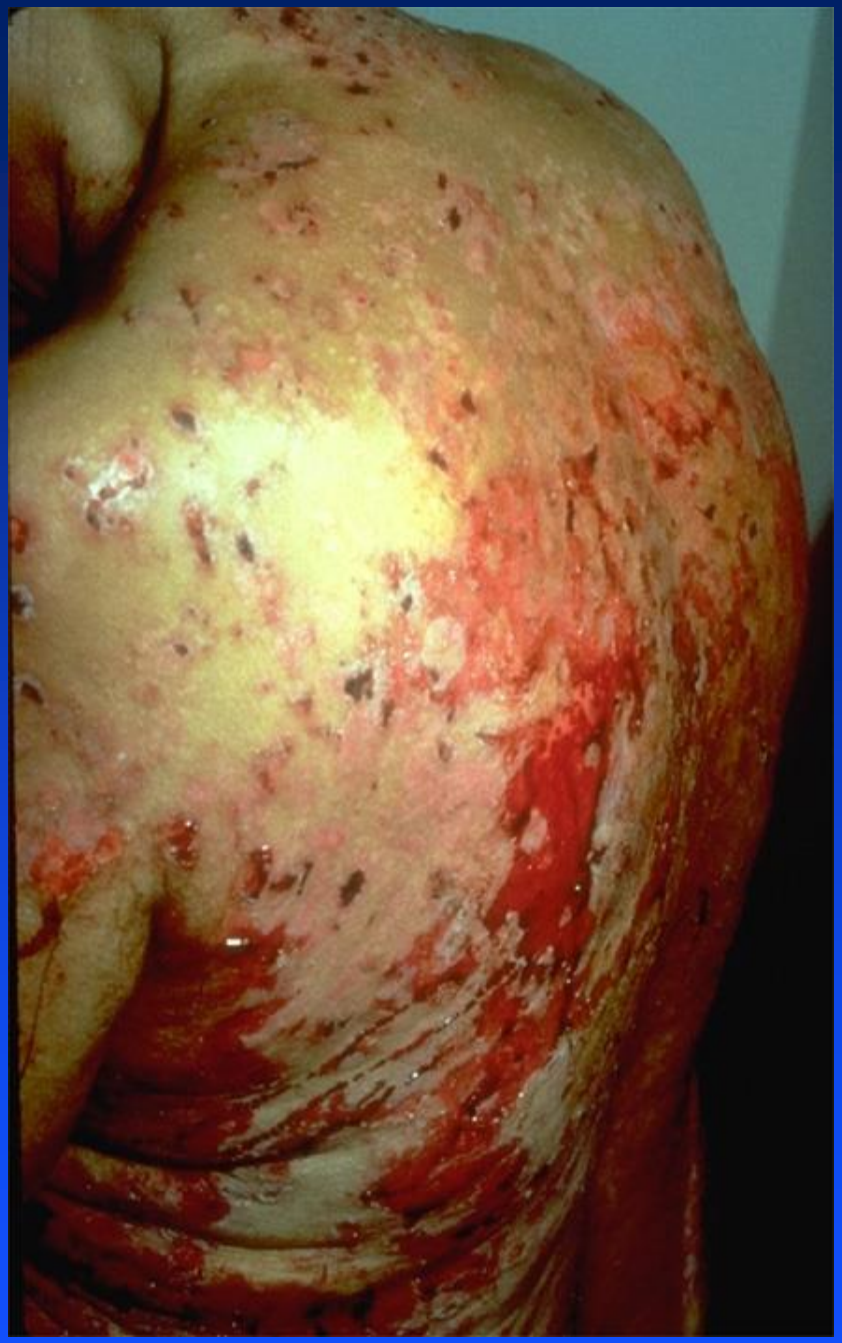
Group II: Intraepidermal/suprabasilar clefts

- Acantholytic-pemphigus vulgaris
- Spongiotic dermatitis
- Infection-herpes, hand foot and mouth
- Acantholytic-Hailey-Hailey

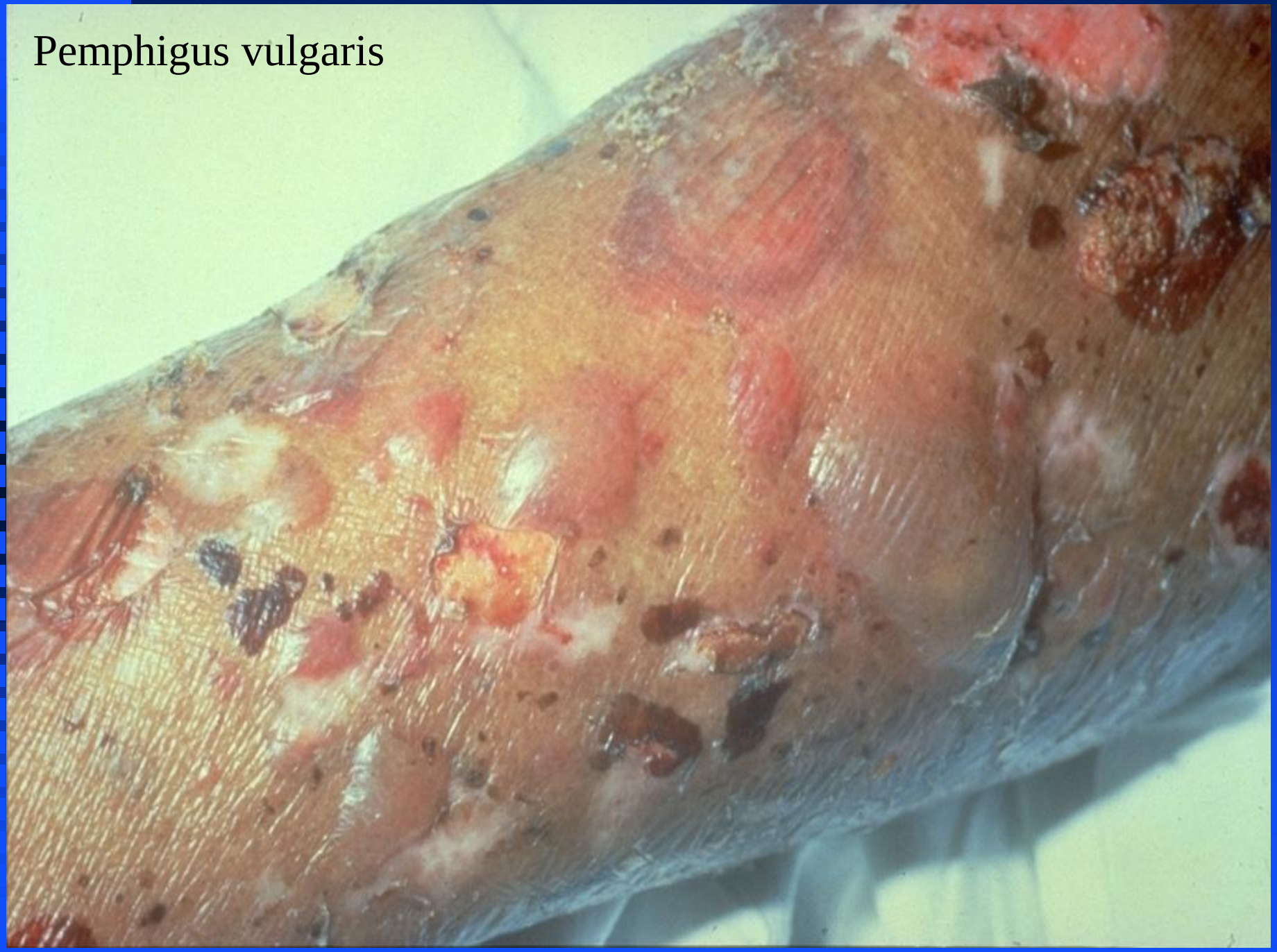
Pemphigus Vulgaris

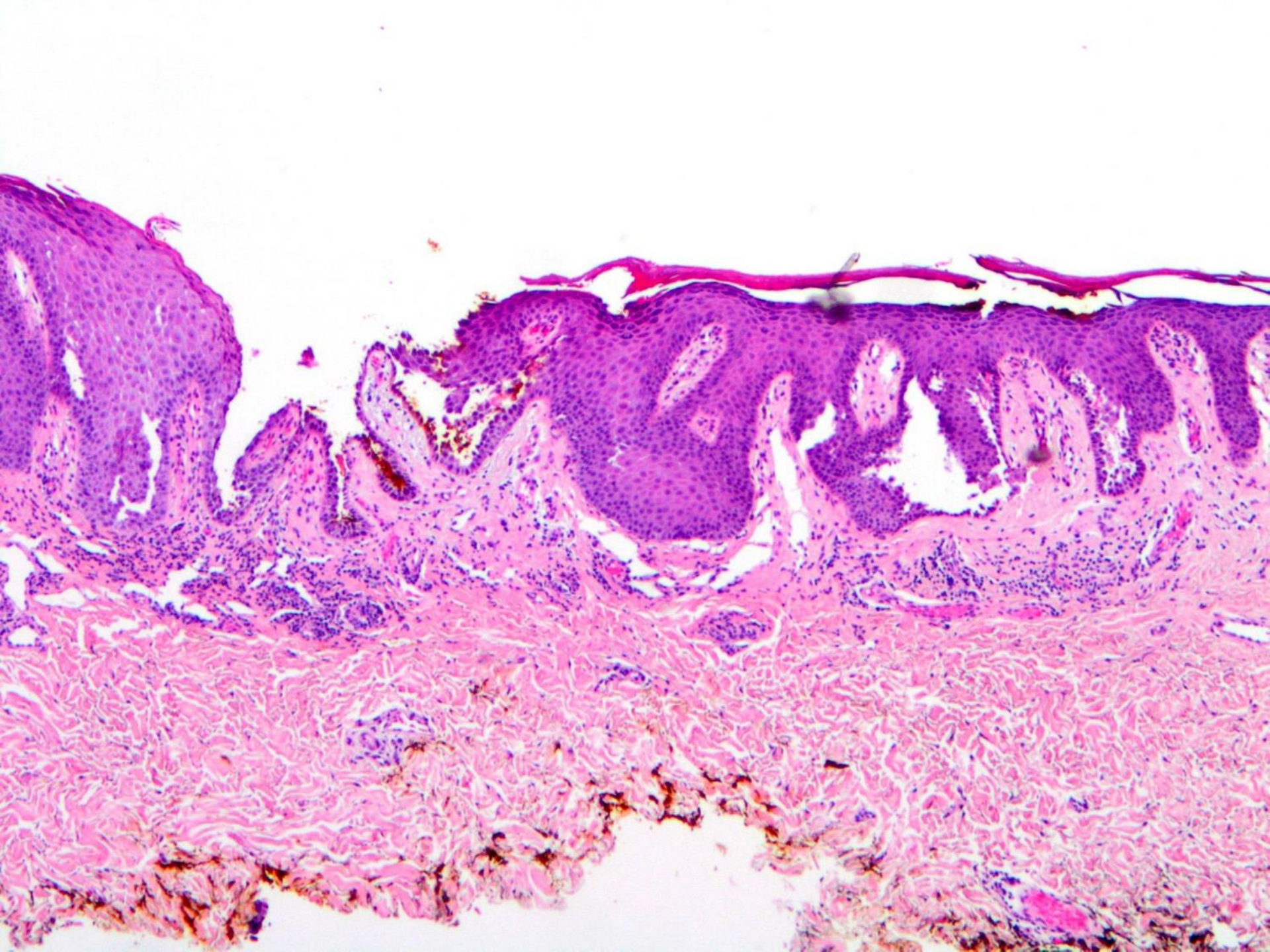


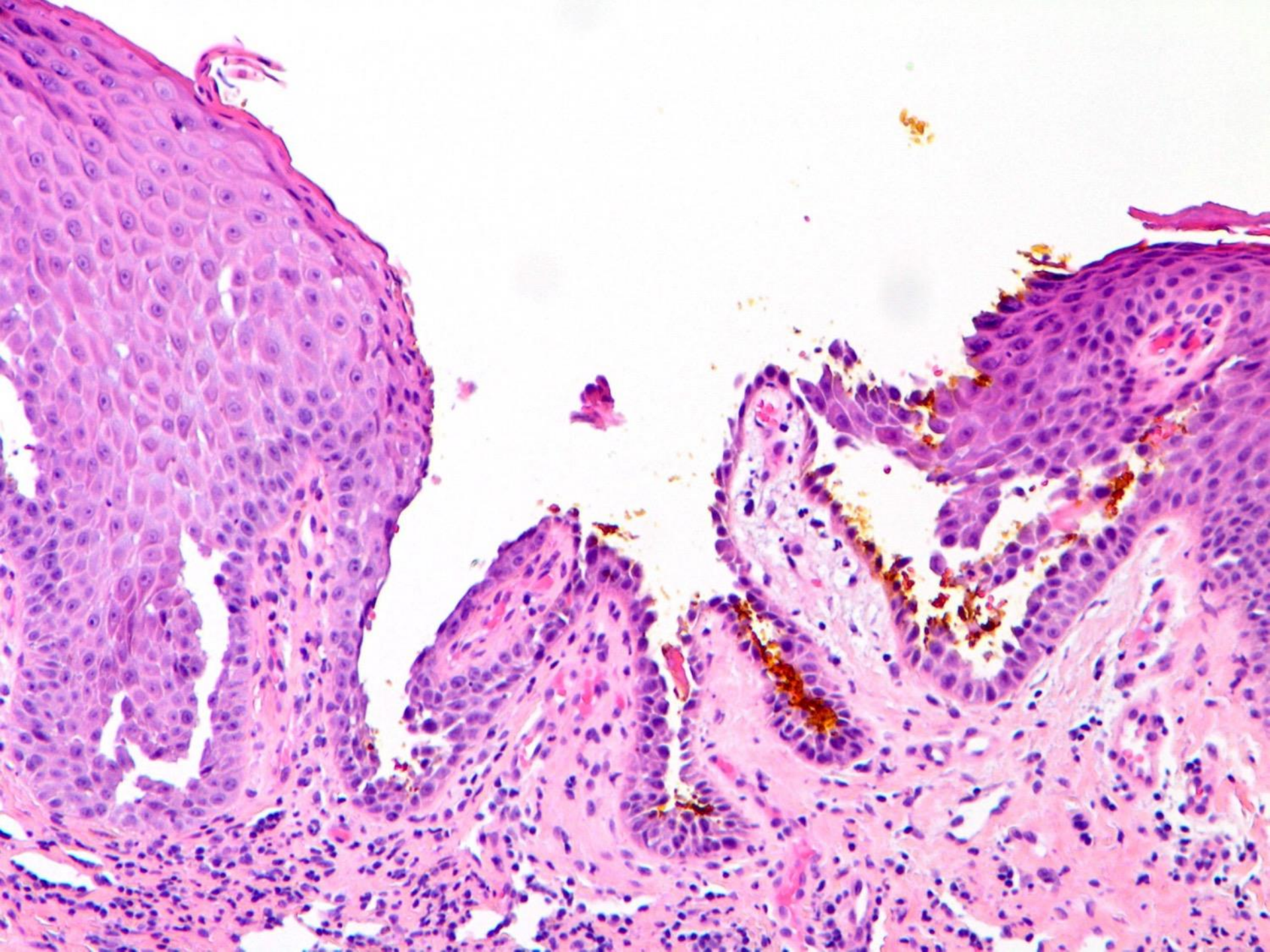
Pemphigus Vulgaris

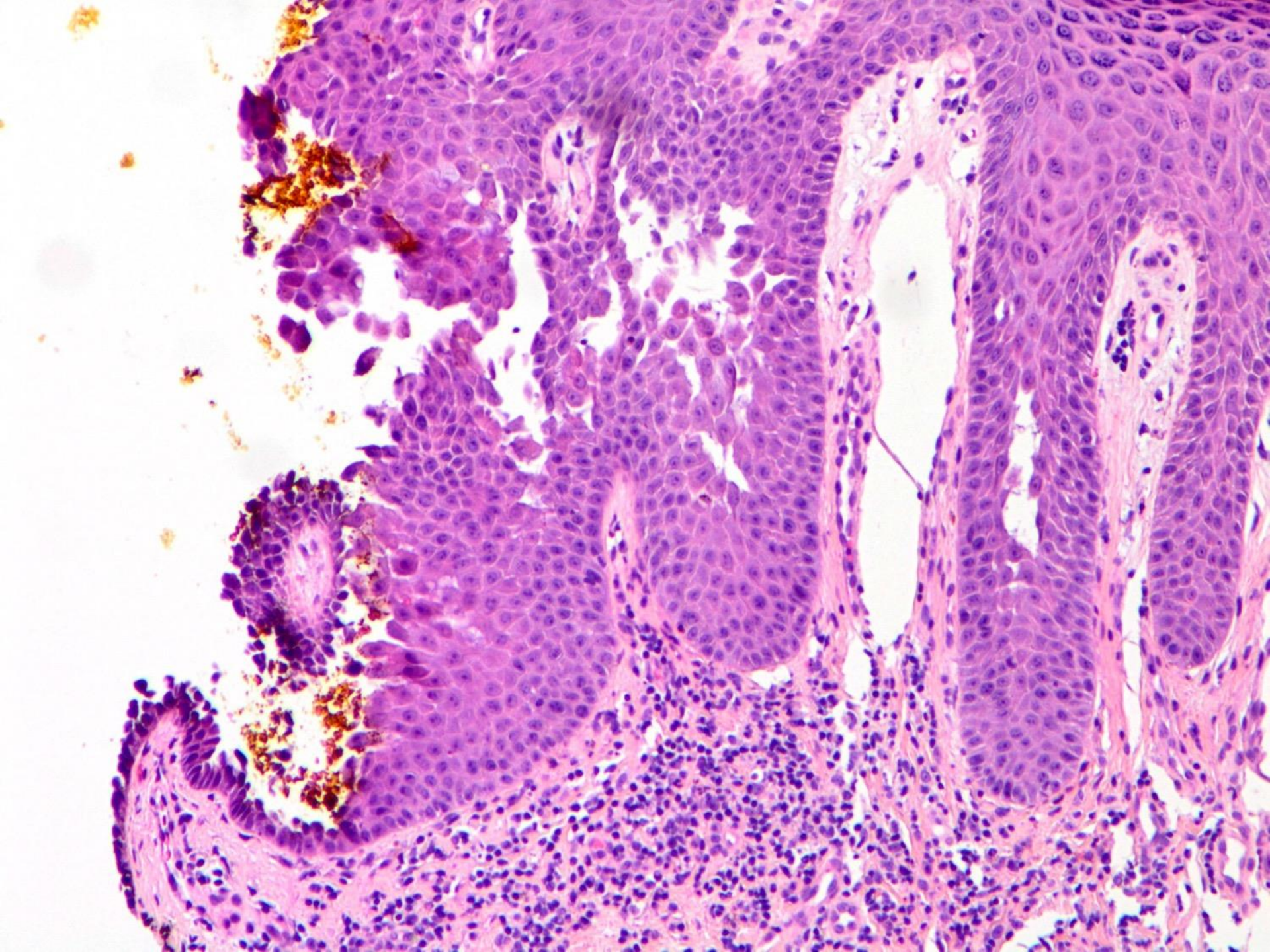


Pemphigus vulgaris









Pemphigus vulgaris

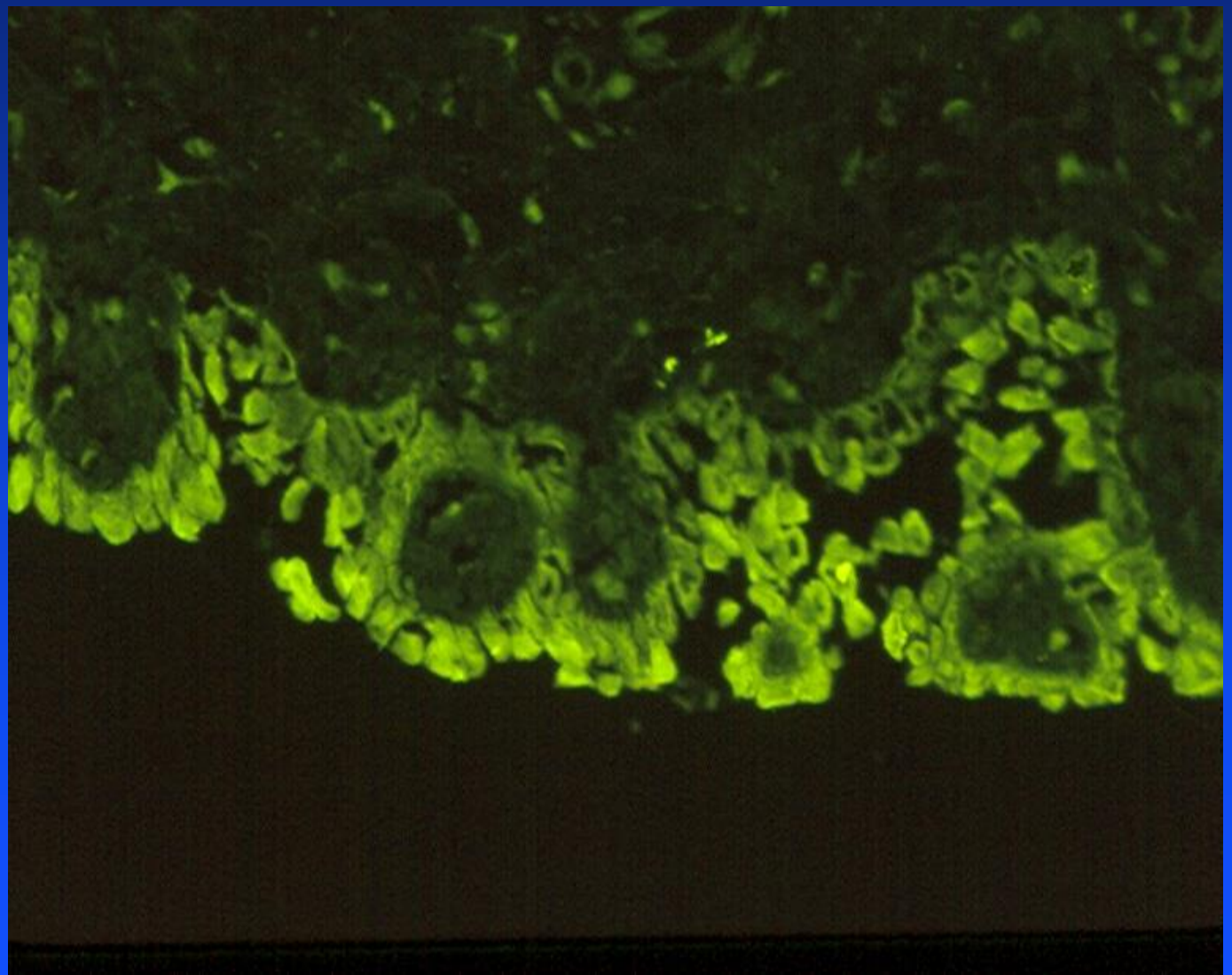
Clinical features

- Older patients 4th to 6th decade
- Flaccid bullae
- Trunk, groins, axillae, scalp face
- Easily extended blisters-Nikolsky and Asboe-Hansen
- Oral and other mucosal involvement up to 75-90%, often is the initial presentation – blisters, ulcers and erosions

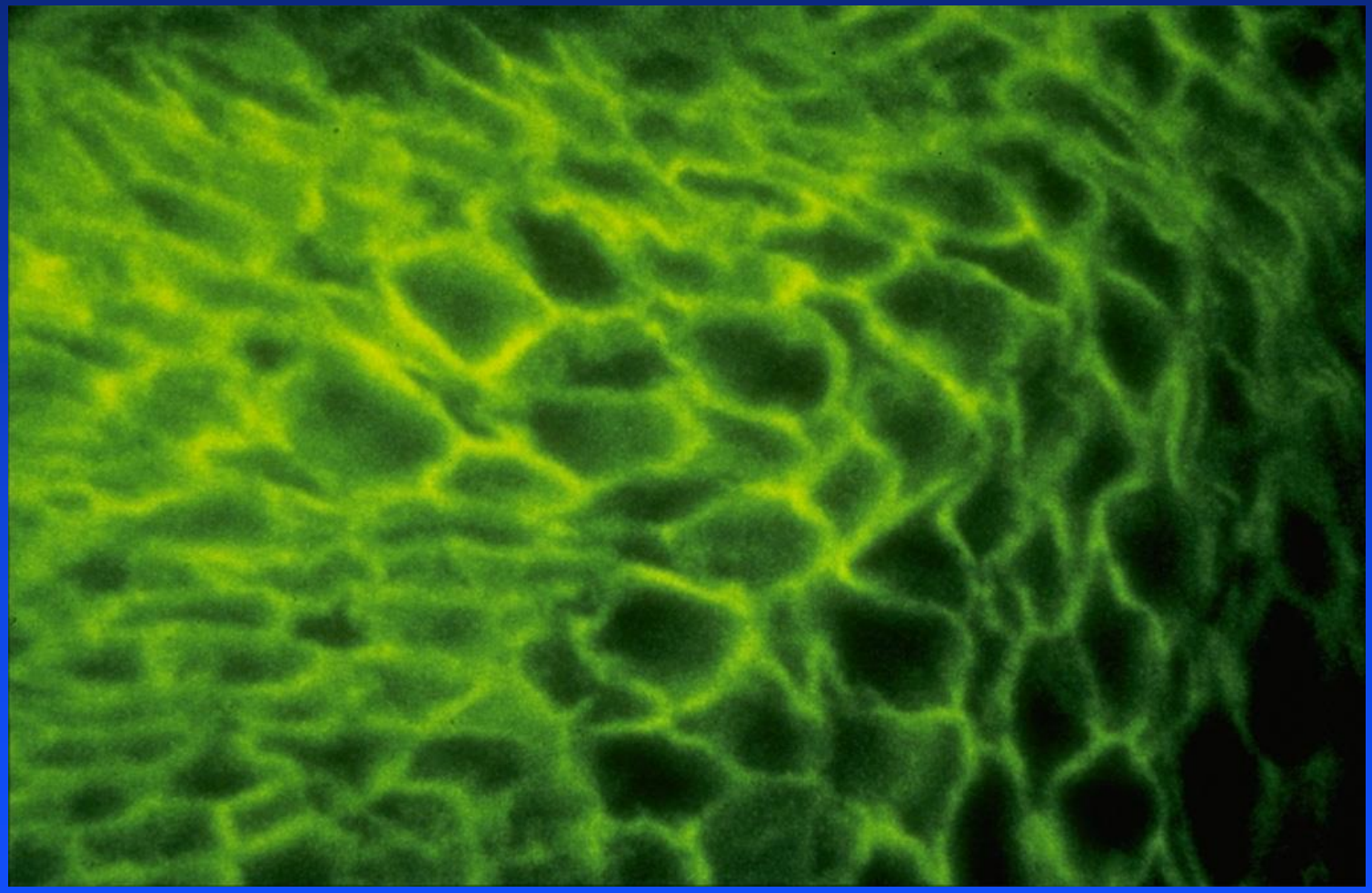
Pemphigus Vulgaris

- Histology
  - Suprabasilar, intraepidermal blister
  - Acantholytic cells within and surrounding blister cavity
  - Extension of acantholytic change down adnexa
  - “Tombstone” formation-basal cells adherent to basement membrane
  - Eosinophilic spongiosis early but not much of an infiltrate

PV: Direct IgG



Pemphigus Vulgaris- Indirect



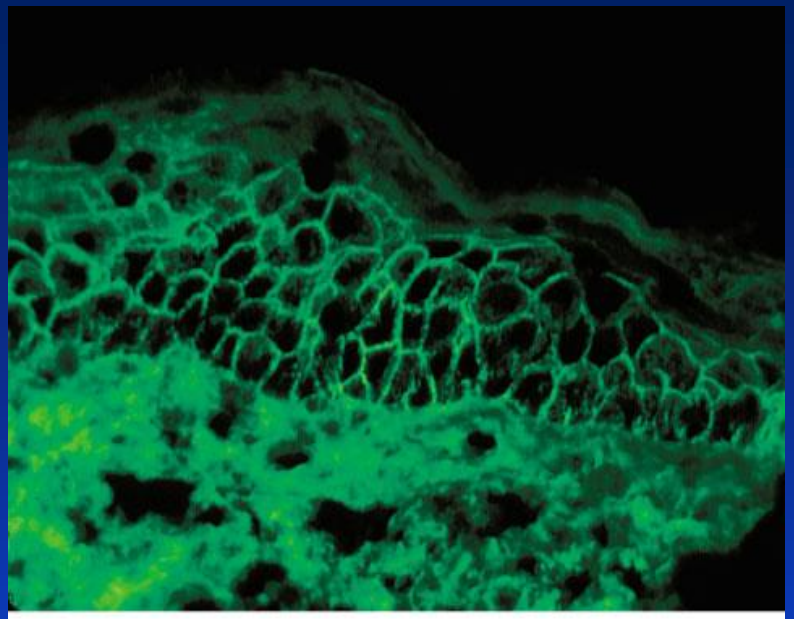
Pemphigus vulgaris:

- Target antigen:
  - Desmoglein 3 130kd (mucosal predominent PV)
  - Desmoglein 3 and Desmoglein 1 160kd (mucocutaneous PV)
- Site: perilesional (anywhere)
- Direct: IgG intercellular all throughout
- Indirect: IgG Monkey esophagus 80-90%
- IgG4, ELISA

Direct
IgG

Immunofluorescence of Pemphigus vulgaris

Indirect
IgG



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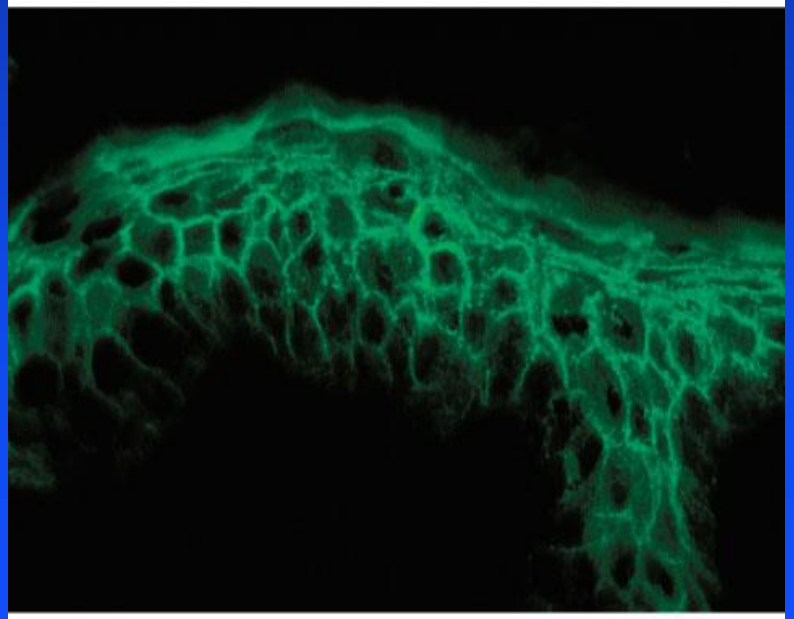

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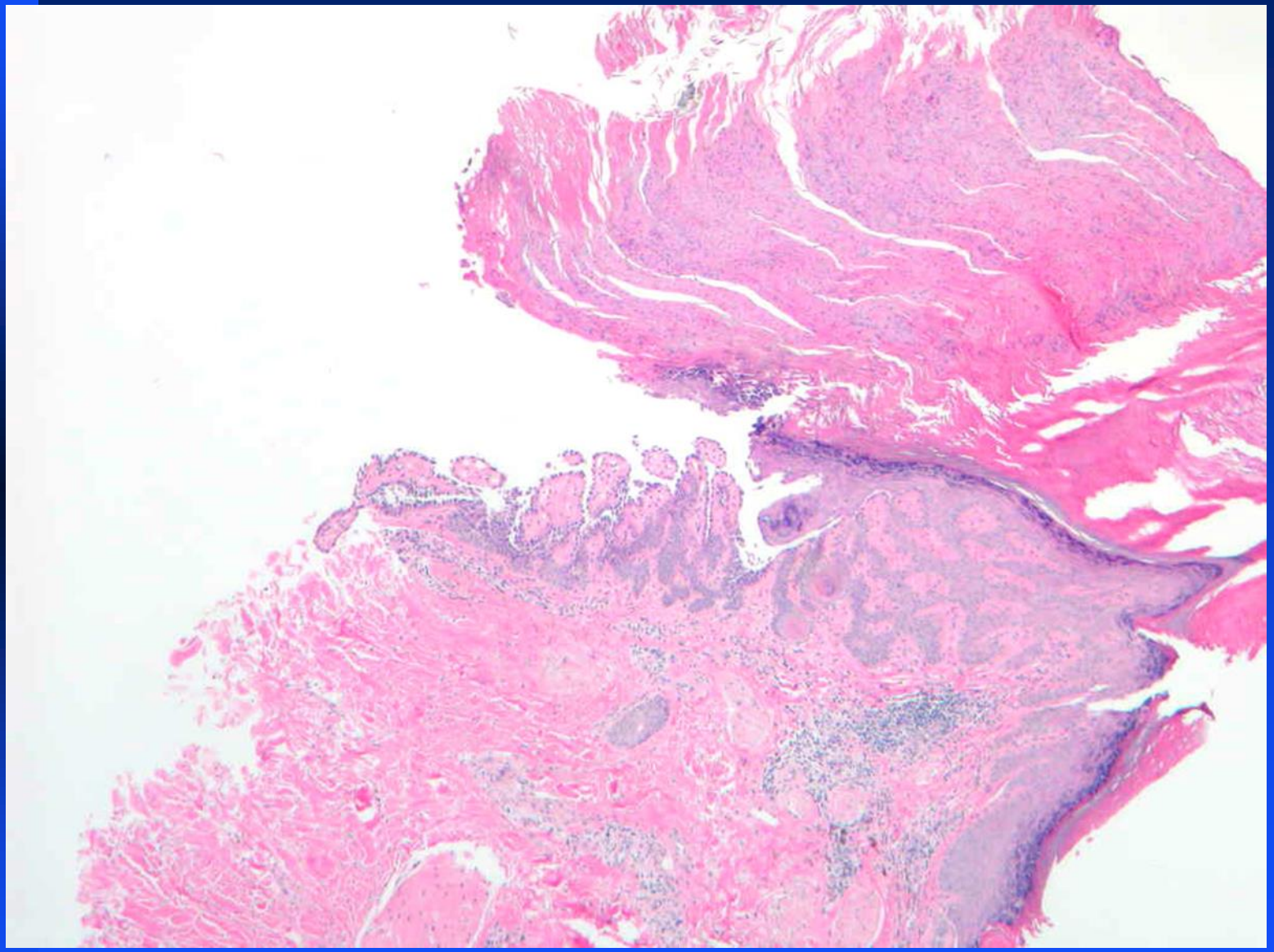
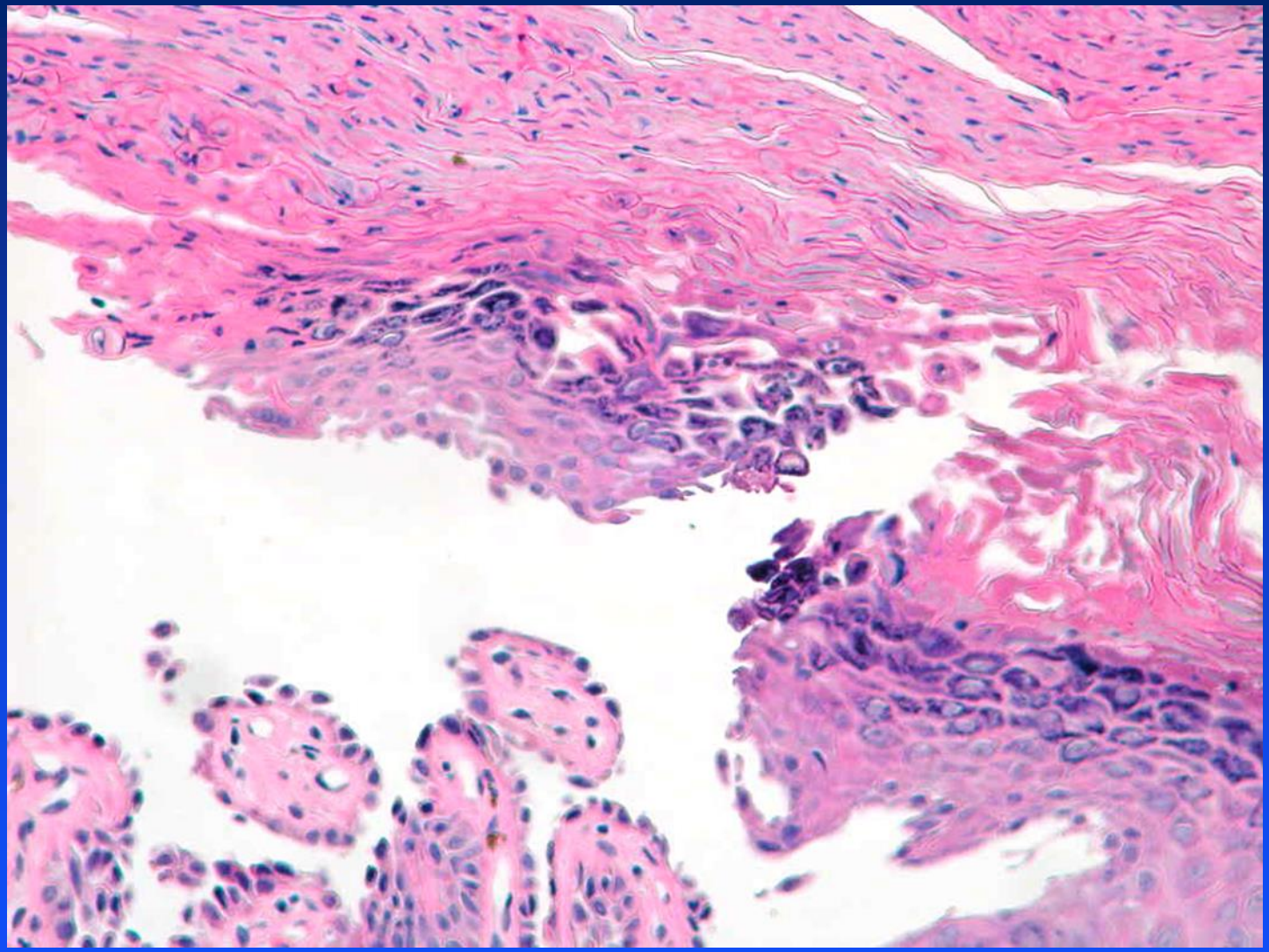
Differential diagnosis

- Hailey-Hailey disease
- Grover's disease
- Darier's disease
- Acantholytic actinic keratosis
- Focal acantholytic dyskeratosis

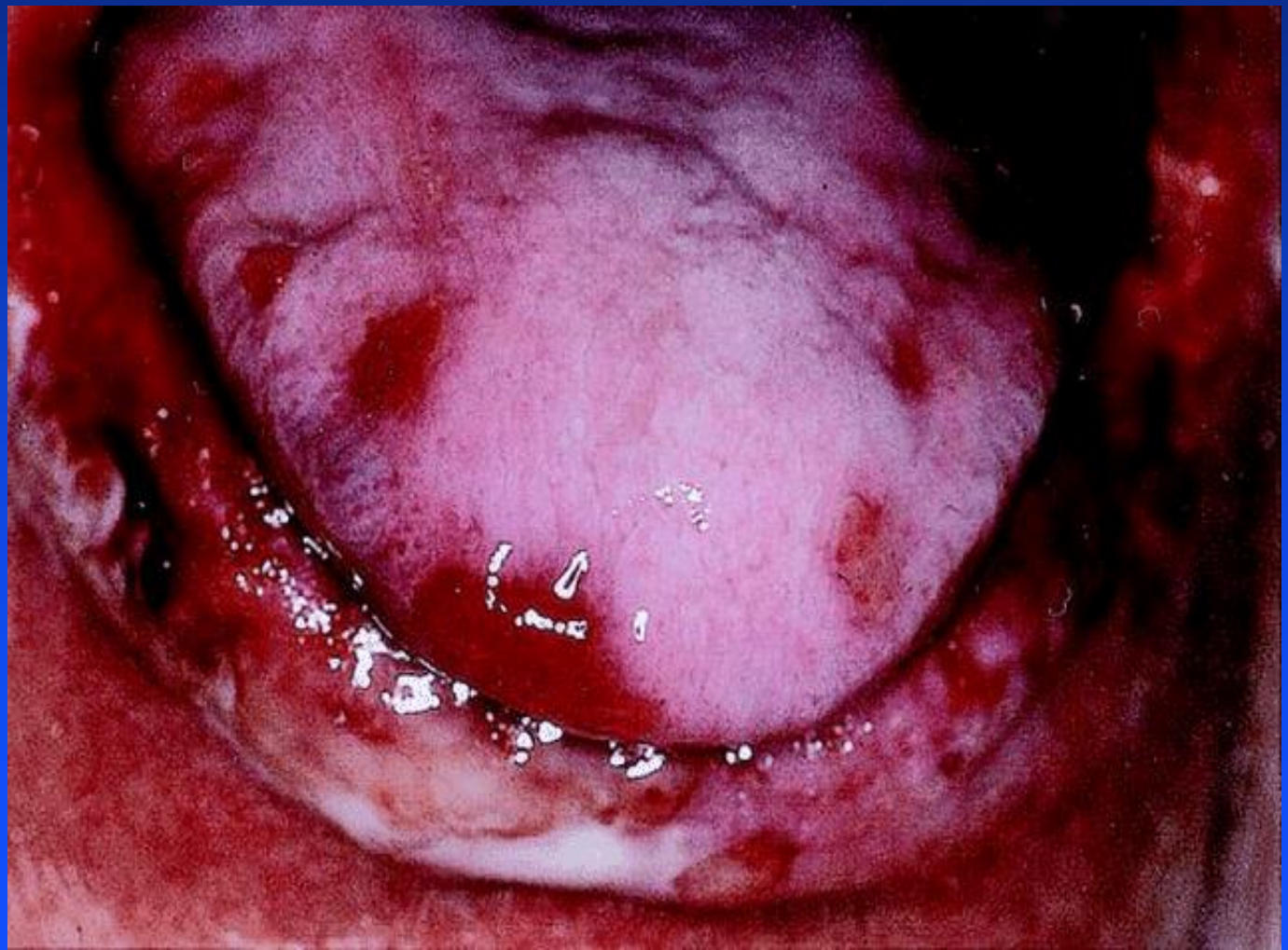


Darier’s

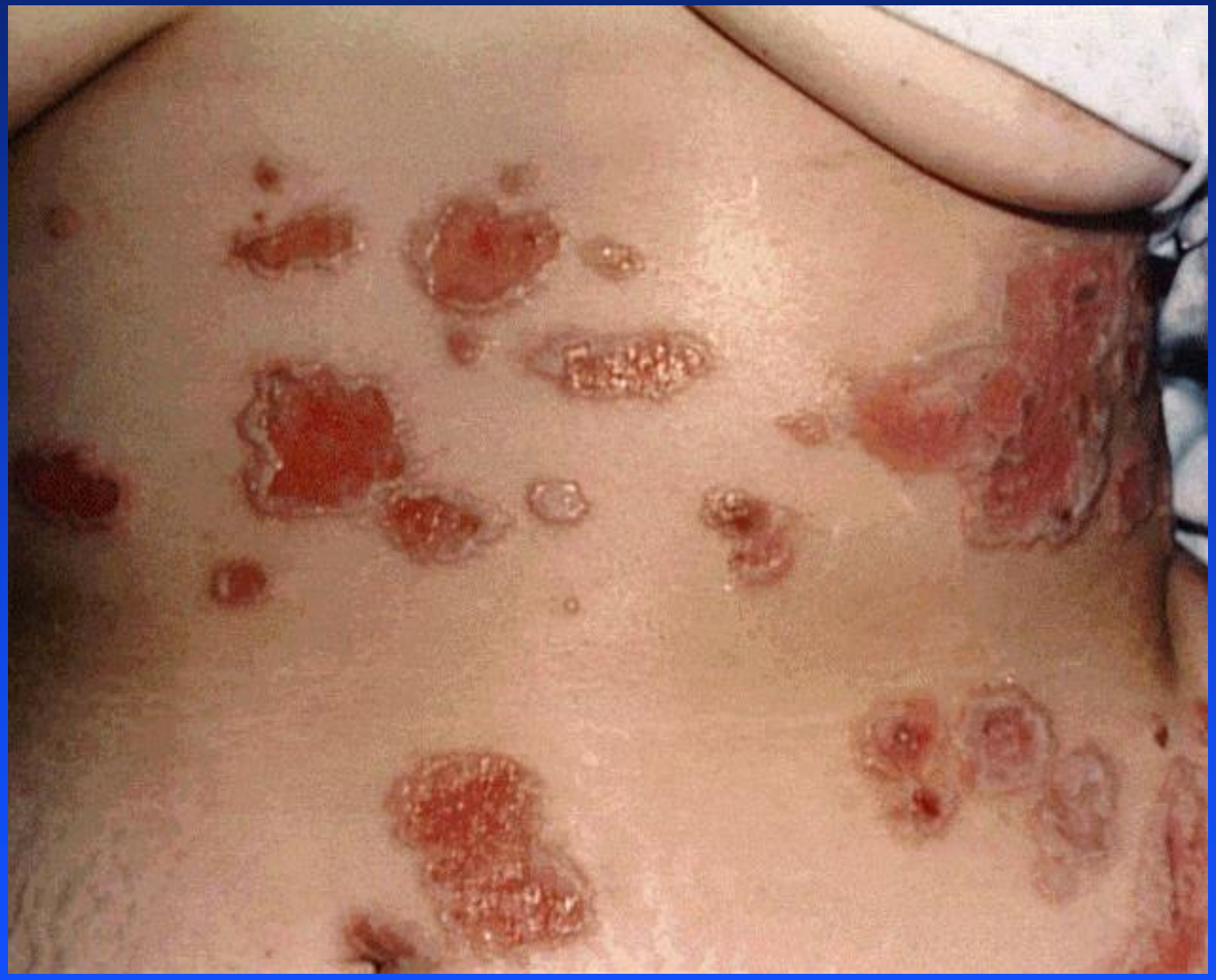


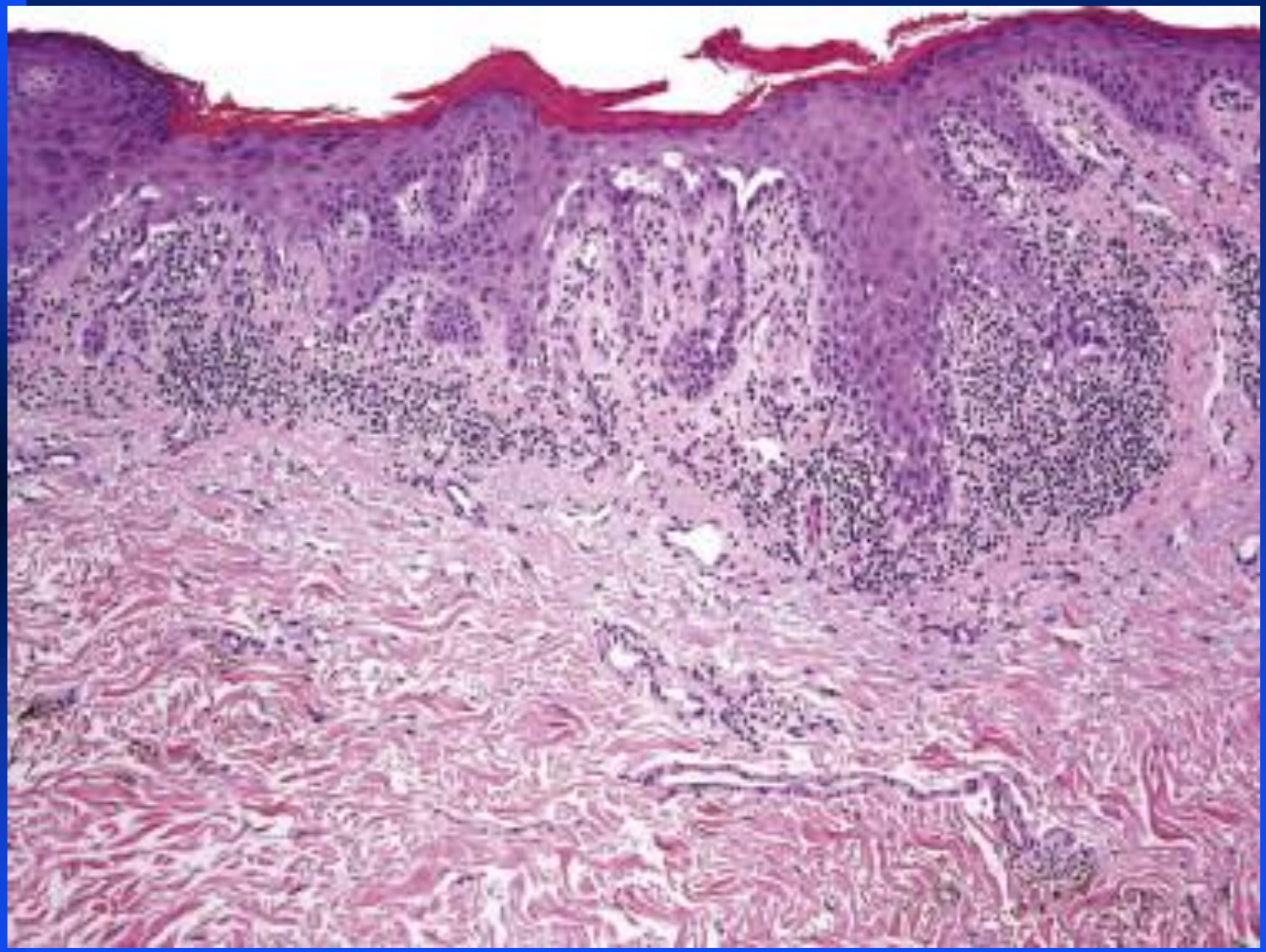
Darier’s

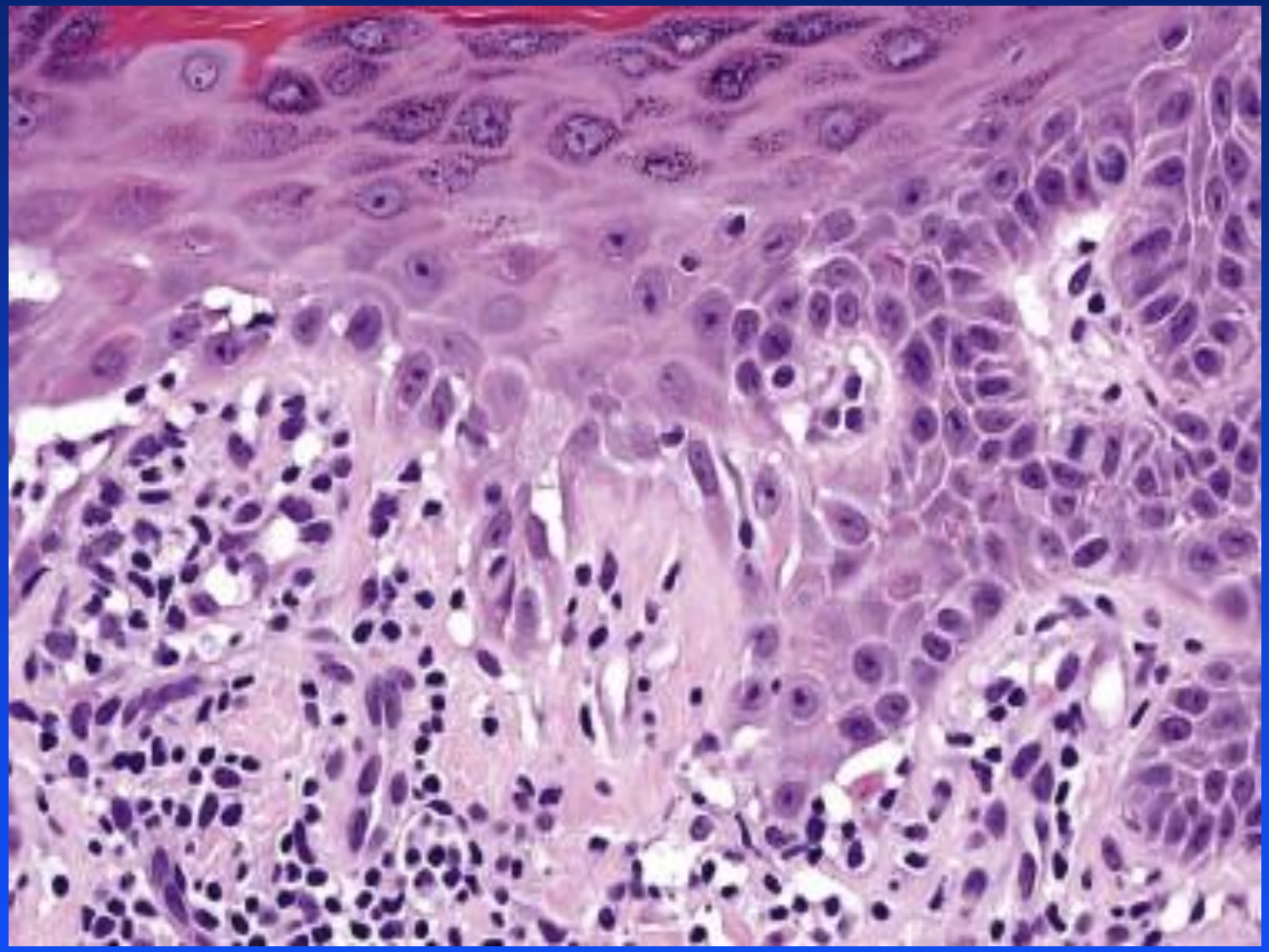
Paraneoplastic Pemphigus

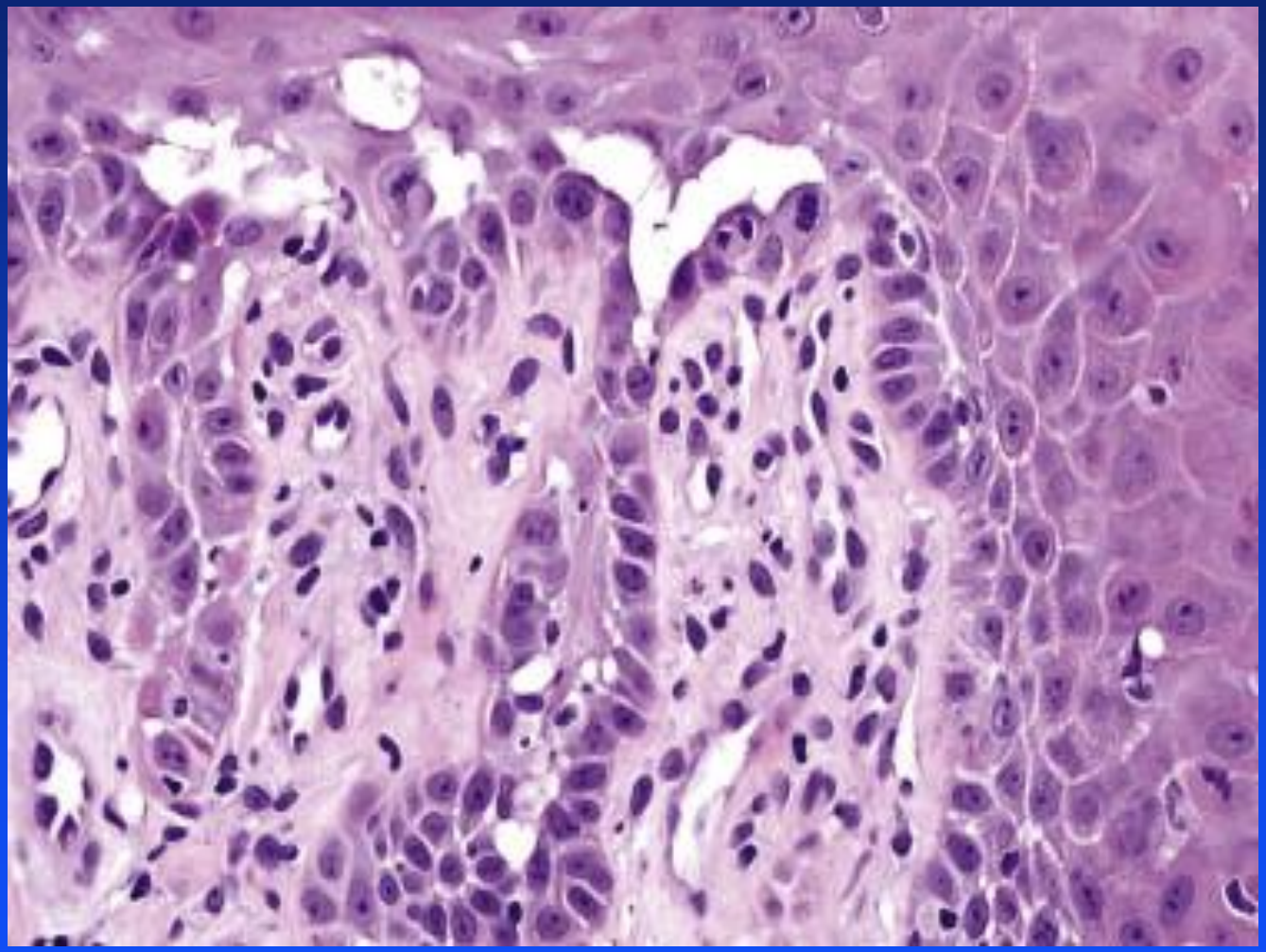


Paraneoplastic Pemphigus









PARANEOPLASTIC PEMPHIGUS

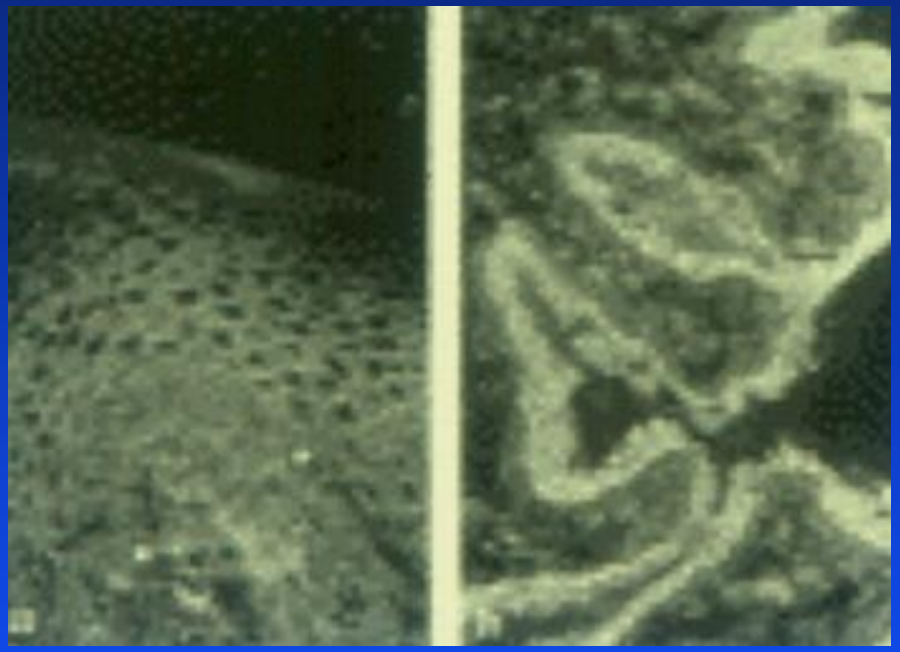
Paraneoplastic Pemphigus

- Clinical
  - Age- adults, older
  - Morphology- polymorphous: vesicles, bullae, targetoid, urticarial, papules, pustules features of both EM and PV; BP or LP
    - Classic lesion- hemorrhagic mucosal erosions
  - Distribution- mucosal surfaces: conjunctiva, oral, intertriginous, scalp
  - Extracutaneous 1) neoplasms-lymphoreticular (CLL, NHlymphomas), Castleman's tumor, many other tumors 2) Br Obl

Paraneoplastic Pemphigus

- Histology
  - PV like- acantholysis with intraepidermal blister formation
  - EM like- lichenoid/interface dermatitis with dyskeratosis, exocytosis
- Immunofluorescence-
  - Direct- IgG or C3 cell surface intercellular frequently also linear/granular at BMZ
  - Indirect- (+) to rat bladder

Paraneoplastic pemphigus



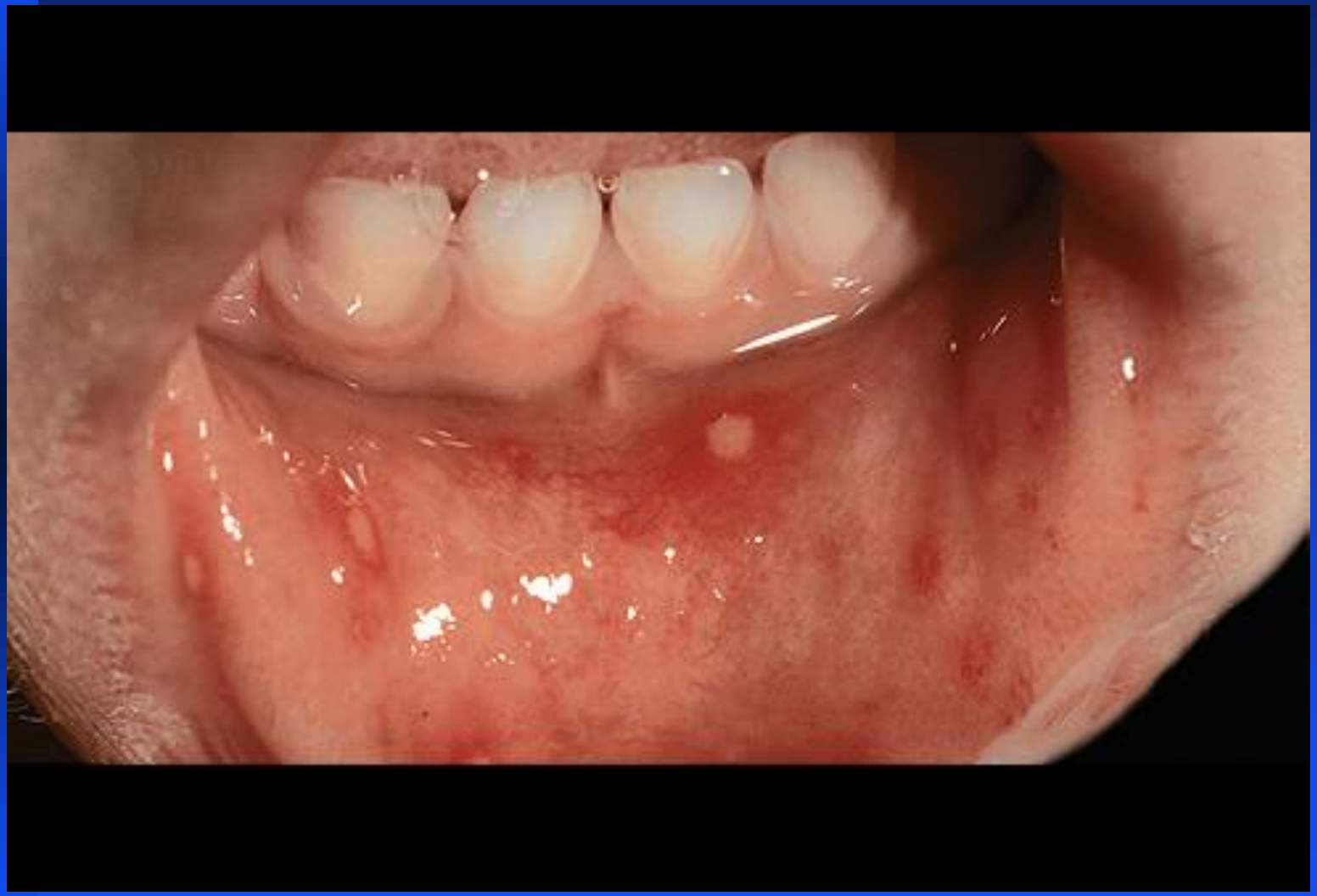
Direct IgG

Indirect: IgG
Rat bladder

Both tests can weakly positve or negative!

Paraneoplastic Pemphigus: Antigens

- 500 kd: plectin
- 250 kd: desmoplakin I
- 230 kd: BP 230
- 210 kd: envoplakin highly specific
- 190 kd: periplakin highly specific
- 170 kd: alpha-2-macroglobulin like 1
- Many others: Dsg1, Dsg3, DC2, 3

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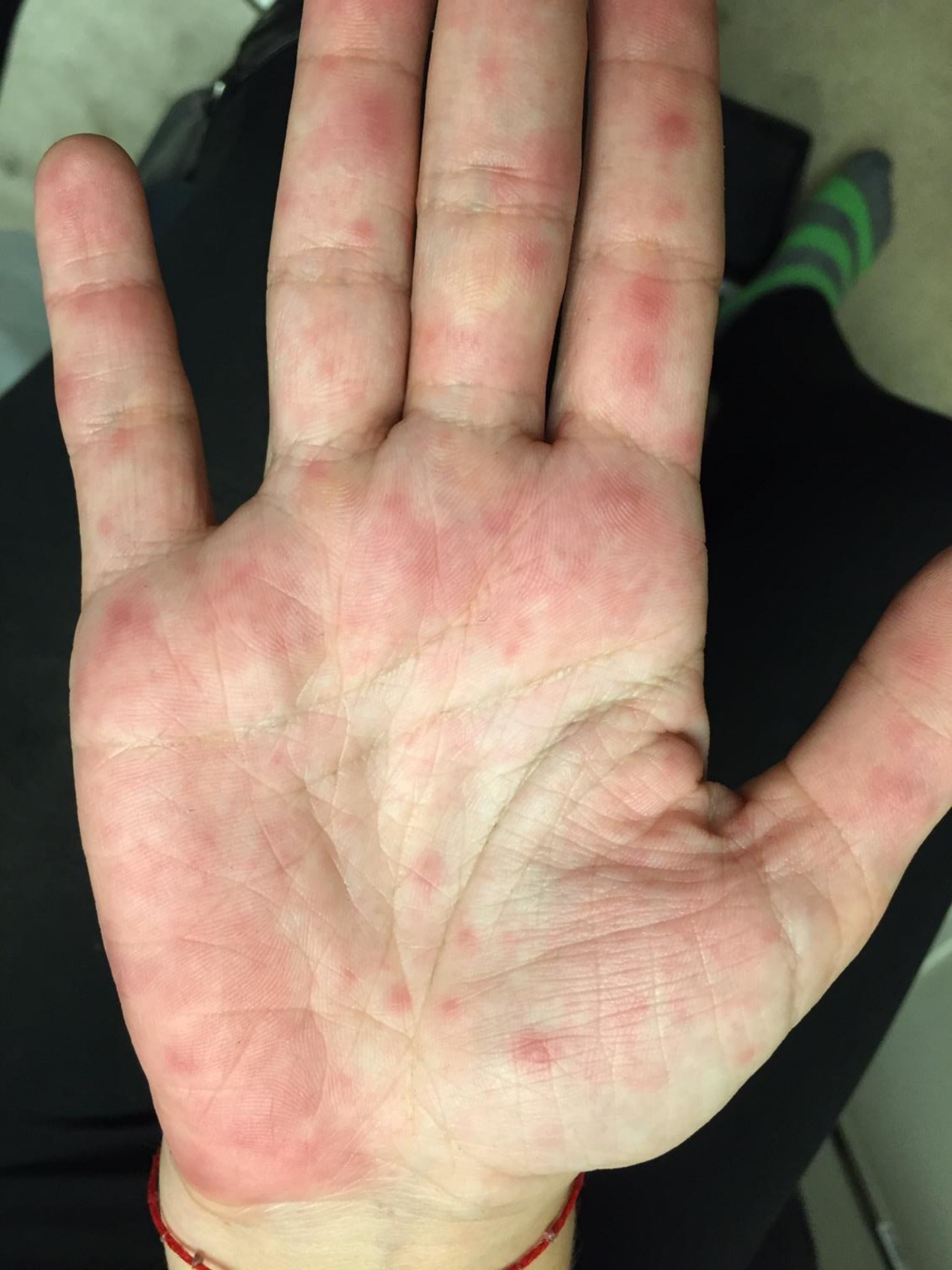
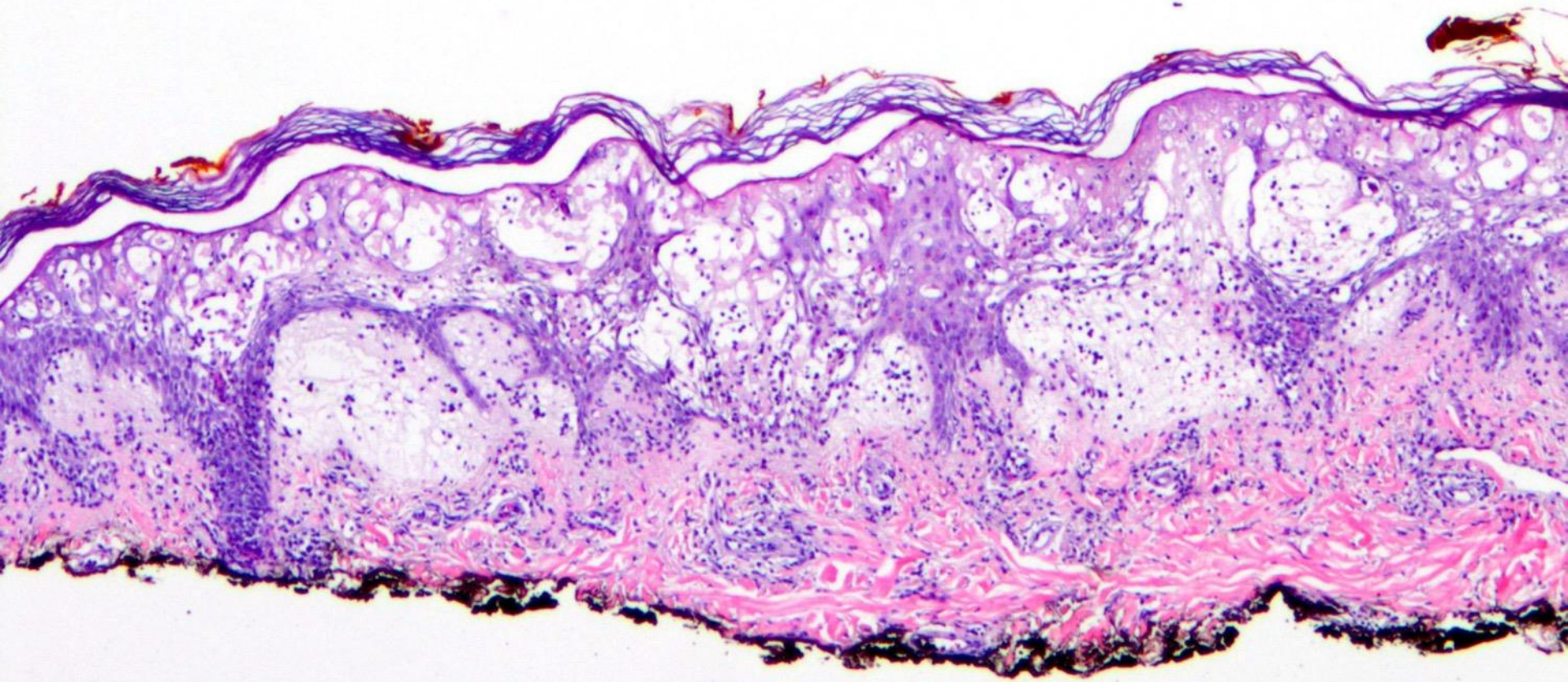
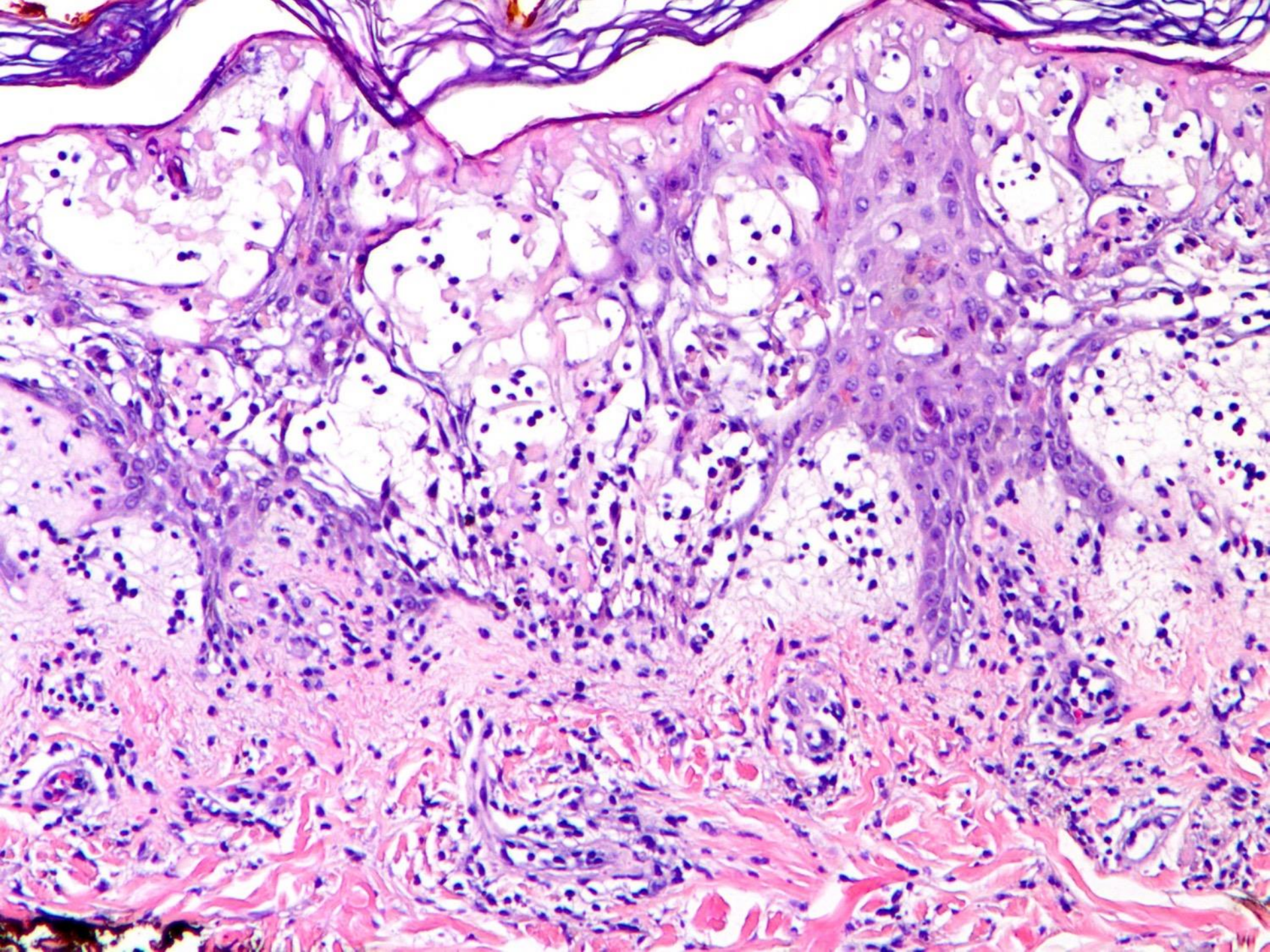
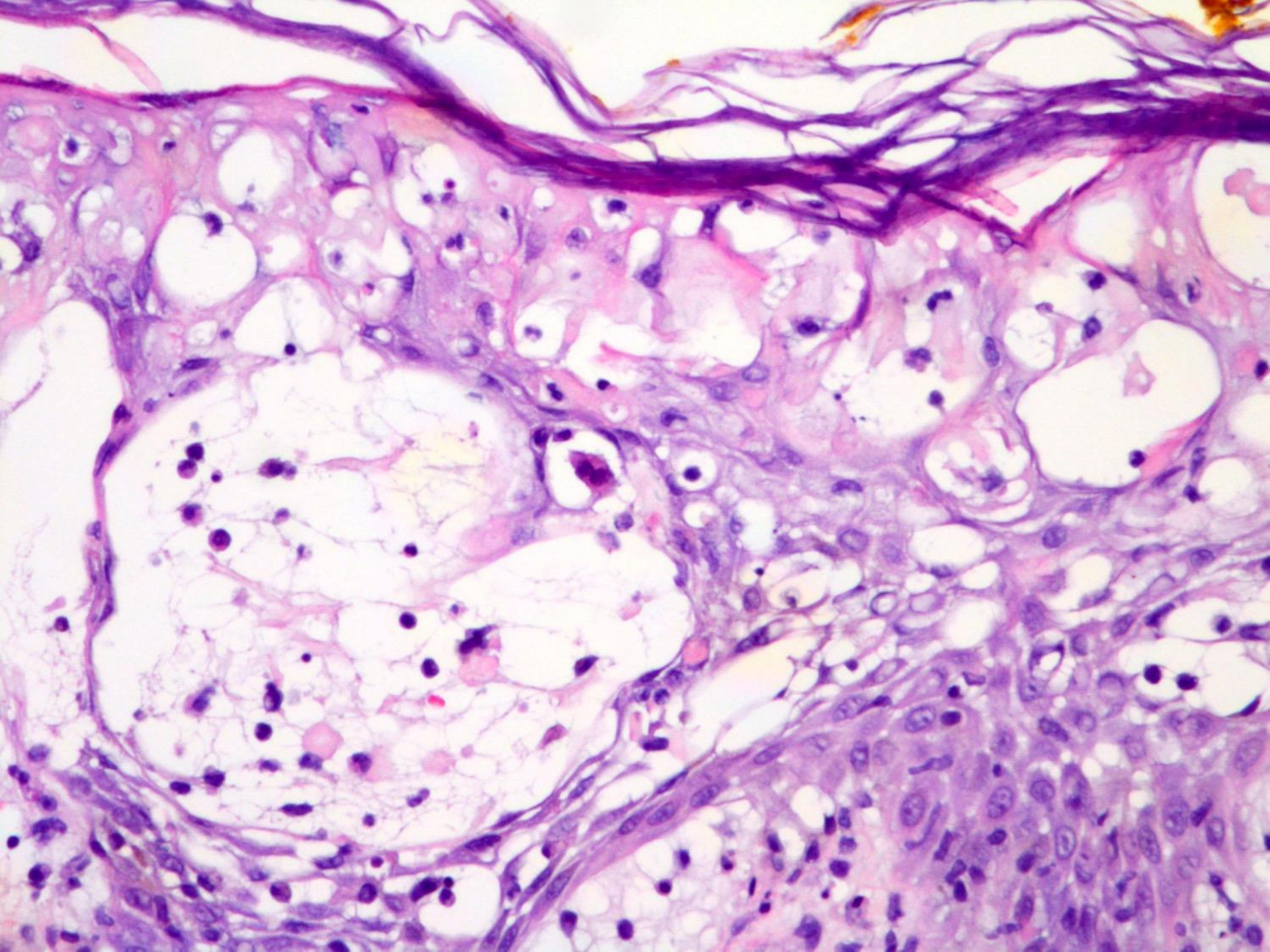








Hand foot and mouth disease

Clinical features

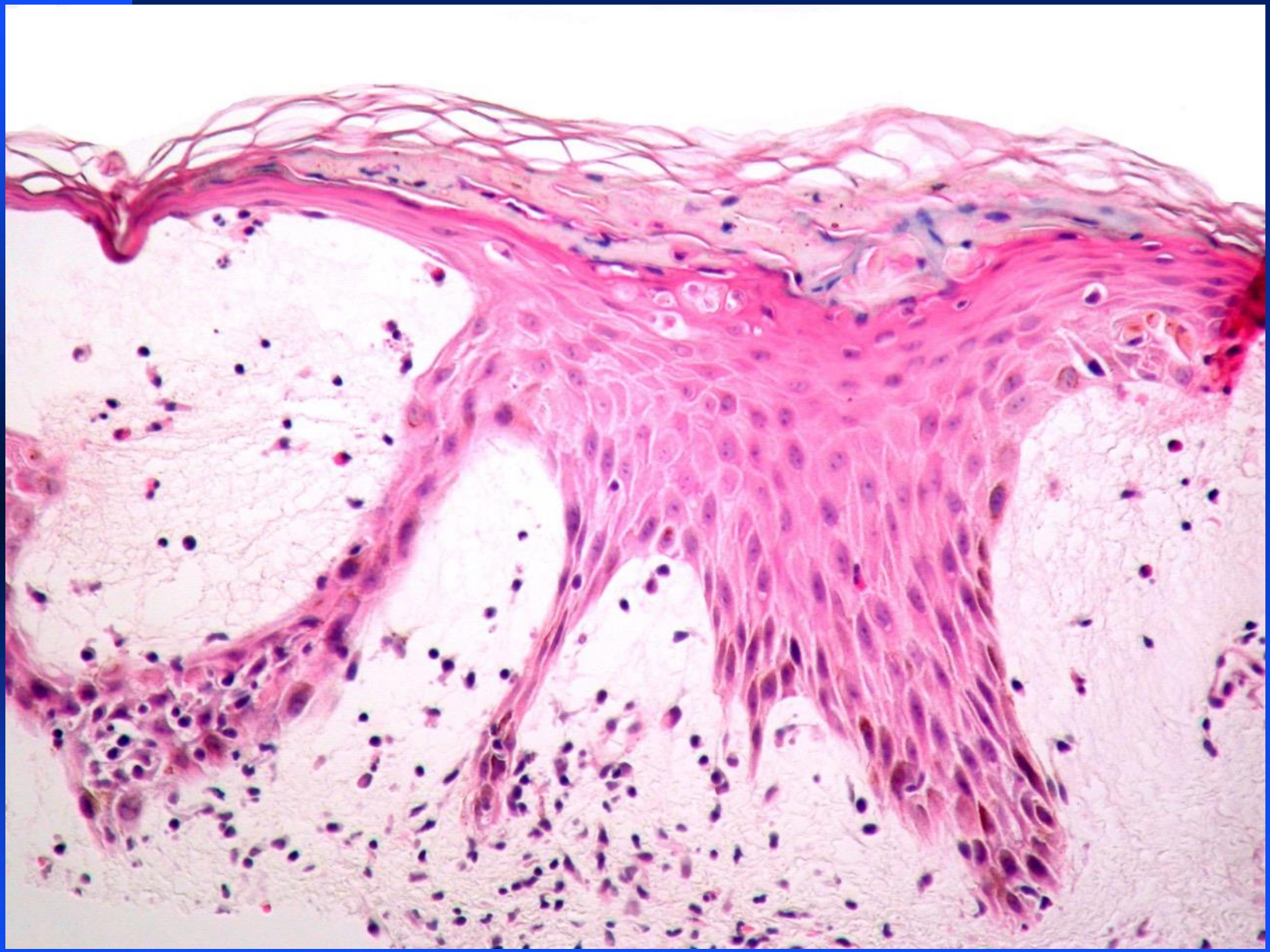
- More often in children
- Fever malaise
- Vesicles in anterior mouth
- Palms and soles vesicles, 3-7mm other sites
- Occasional cases with systemic disease, neurologic
- Coxsackie virus A16, Enterovirus 71

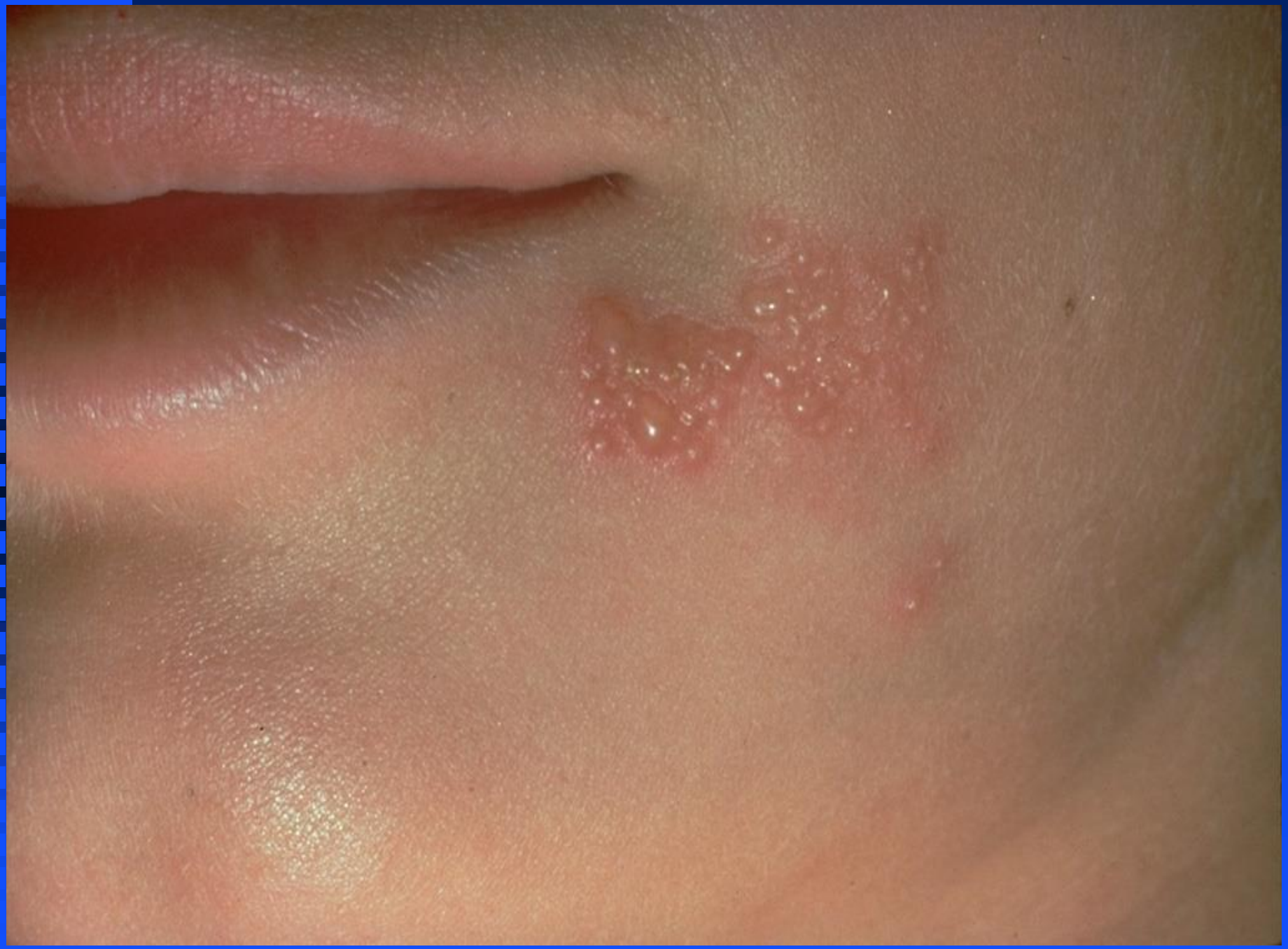
Pathology

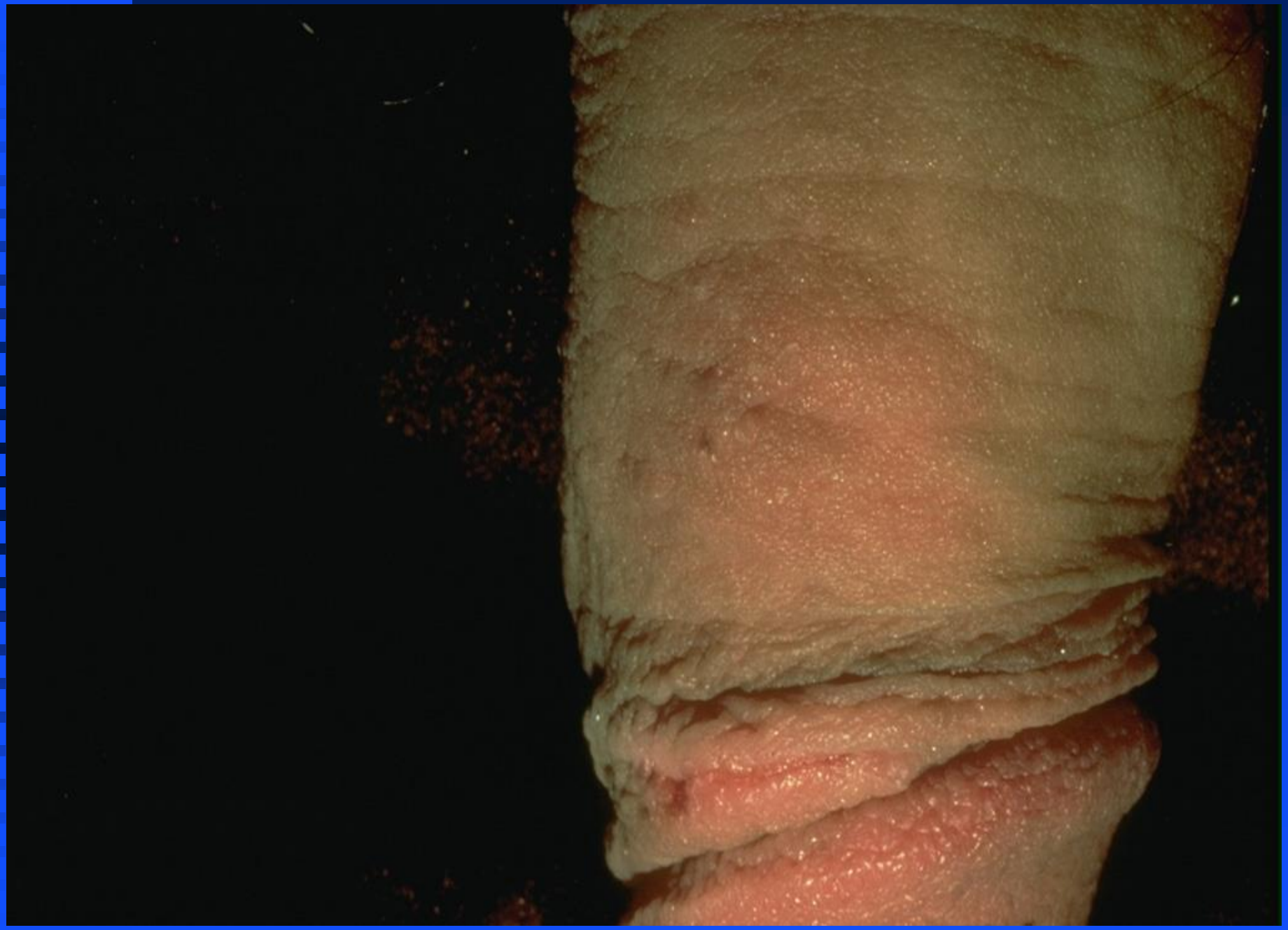
- Intraepidermal vesicle
- Massive reticular and ballooning degeneration (edema) of the epidermis
- No inclusions
- Massive edema of the papillary dermis
- Perivascular infiltrate

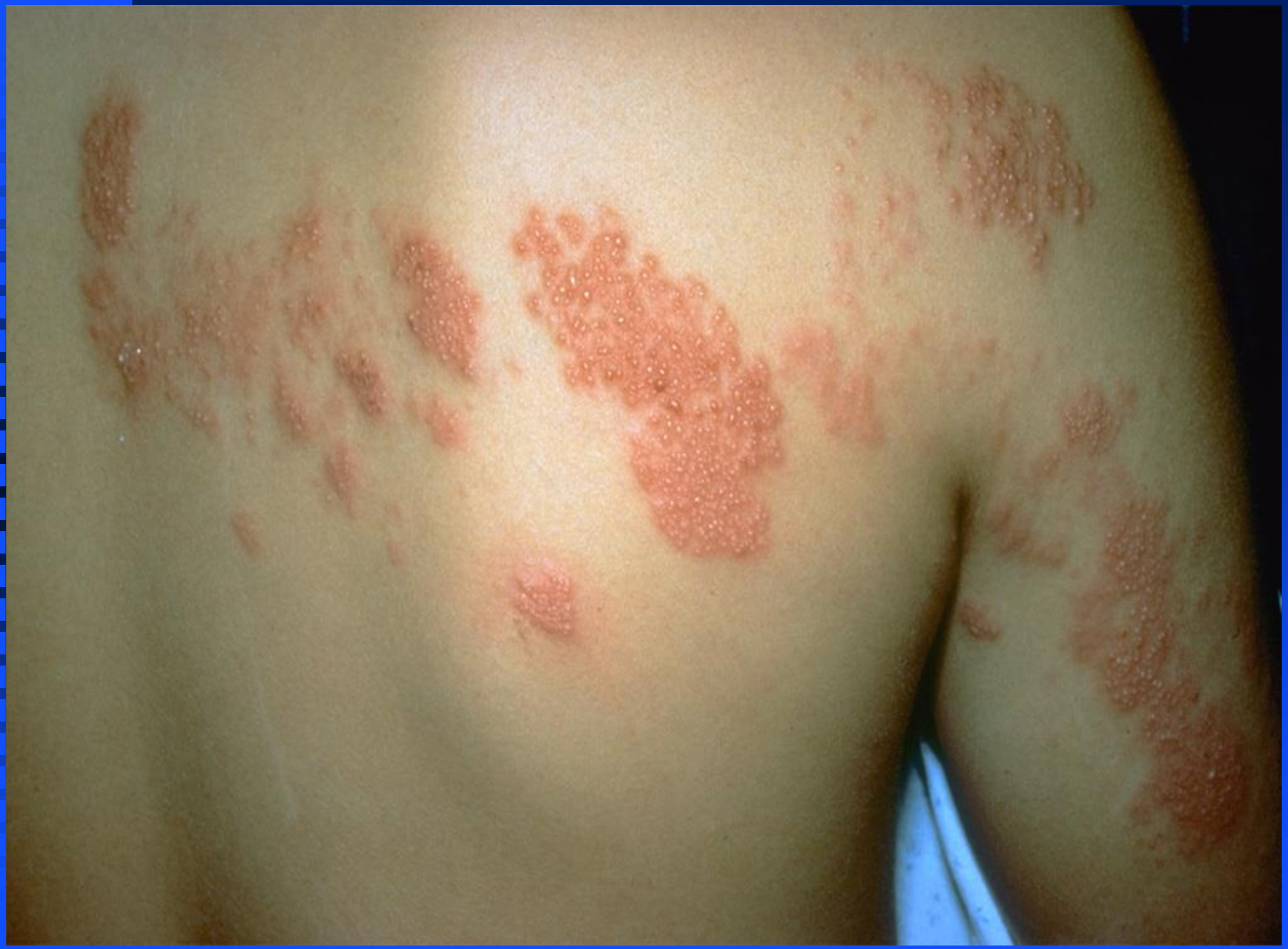
Differential diagnosis

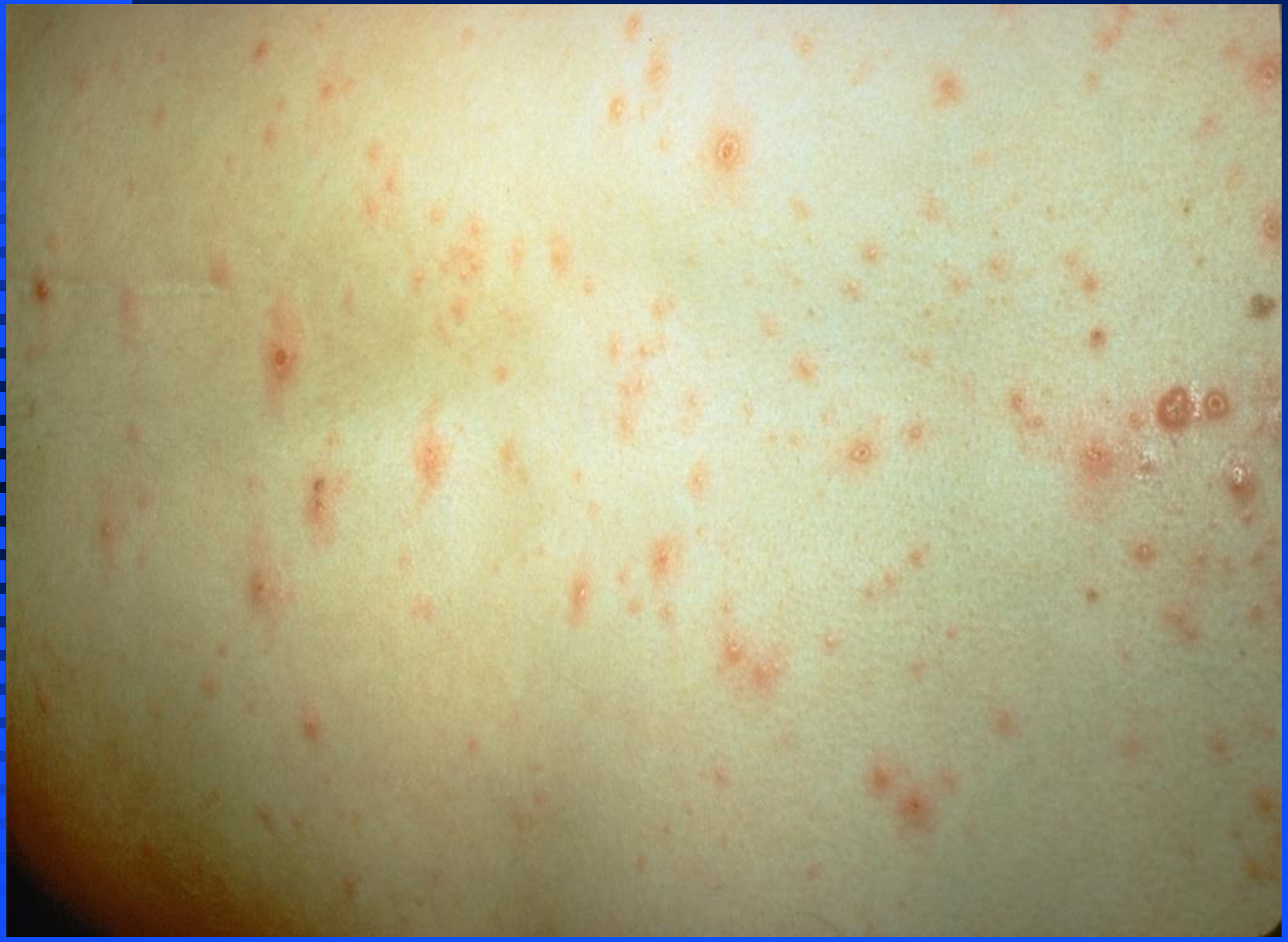
- Erythema multiforme
- Other viral infections-pox, herpes
- Severe acute spongiotic (irritant) dermatitis

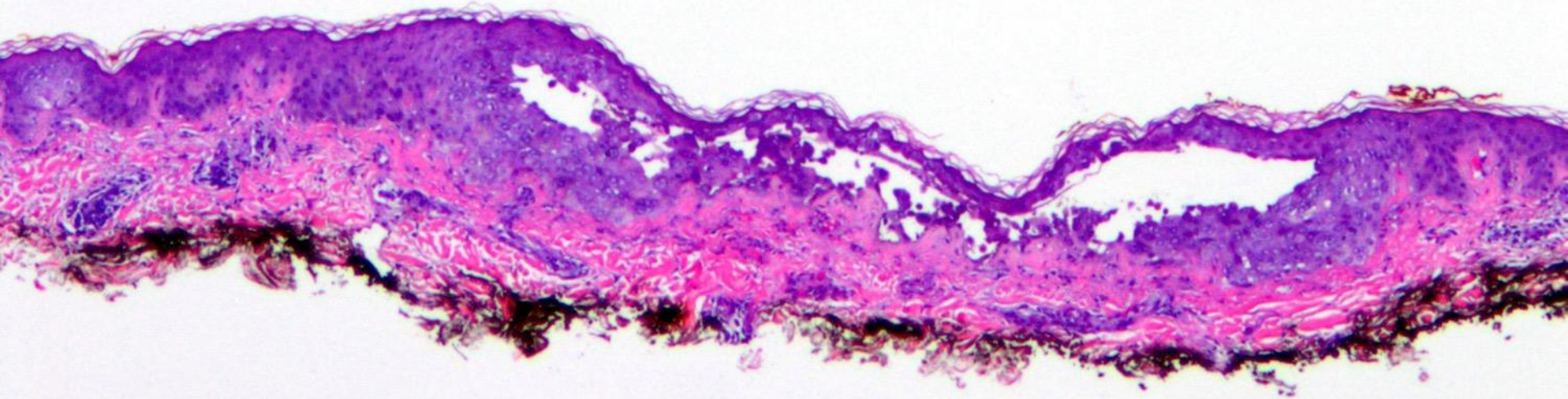


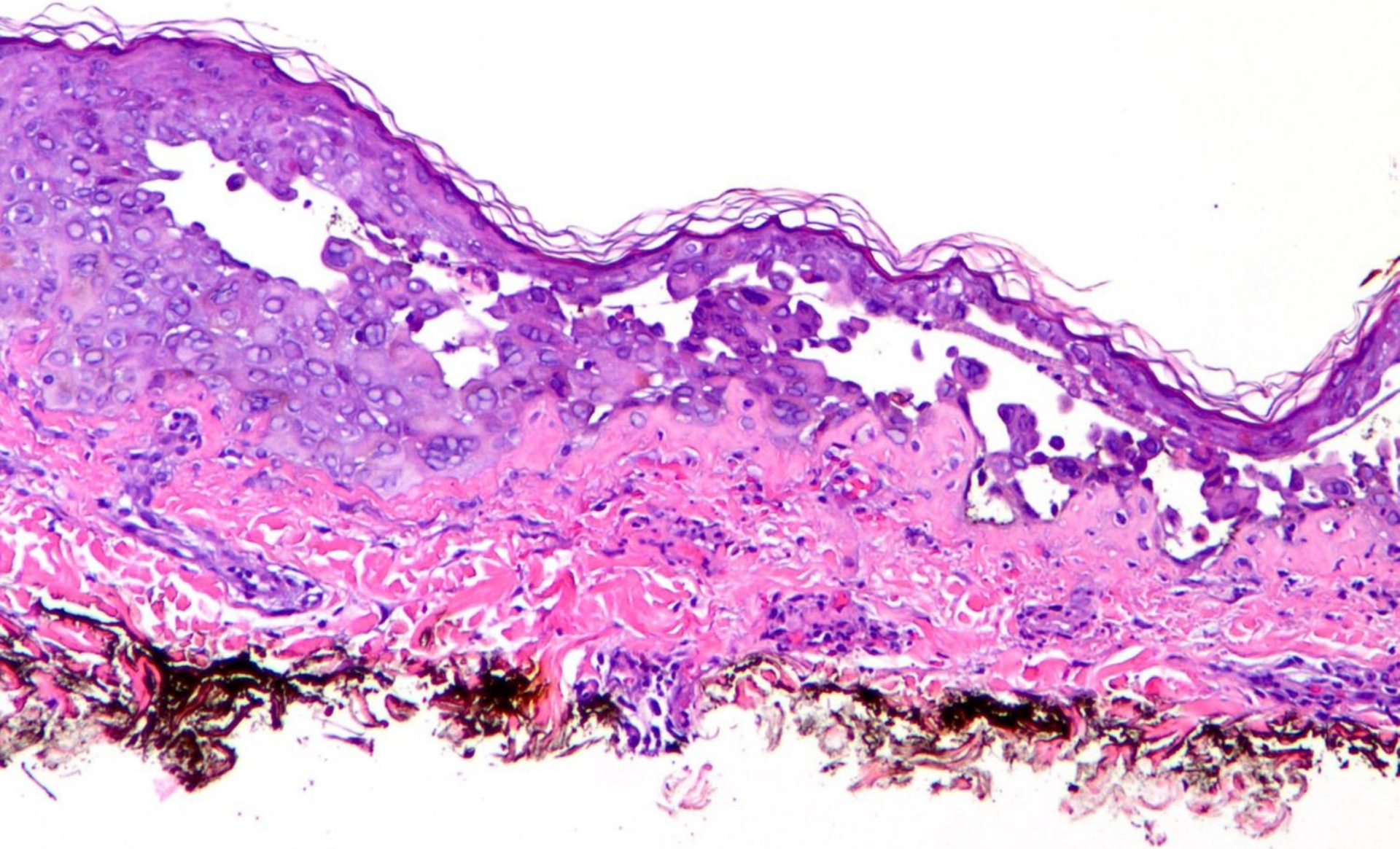


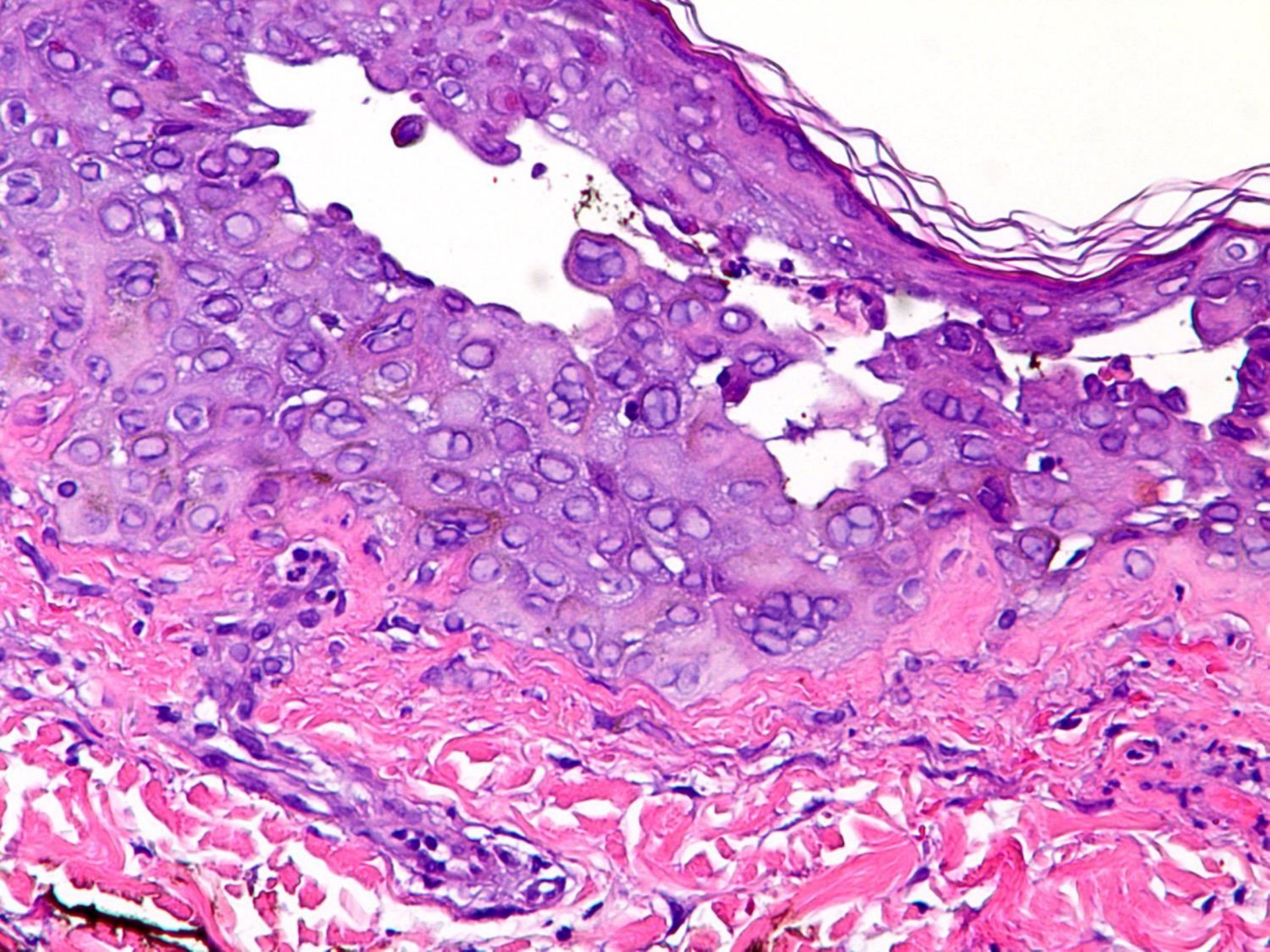


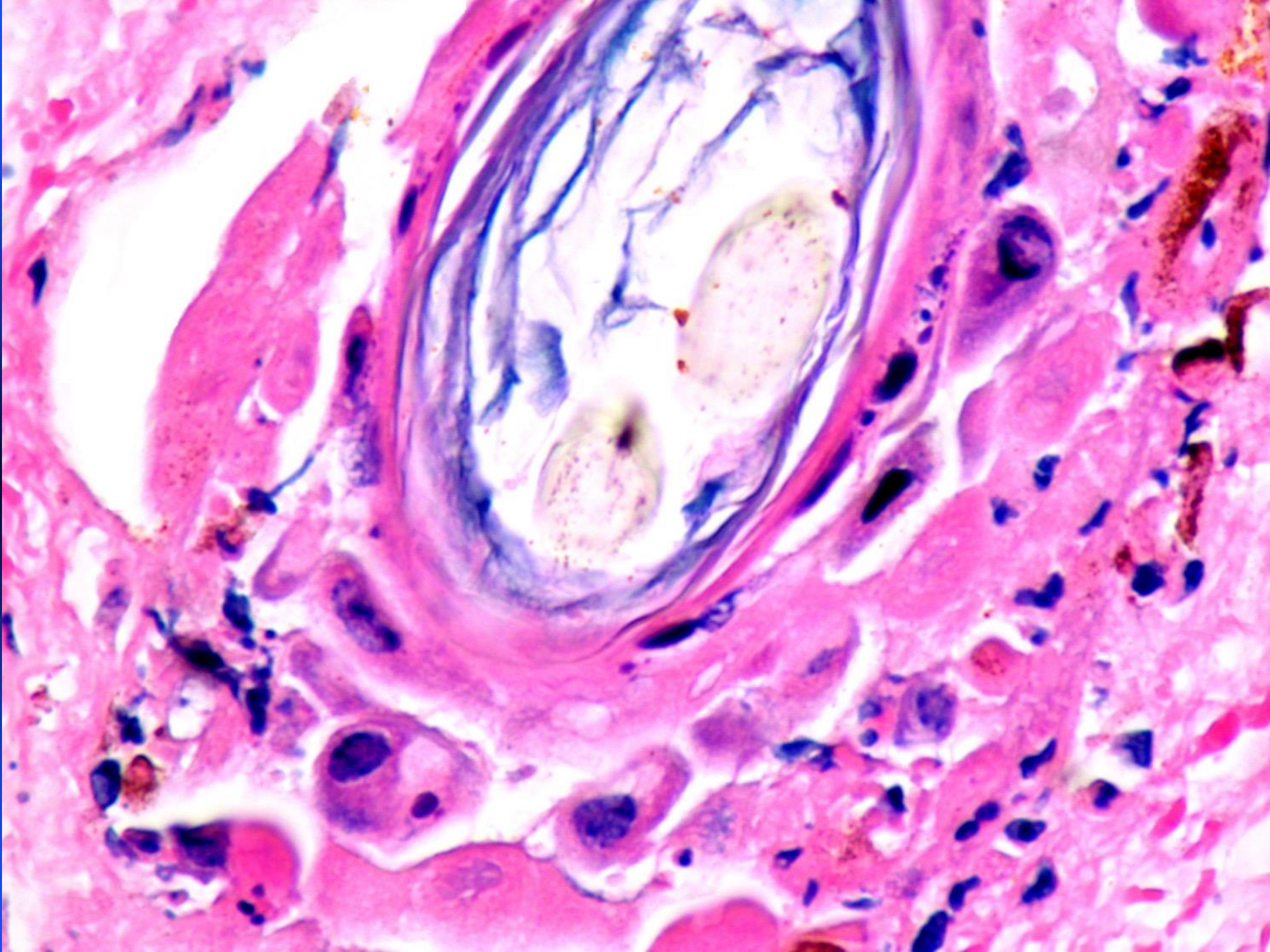


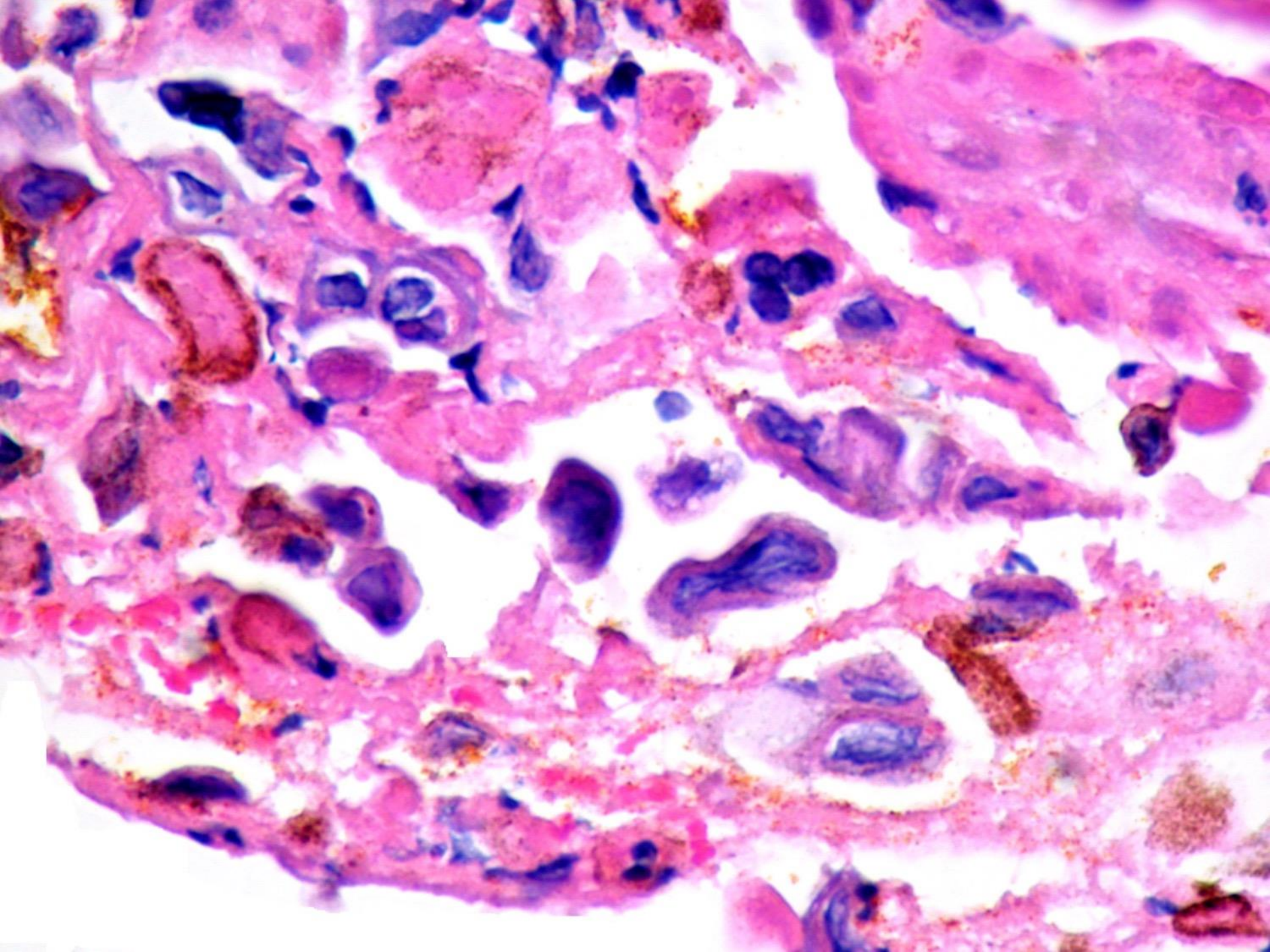












Herpes infection: HSV1, HSV2, VZV

Clinical features

- Depends on type
- HSV1, 2 - grouped vesicles
- VZV, zoster-zoster grouped vesicles corresponding to a dermatome
- VZV, varicella, -disseminated eruption dewdrops on a rose petal

Herpetic infections: pathology

- Varicella versus Zoster versus herpes simplex
- The pathology of all four types of herpes can be identical; though there may be differences

Herpetic infections: pathology

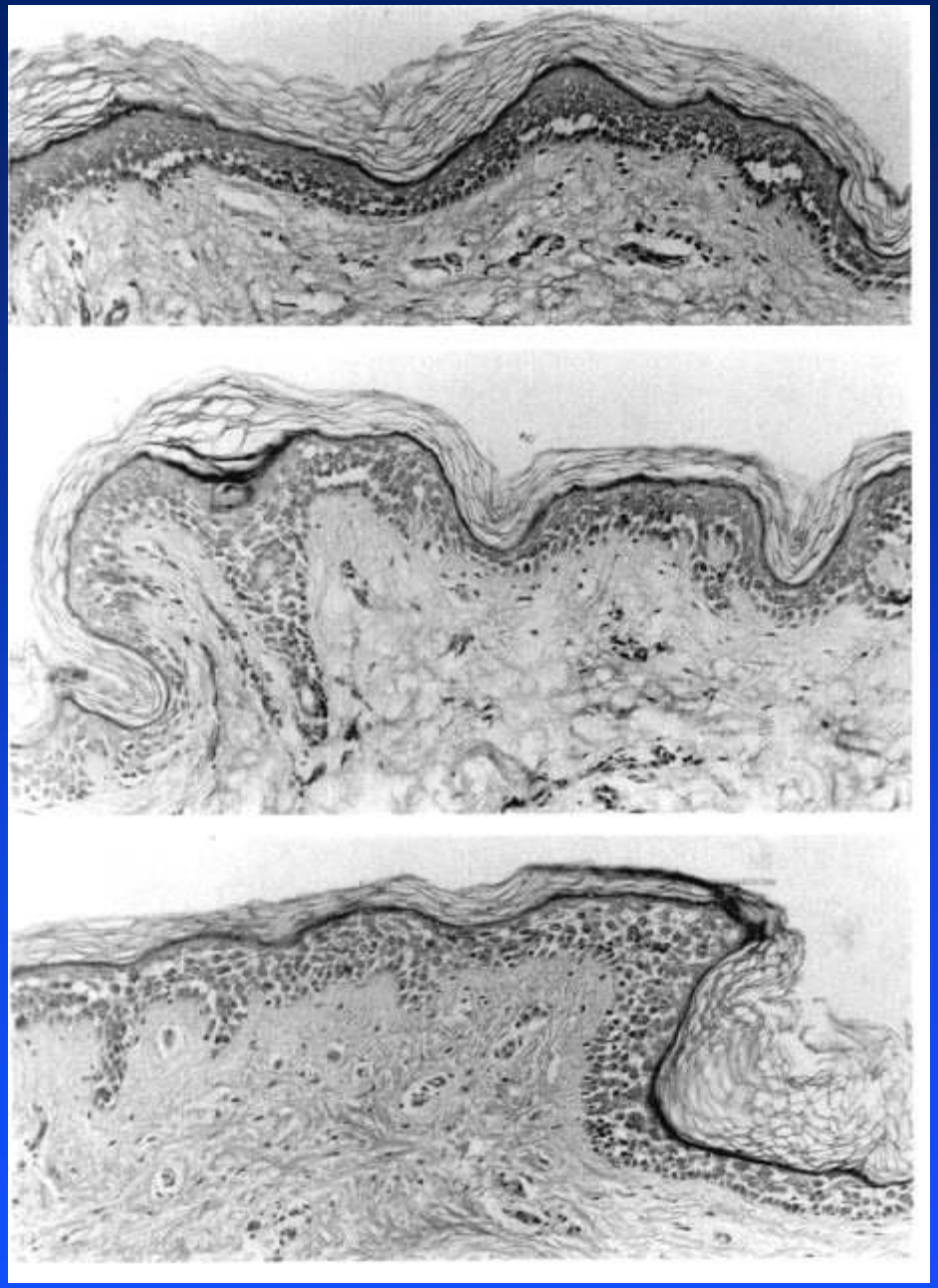
- Inclusions: clumping of chromatin, ground glass appearance
- Mulinucleated keratinocytes
- Ballooning degeneration, reticular degeneration, necrosis
- Secondary acantholysis
- Vesiculation
- Variable infiltrate, neutrophilic,

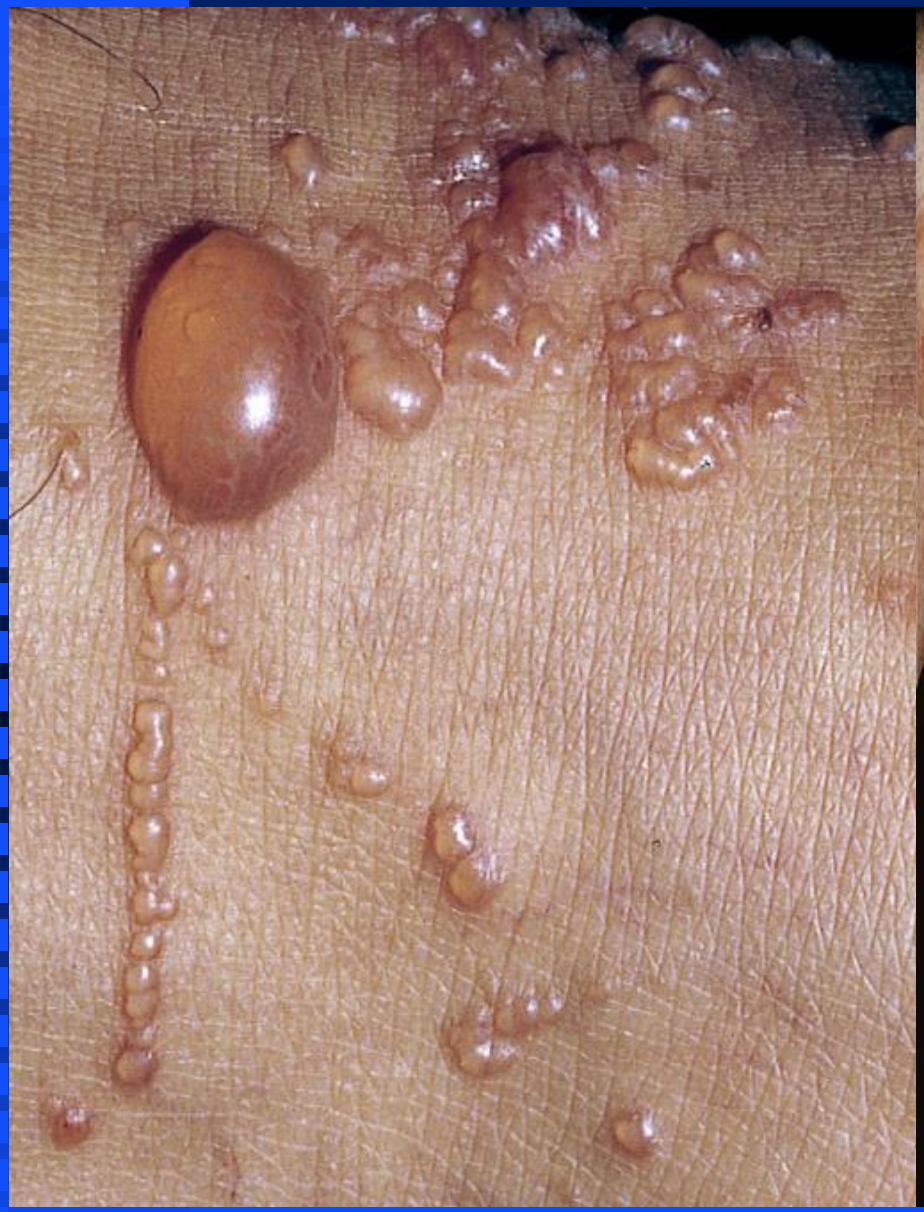
Herpetic infections: pathology

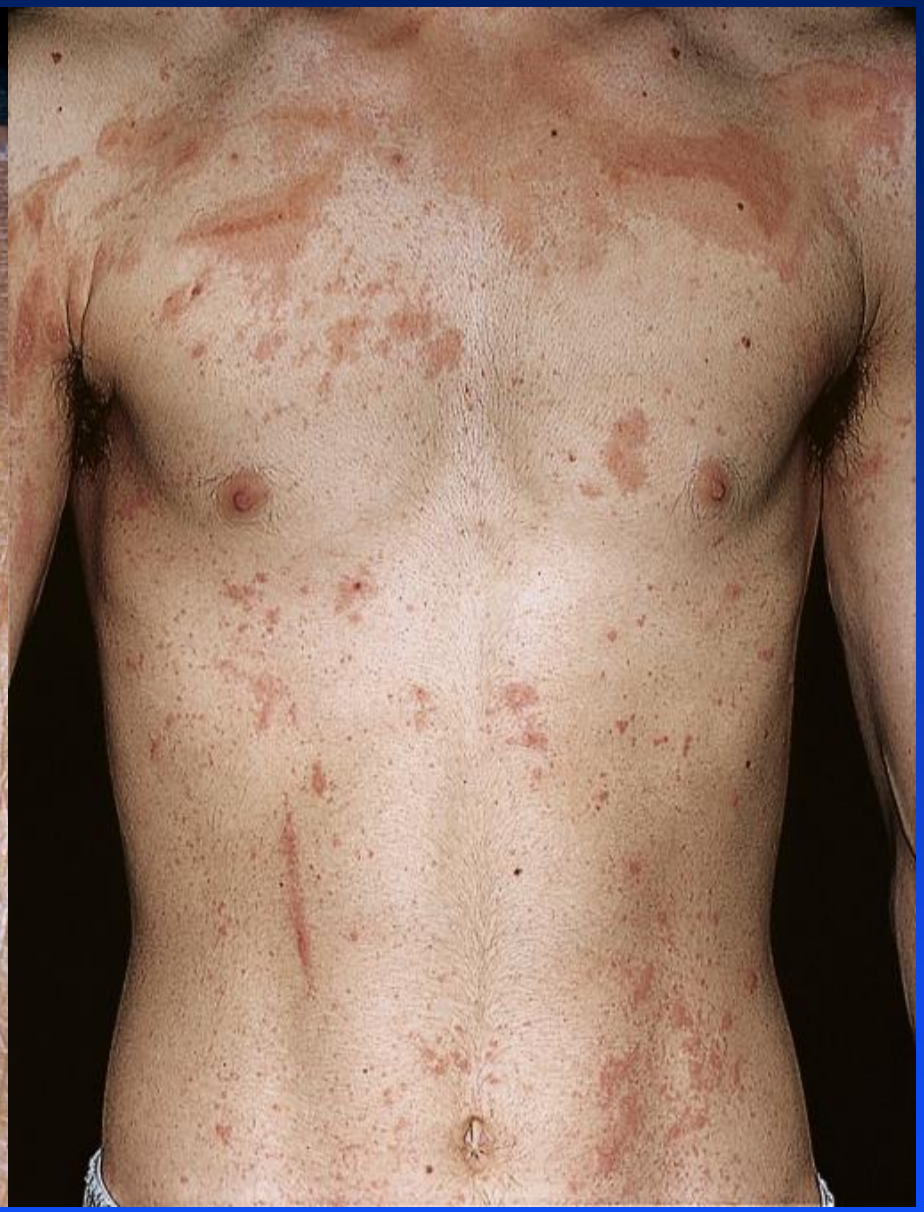
- Herpetic vasculitis
- Herpetic folliculitis
- Neuronal involvement
- All more common with VZV

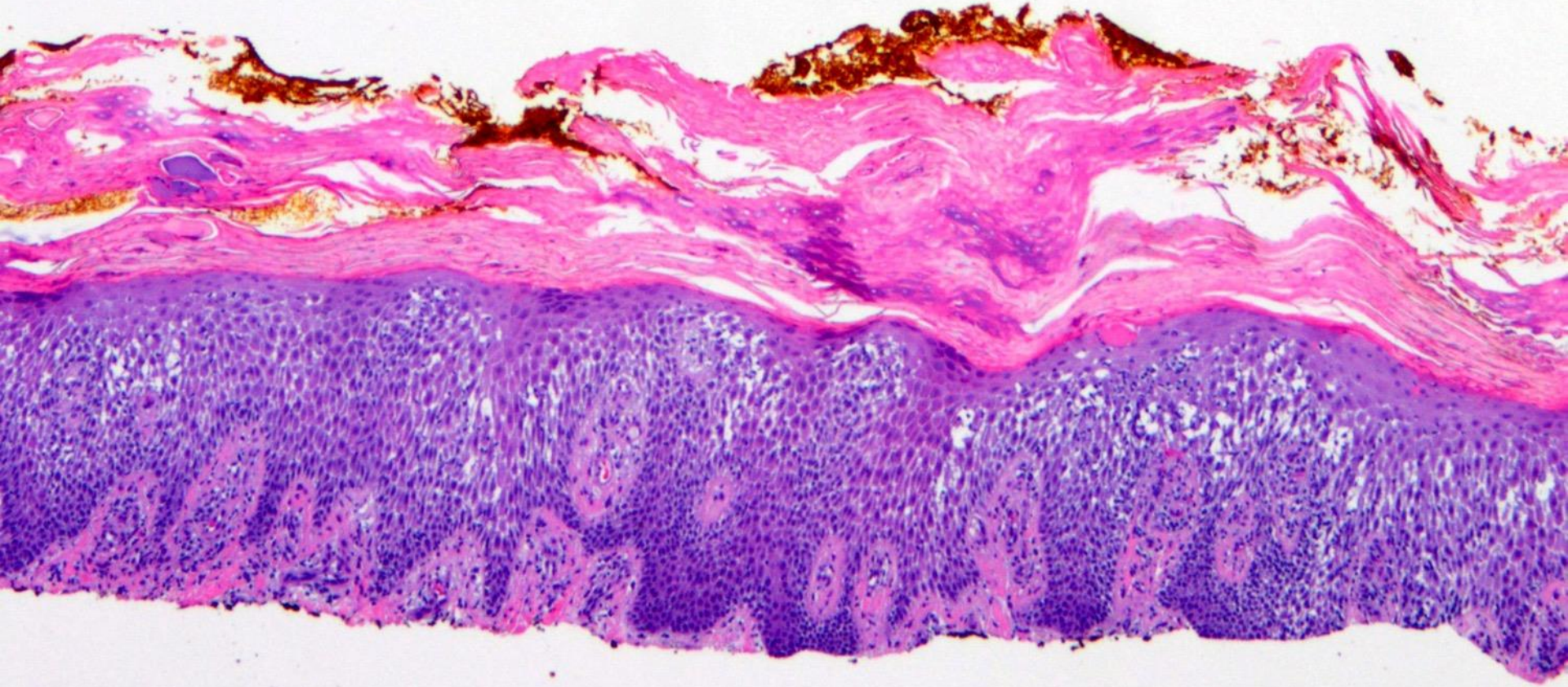
Differential diagnosis

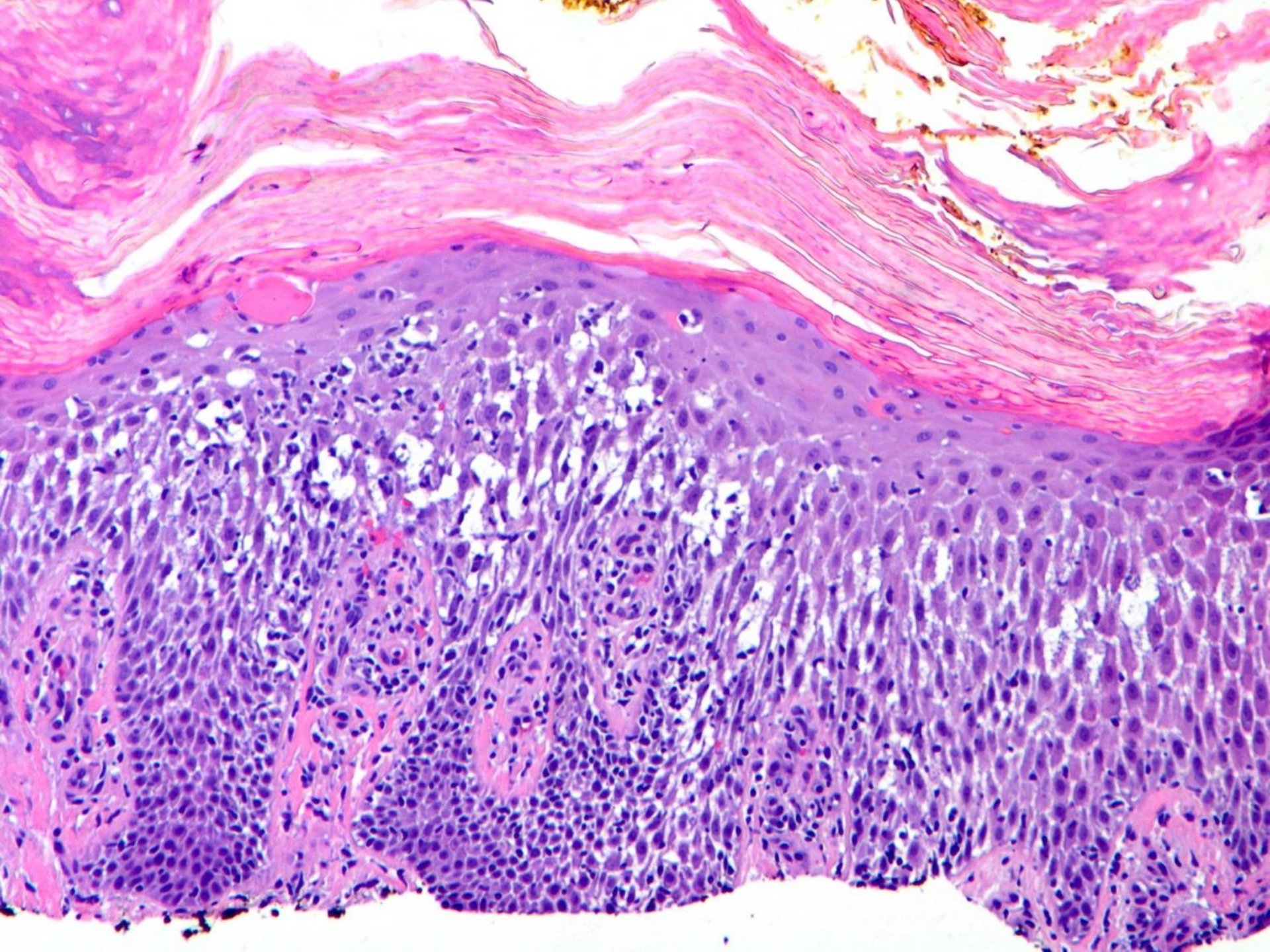
- Acantholytic disorders
- Severe acute contact with acantholysis (cantharidin)
- Erythema multiforme

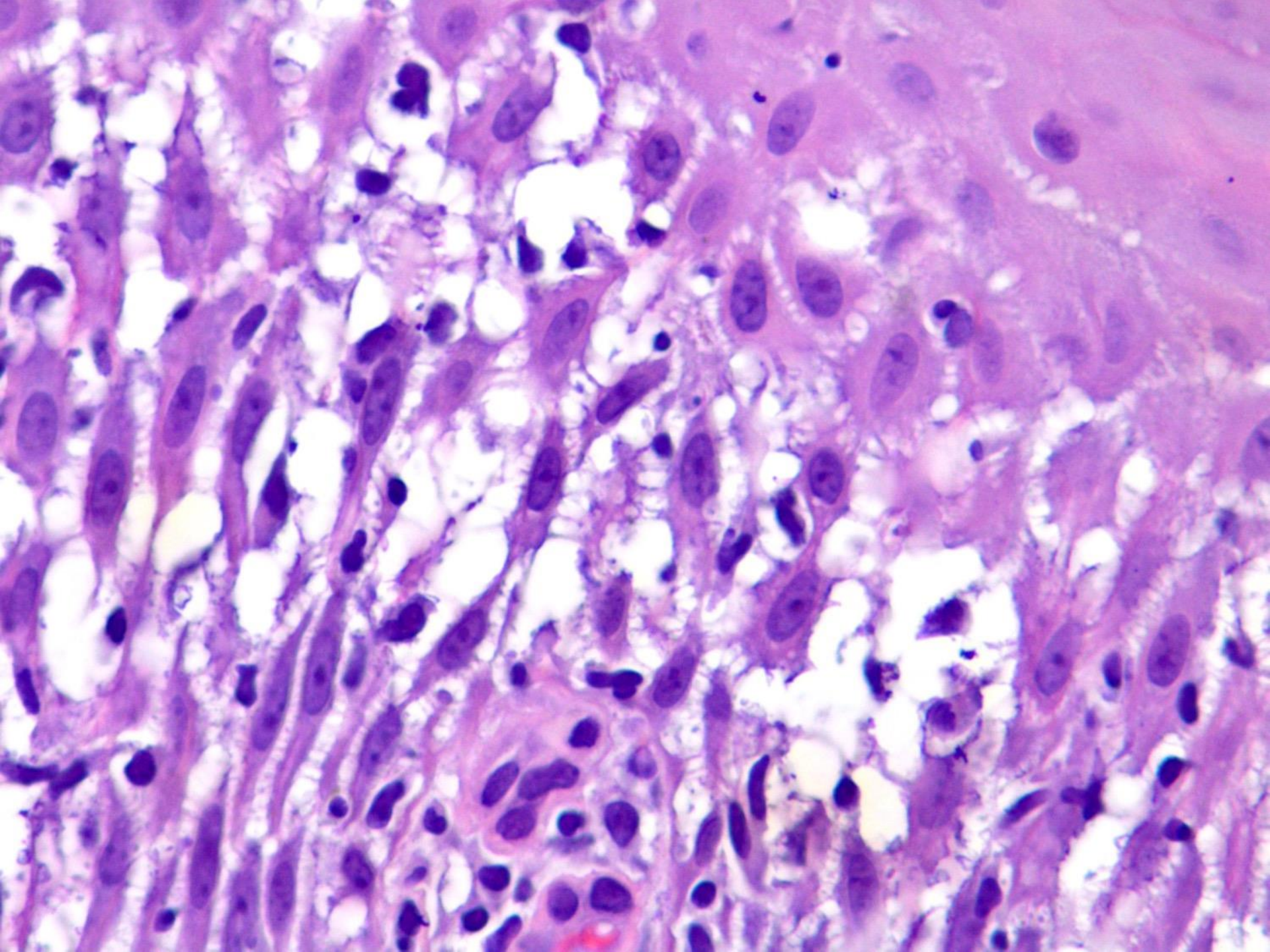












Subacute spongiotic dermatitis

Clinical features

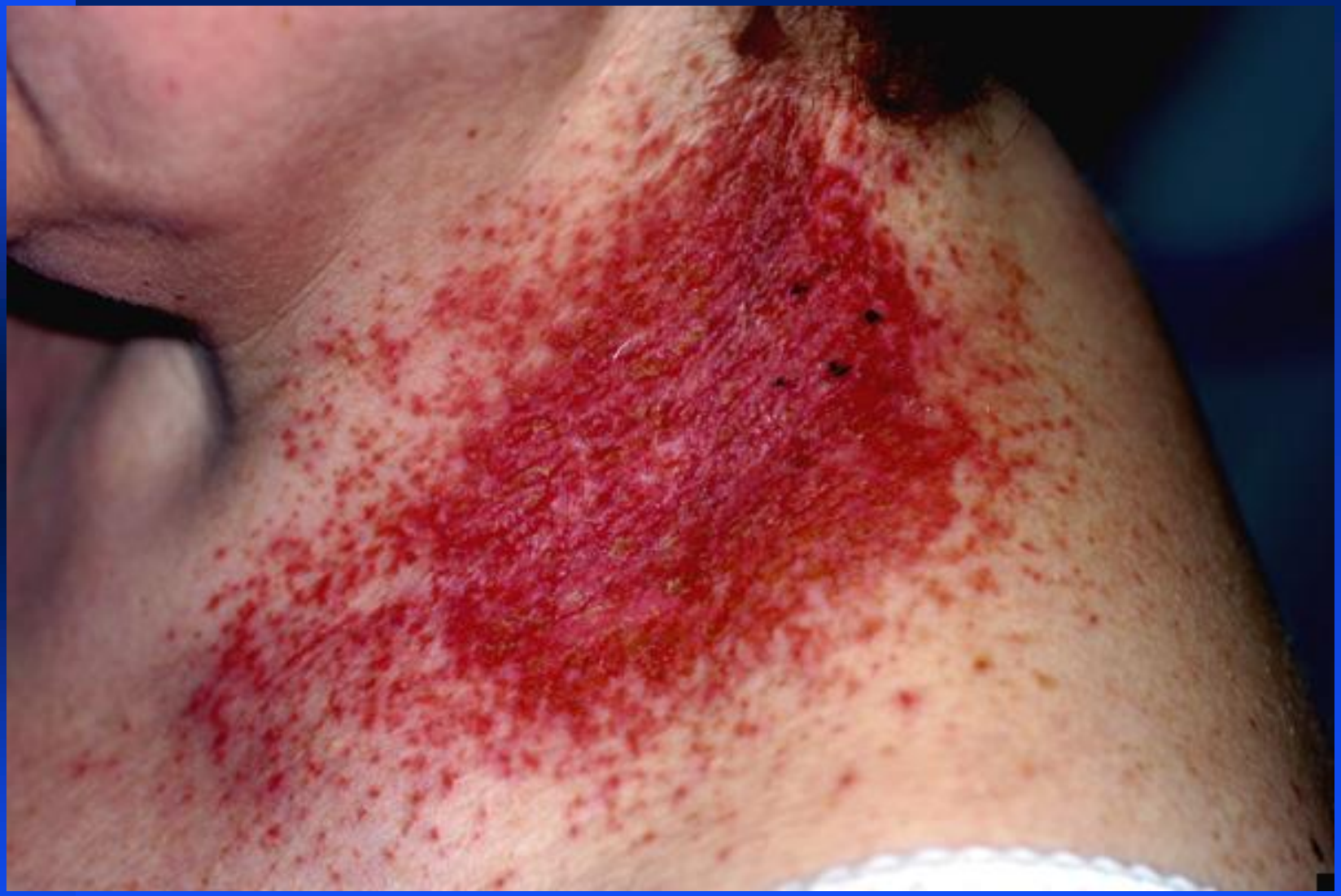
- Erythema, swelling
- Papules and vesiculation
- Scaling and lichenification if chronic
- Follows distribution of contact-often linear or in bizarre configuration

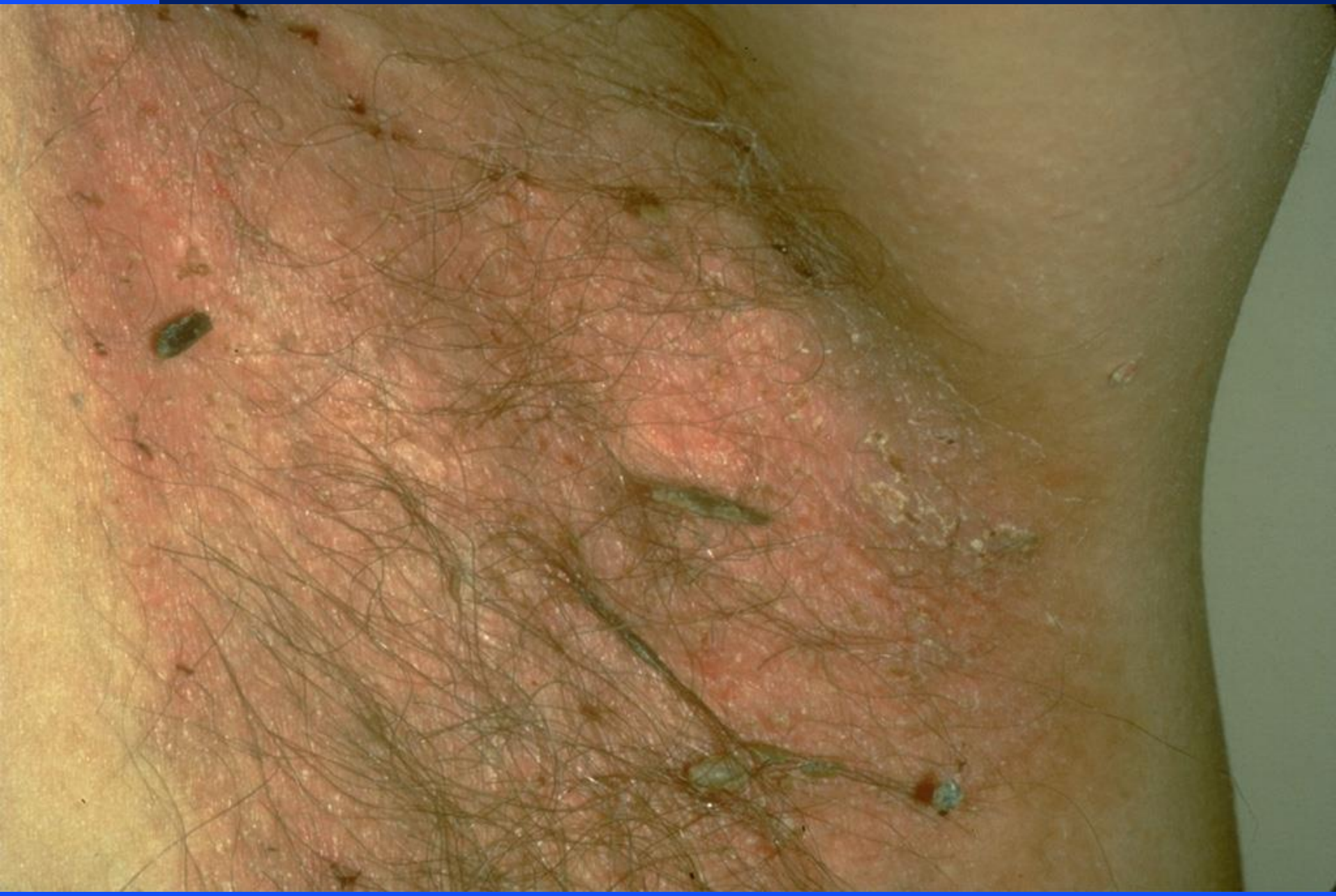
Pathology

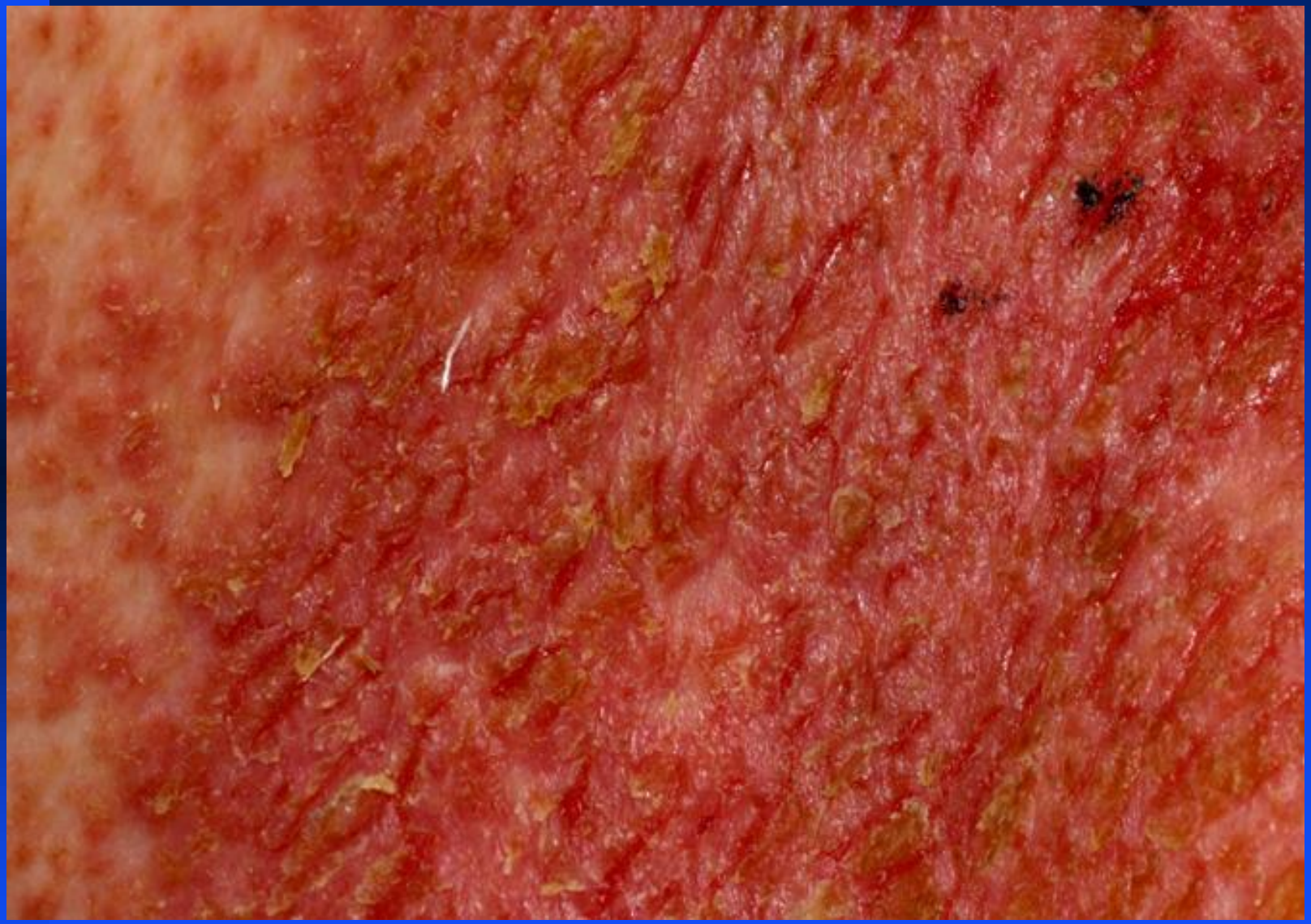
- Spongiosis: Intraepidermal and intercellular edema
- Widened intercellular spaces
- Varies considerably in amount and in different areas of the epidermis
- Parakeratotic scale
- Plasma in the horn
- Dermal mononuclear infiltrate sometimes with eosinophils

Differential diagnosis

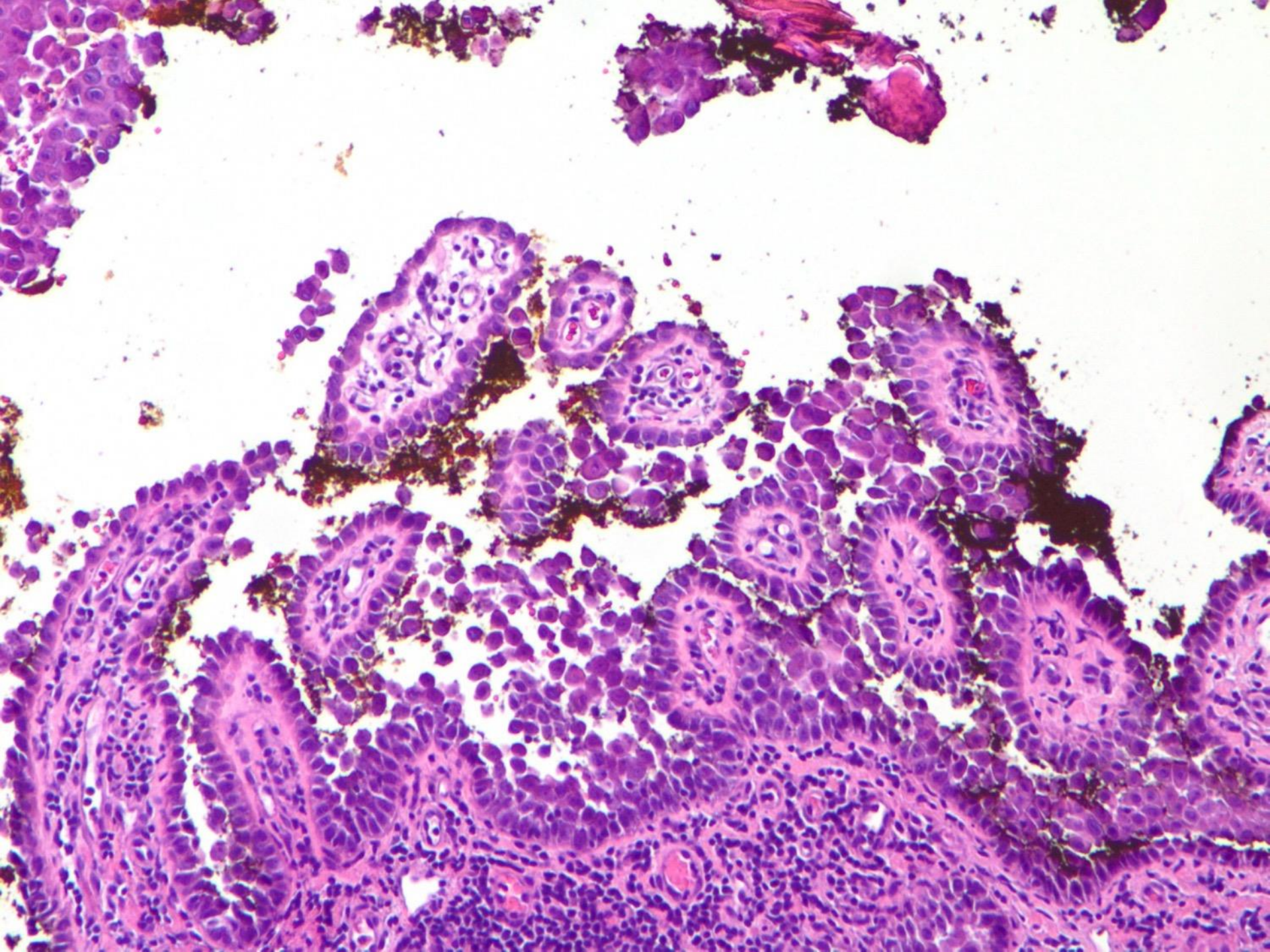
- Pityriasis rosea, papular type
- Vesicular arthropod reactions
- Spongiotic types of bullous disease (bullous pemphigoid).

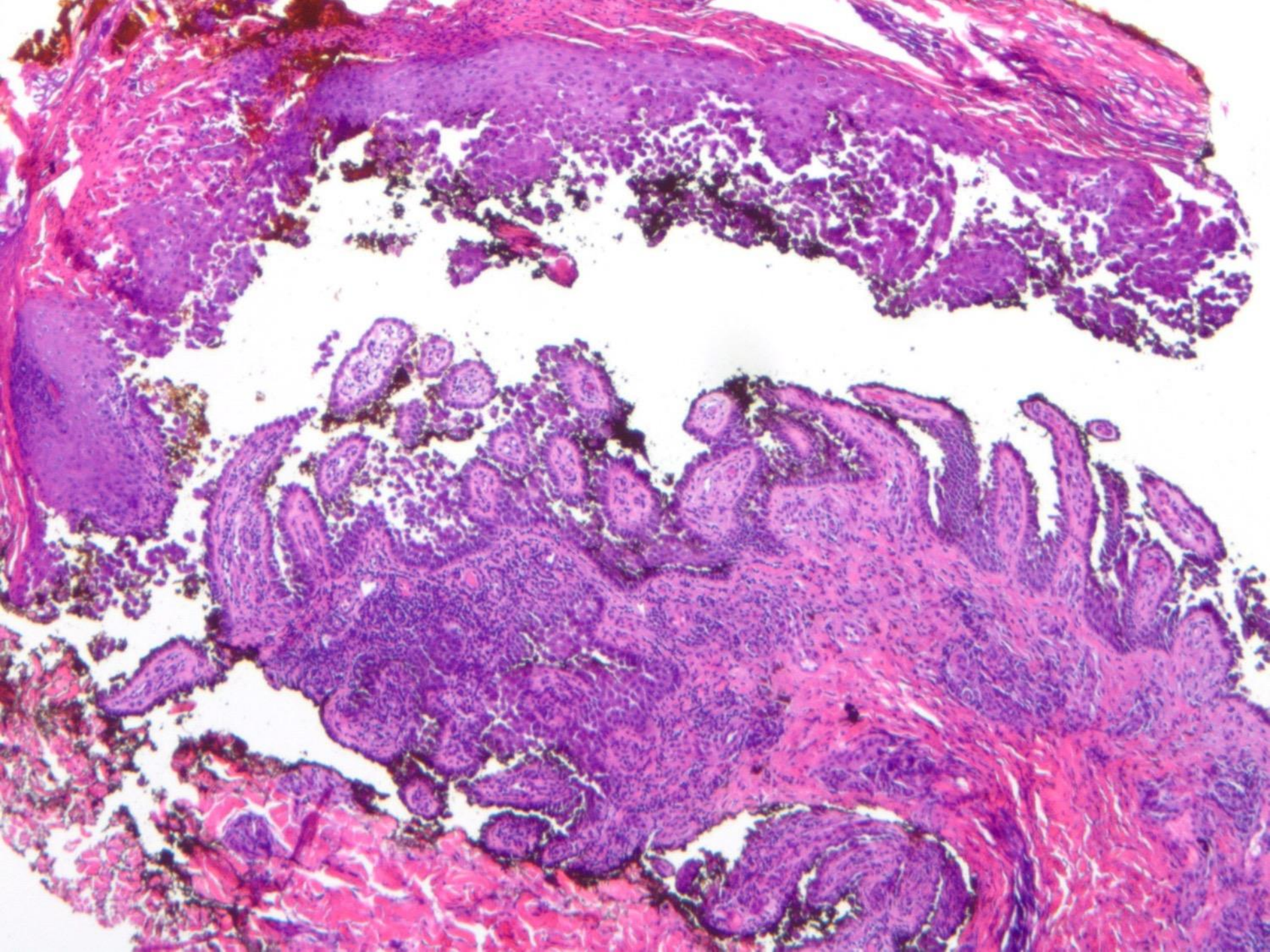


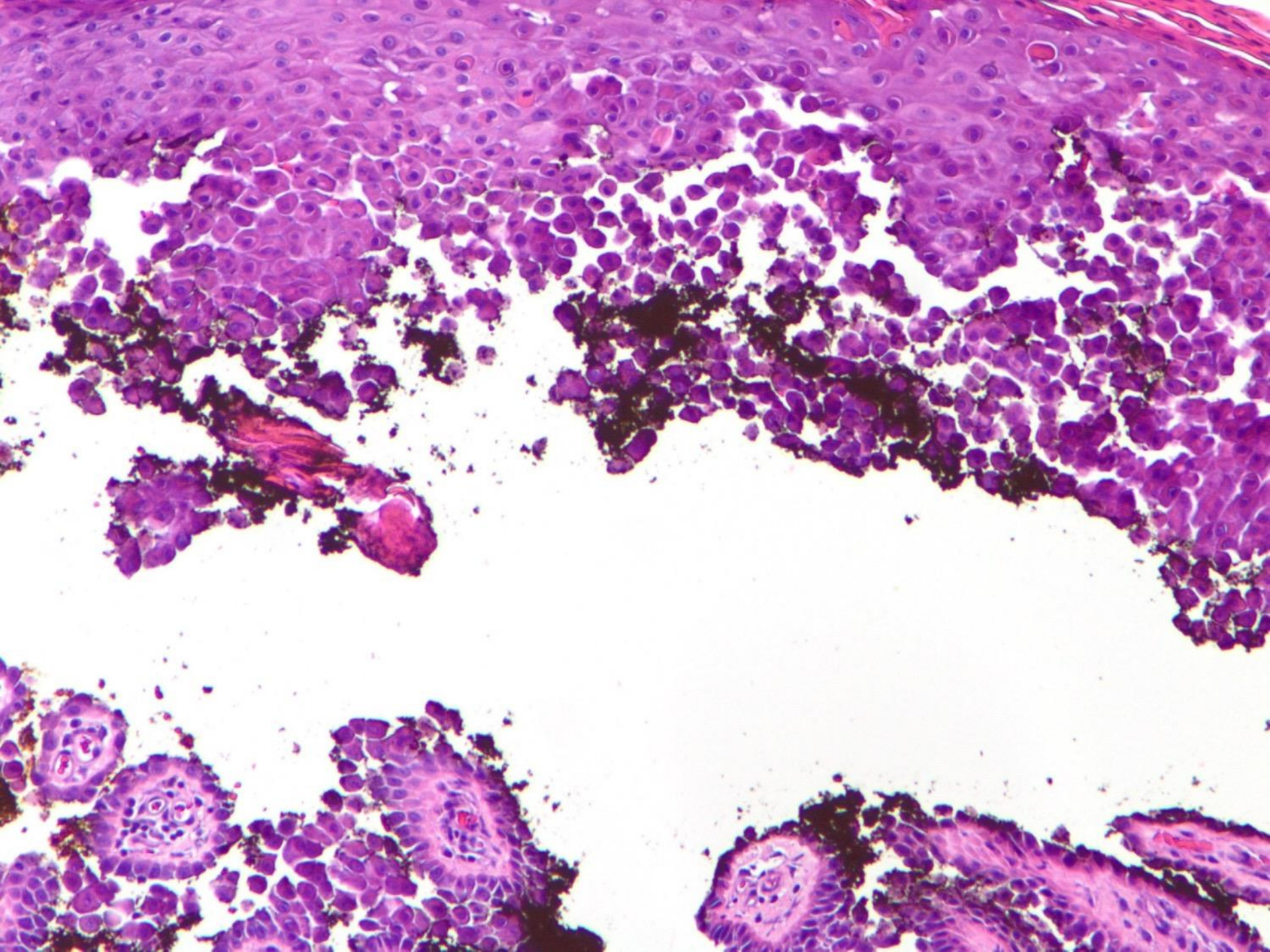


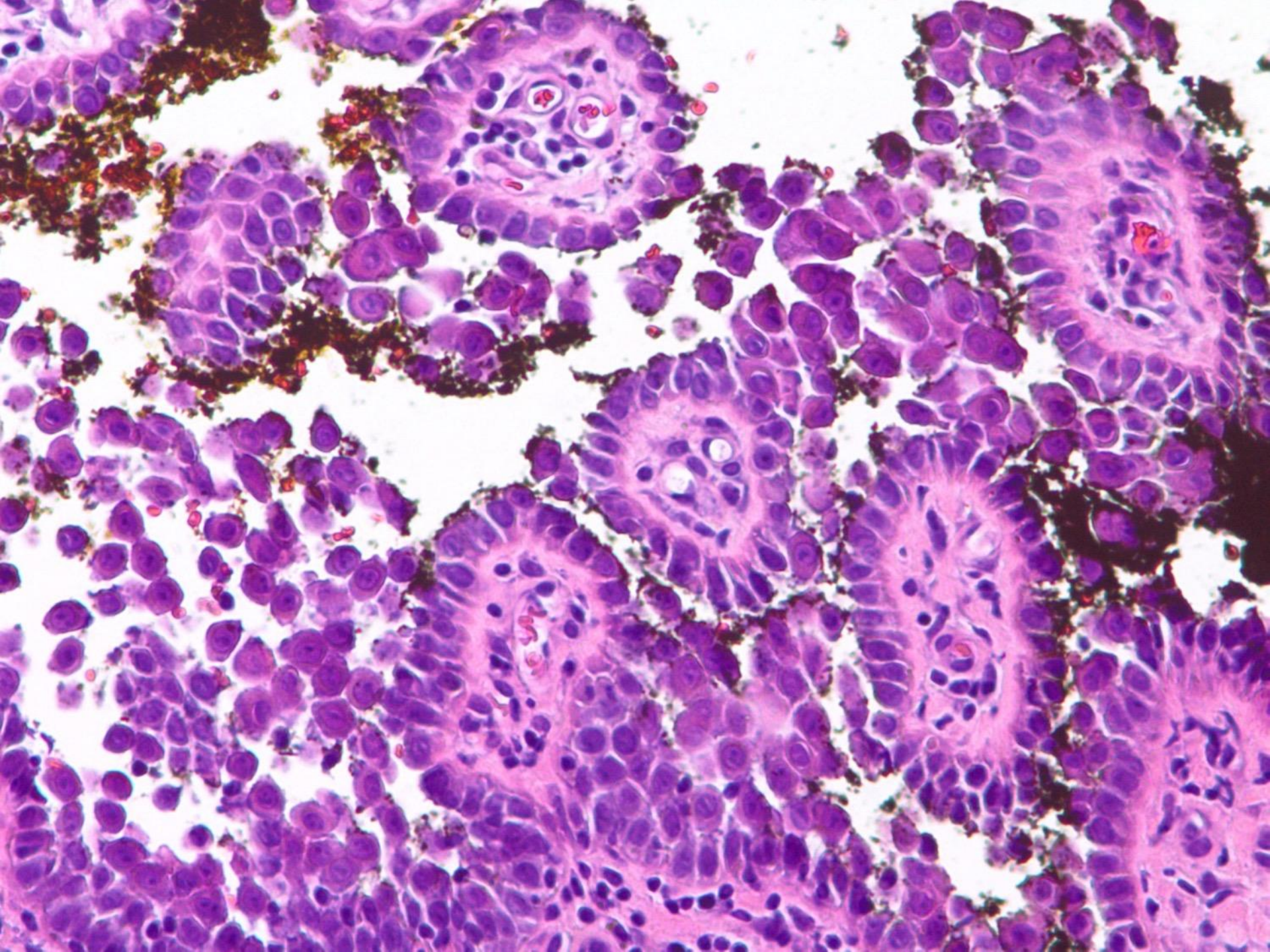


Hailey-Hailey disease









Clinical features

- Vesicular plaques which rupture and crust
- Neck, axillae, groin
- Calcium pump protein ATP2C1

Pathology

- Lacunae
- Extensive acantholysis “dilapidated brick wall”
- Associated with suprabasal vesicles
- Only rare foci of dyskeratosis
- Sparing of adnexal epithelium

Etiology

- ATP2C1 gene
- Calcium regulation in keratinocytes impaired
- No cell to cell cohesion

Differential diagnosis

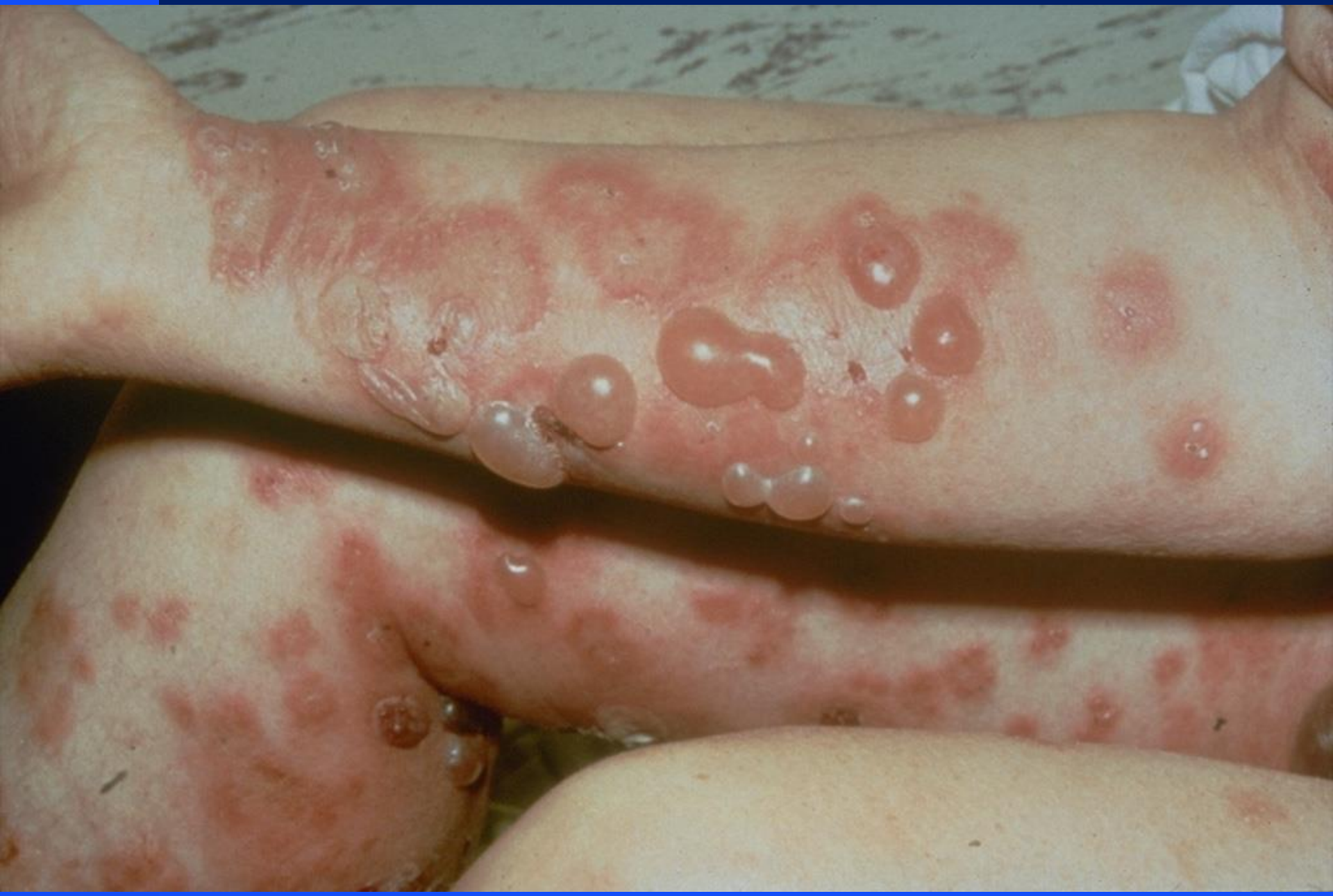
- Pemphigus vulgaris
- Darier's disease
- Grover's disease
- Irritant dermatitis (cantharidin)
- Herpes infections

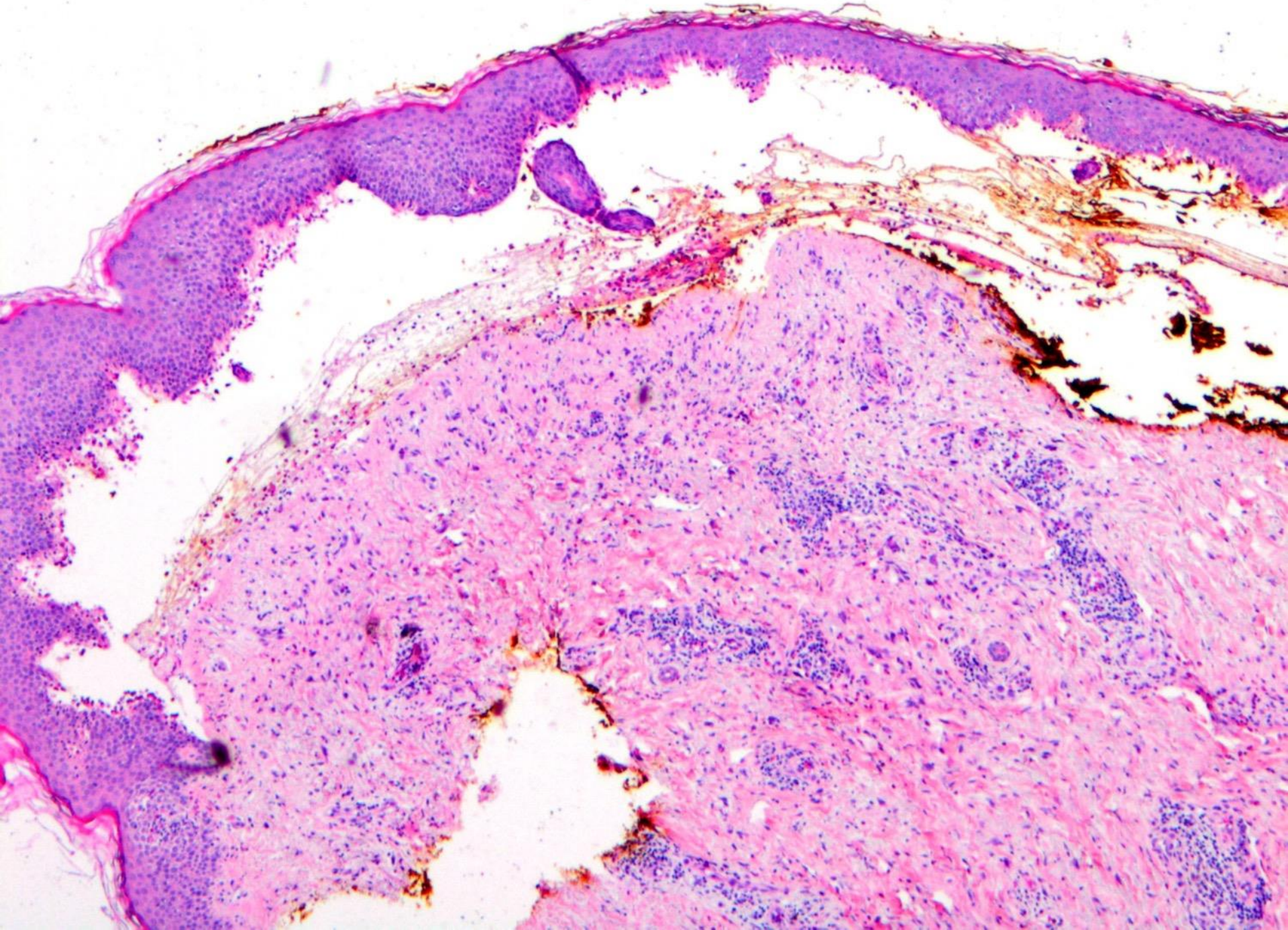
Subepidermal blistering disorders

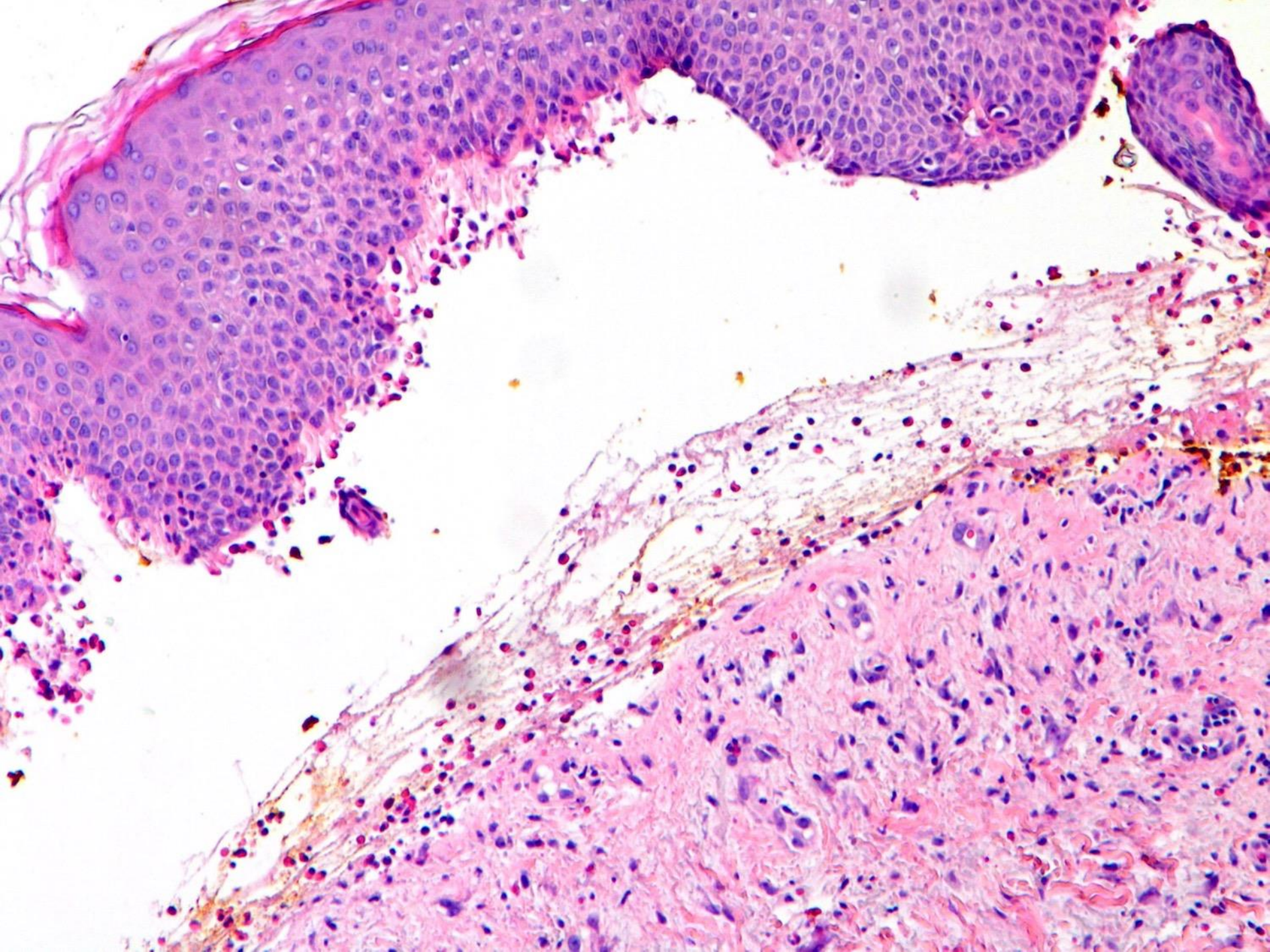
- Bullous pemphigoid
- Dermatitis herpetiformis
- Linear IgA bullous dermatosis
- Epidermolysis bullosa Acquitisita
- Epidermolysis bullosa (most types)
- Porphyria cutanea tarda
- Cicatrical pemphigoid

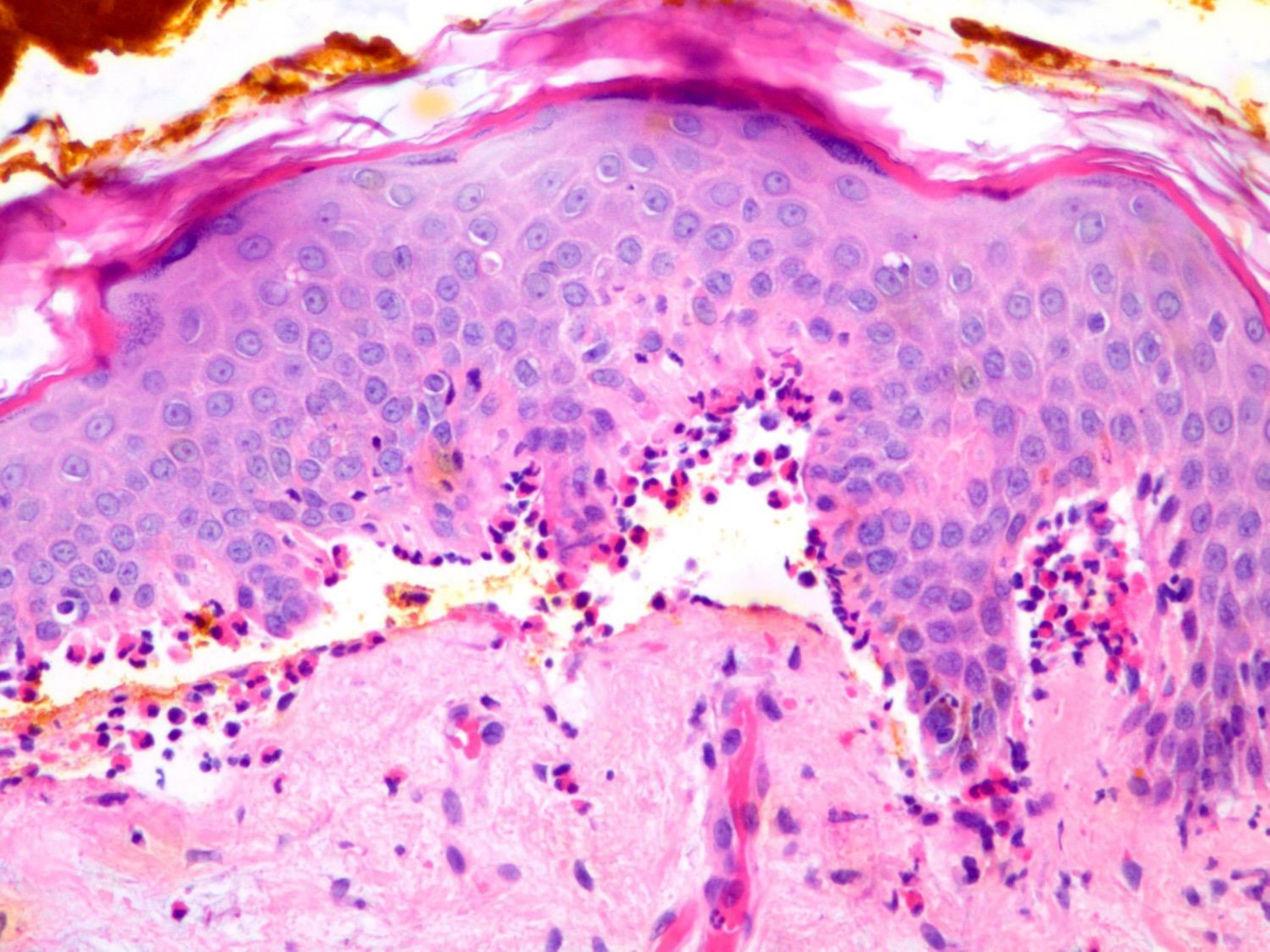
Subepidermal bullous disorders

- Inflammatory
  - Eosinophil rich (BP)
  - Neutrophil rich (DH, LABD)
  - Lymphoid (CP)
- Non inflammatory (CP, EBS, PCT)
- There is overlap and one disorder can have more than one pattern! These are now immunologically/genetically defined









Bullous pemphigoid

Clinical features

- Primarily in elderly
- Most common bullous dermatosis
- Tense bullae on normal or erythematous skin, and mucosa
- Urticarial lesions, erosions, dermatitis, dyshidrosis like, diffuse pruritus; many clinical patterns depending on stage

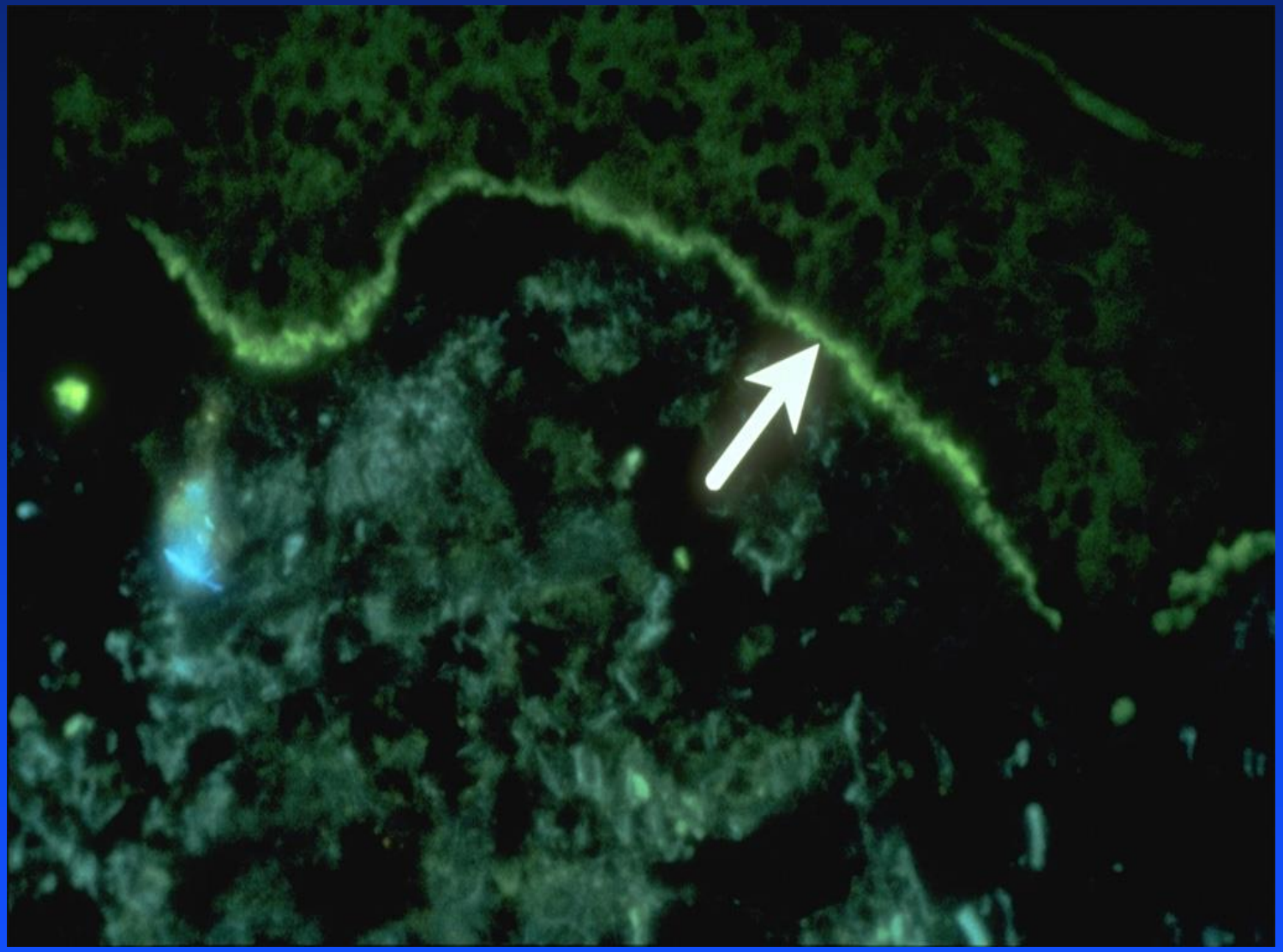
Bullous Pemphigoid

- Histology
  - Subepidermal blister
  - Inflammatory infiltrate- variable from cell poor to eosinophil-rich or mixed
  - Classically eosinophils and fibrin in blister cavity, eosinophils may be seen beneath BMZ, eosinophilic spongiosis may also be seen
  - Neutrophils more common in childhood variant

Bullous Pemphigoid: immunopathology

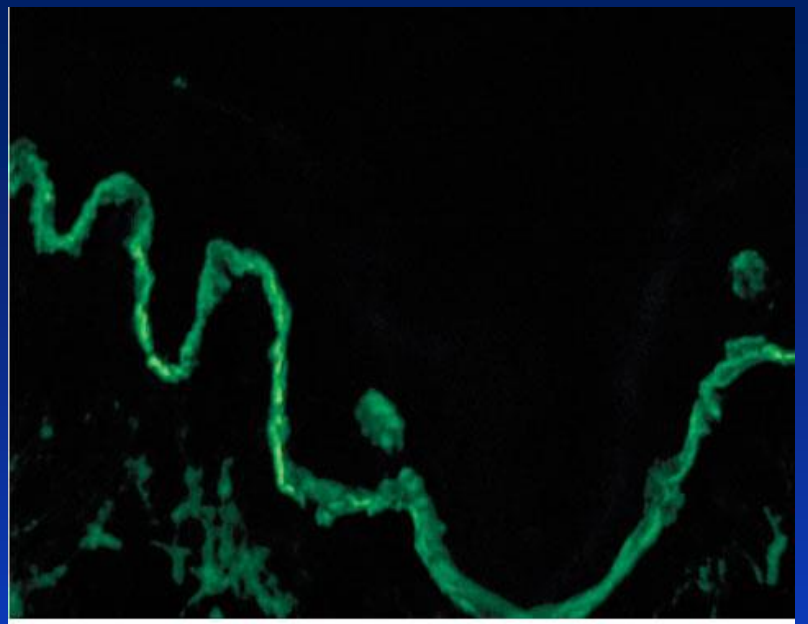
- Ag: BP 230, 180
- Site: perilesional
- DIF: C3 100%; IgG 90% (IgG 4); linear BMZ
- Indirect 70% linear BMZ
- Cleavage: lamina lucida

Bullous Pemphigoid



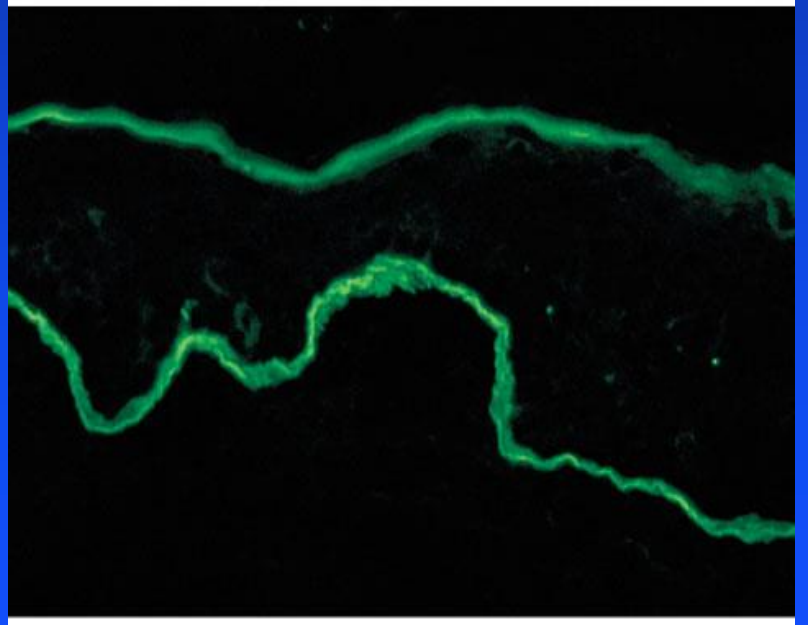
Immunofluorescence of Bullous pemhigoid

Direct IgG



A.

Indirect IgG



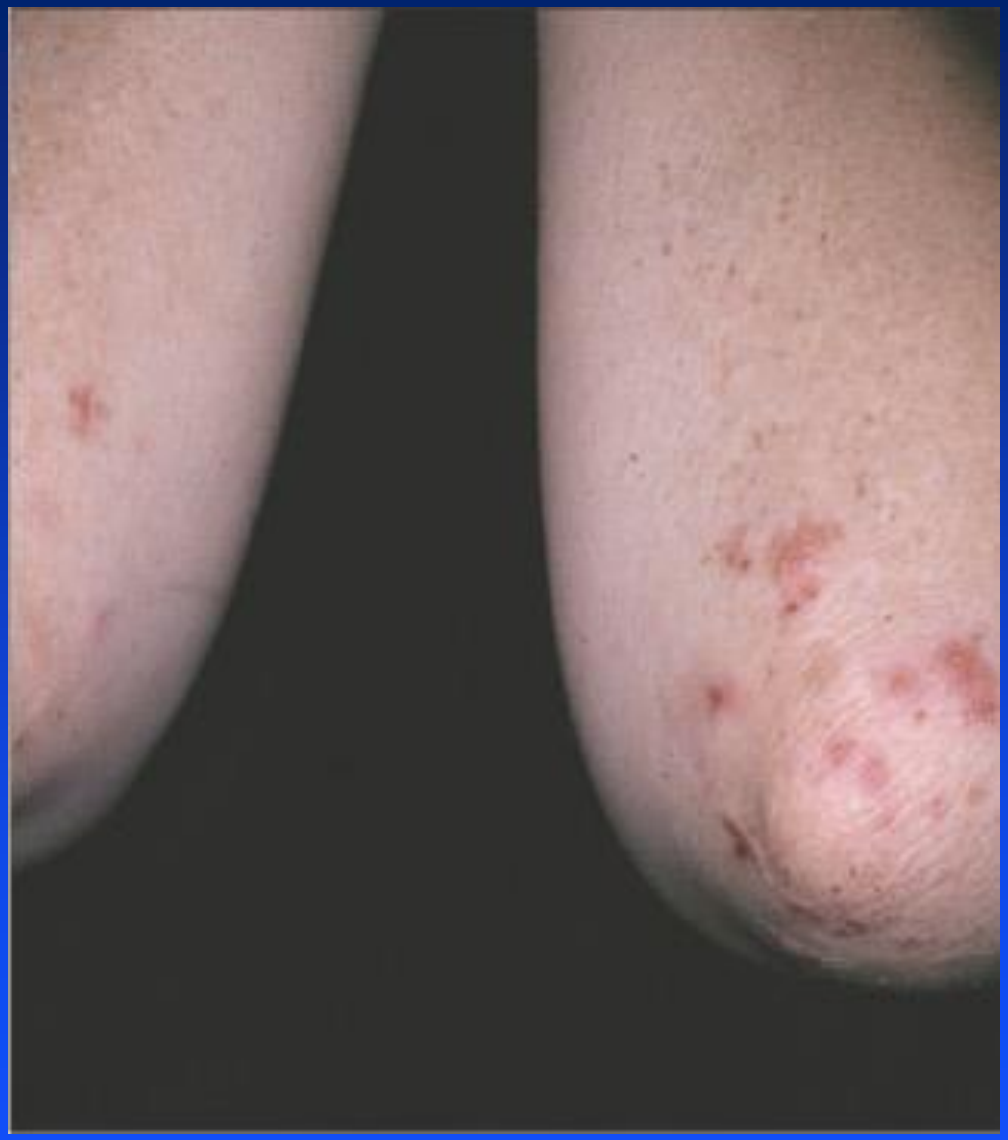
B.

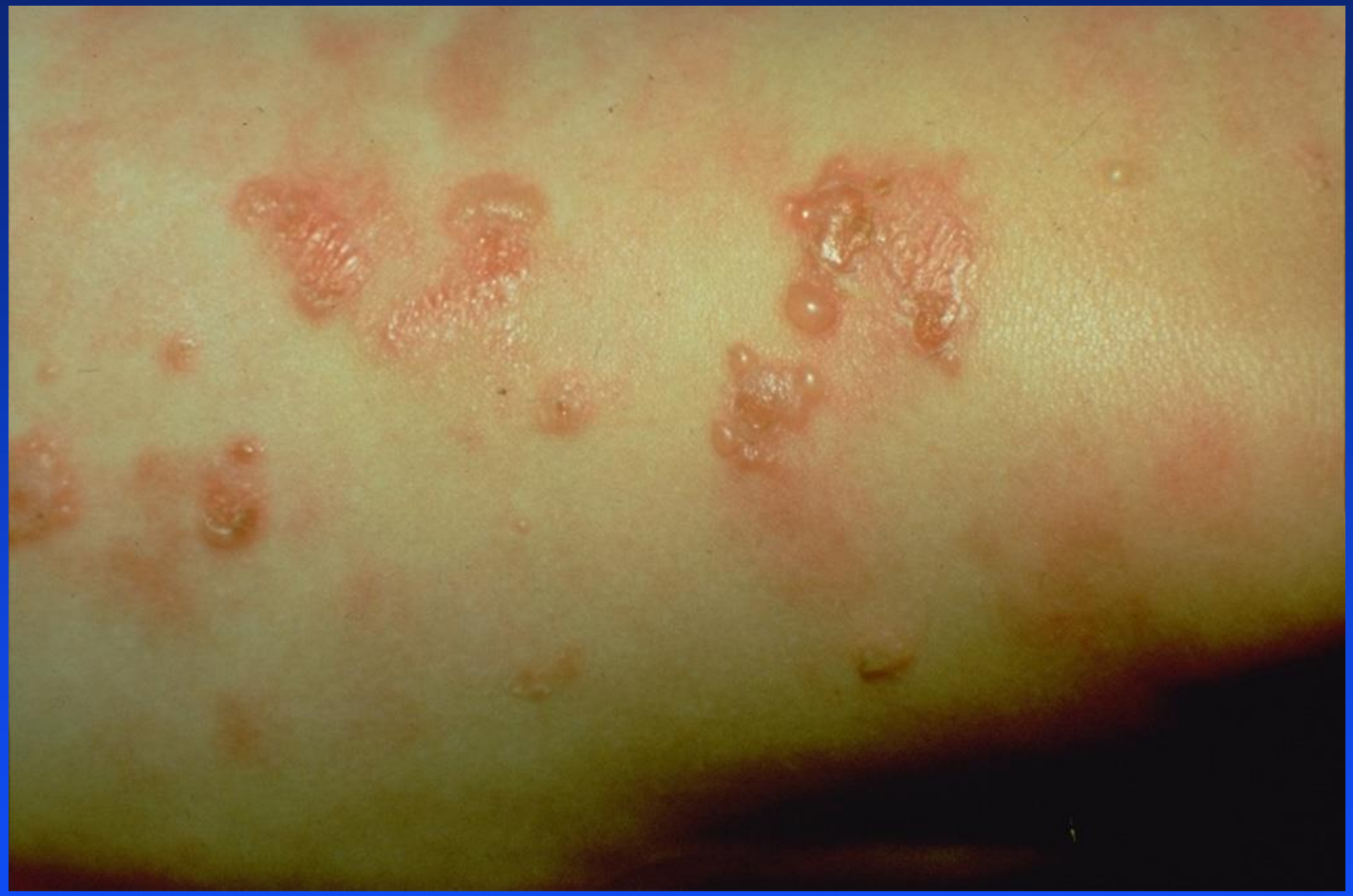
Bullous Pemphigoid

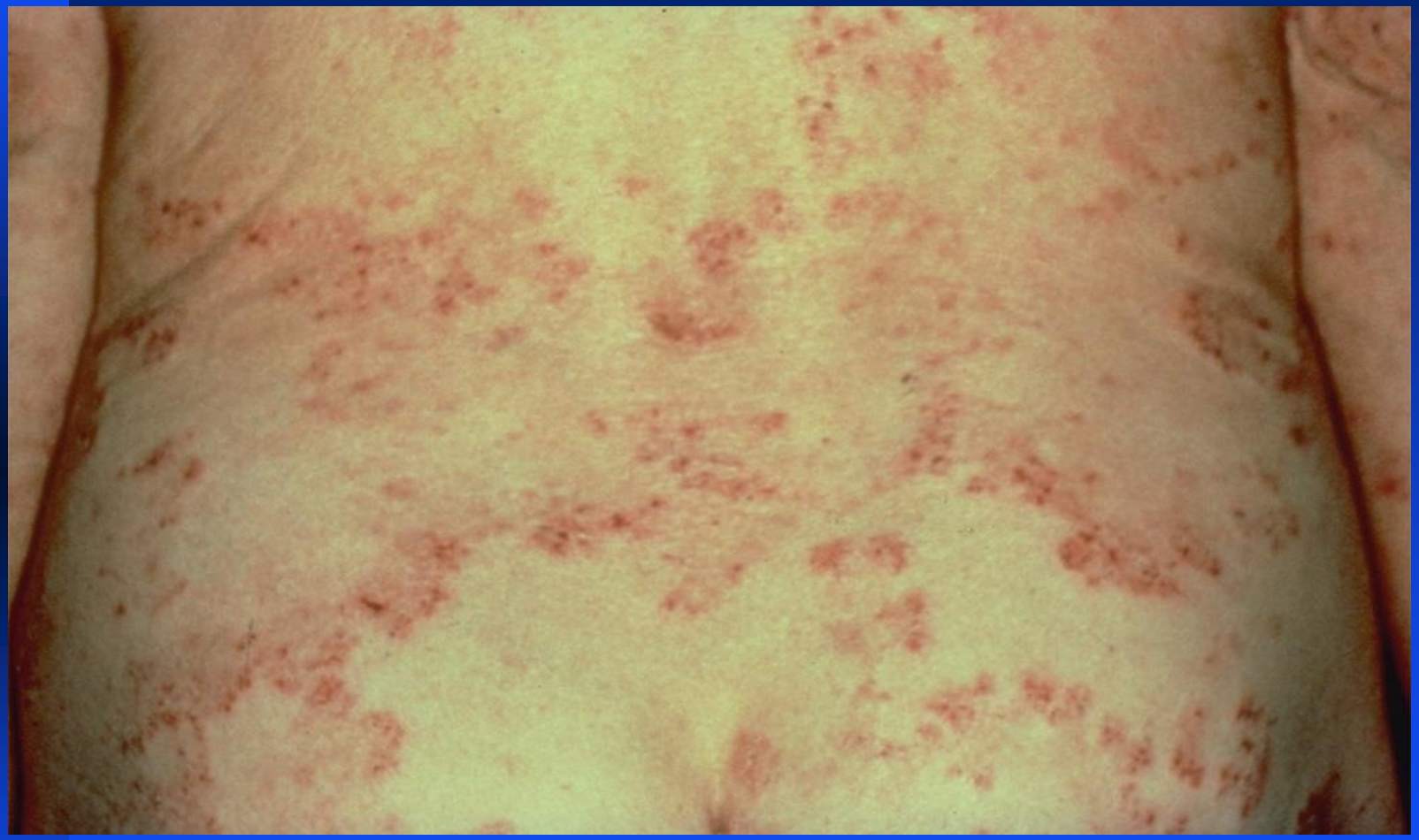
- Antigens
  - BP180 (BPAG2, Type XVII collagen)
  - BP230 (BPAG1, HD protein)

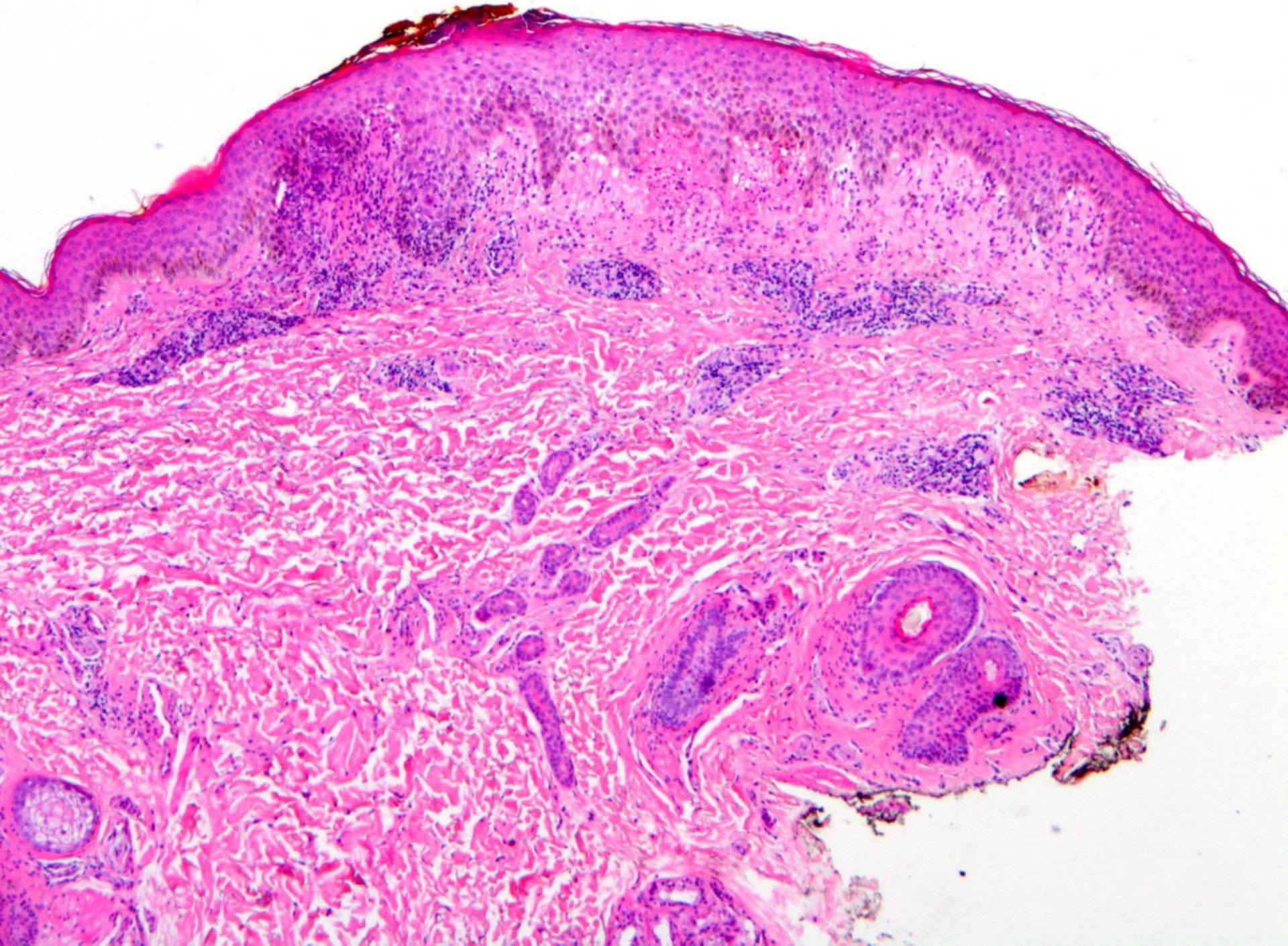
Differential diagnosis

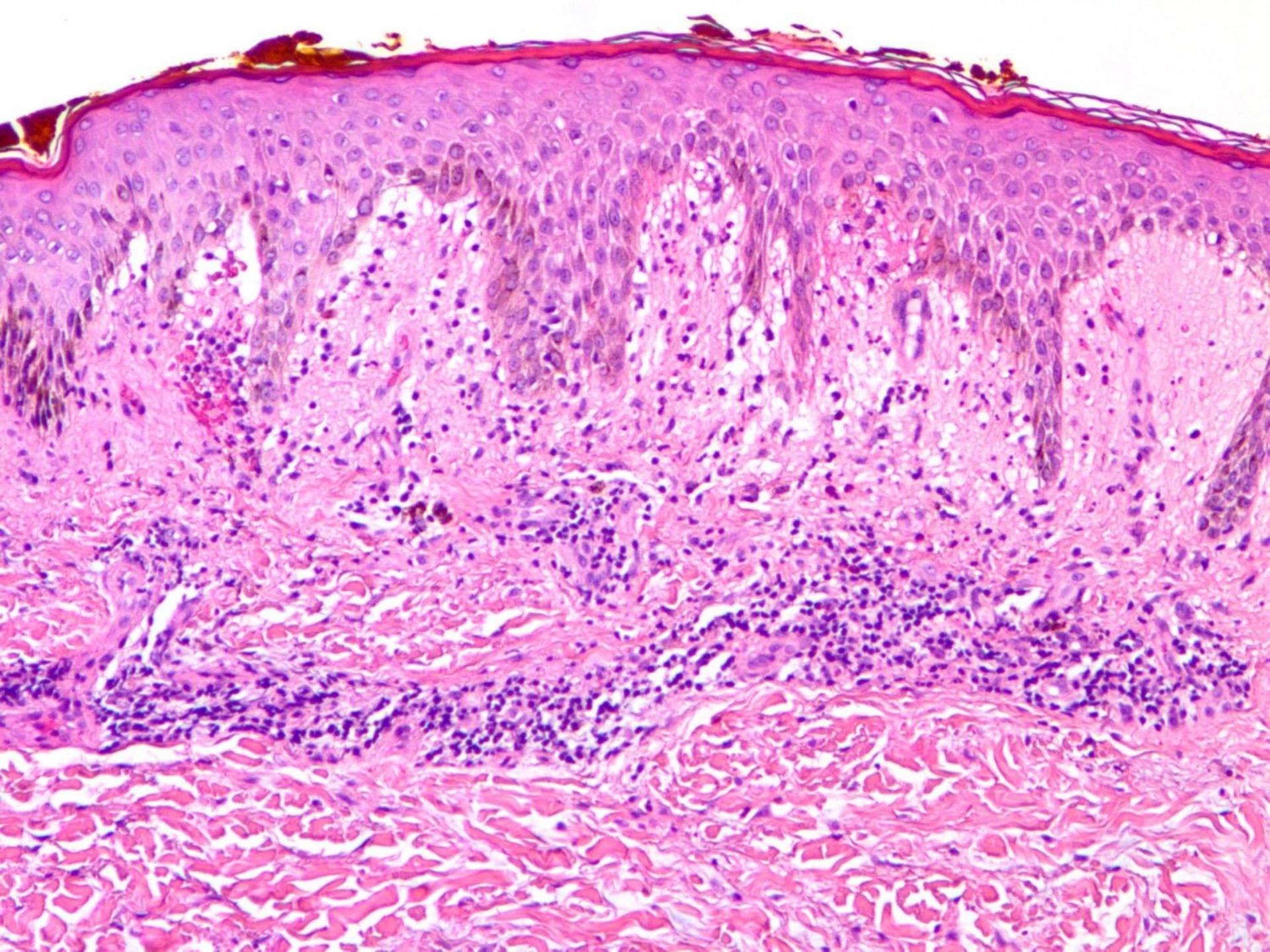
- Cicatricial pemphigoid
- Inflammatory type of EBA
- Can sometimes only be distinguished by blotting/ELISA/salt split skin

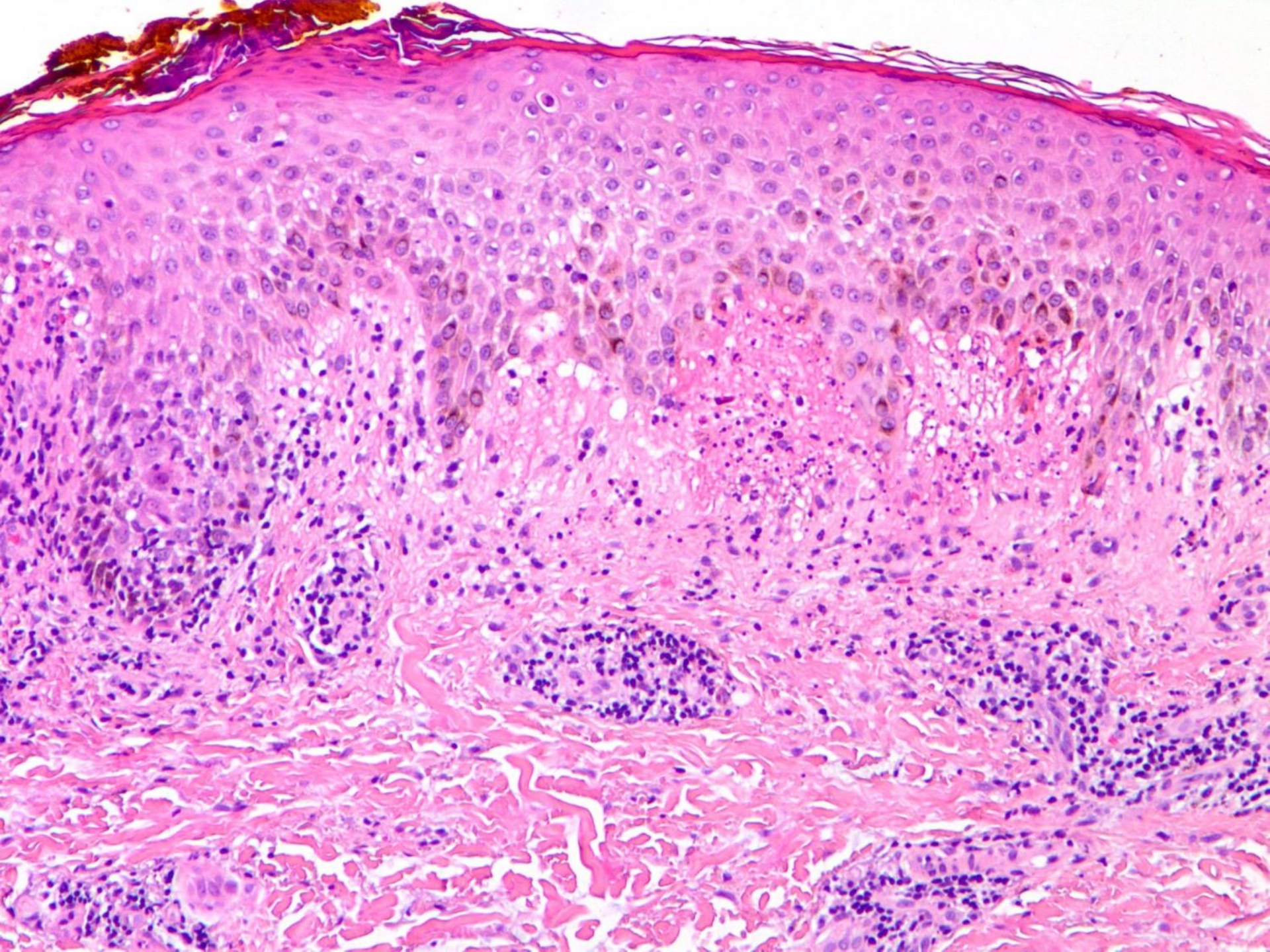


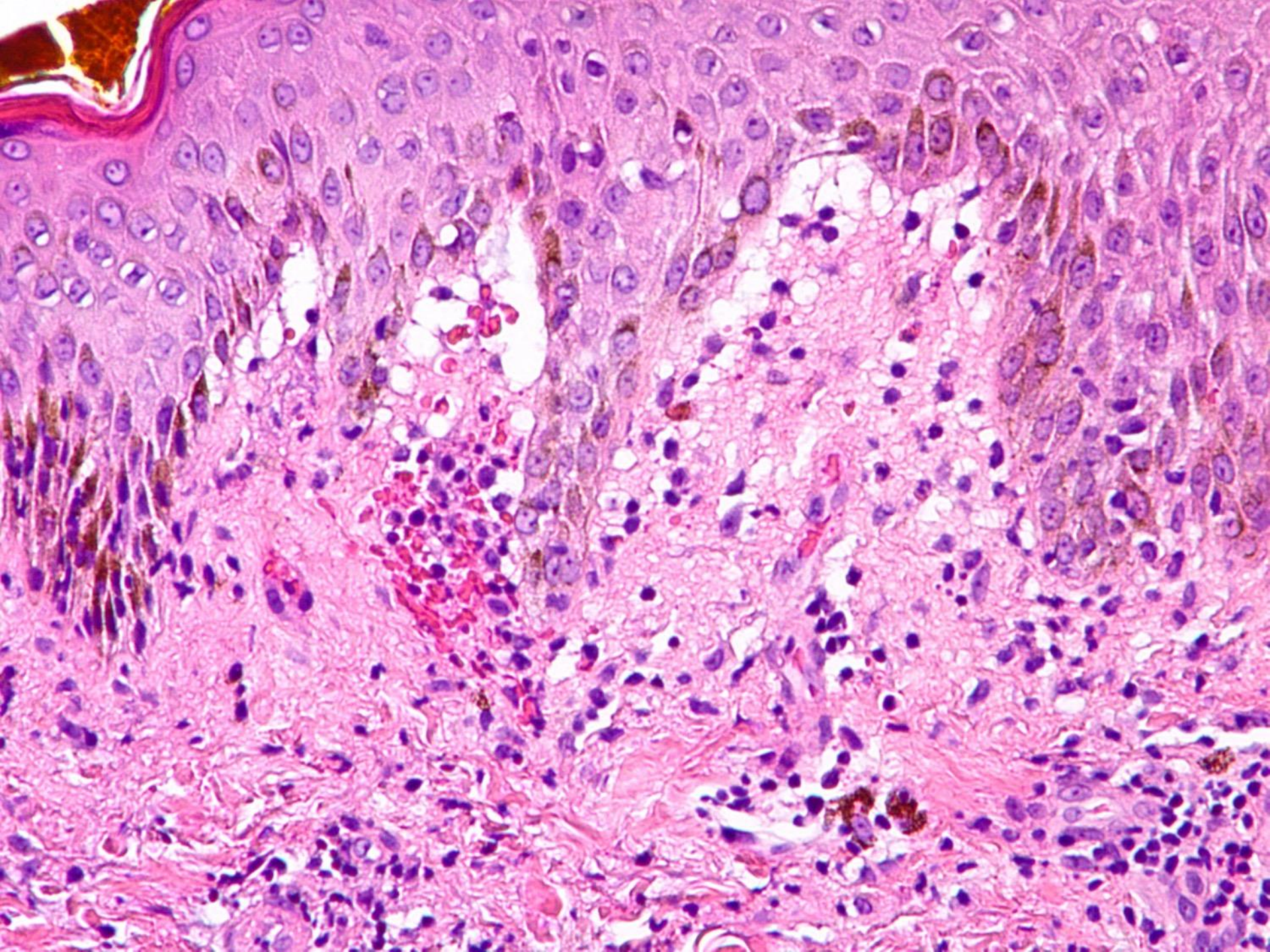












Dermatitis herpetiformis

Clinical features

- Any age including children
- Pruritic papules and vesicles, often grouped
- Extensor surfaces-elbows, knees, nape of the neck, sacral area
- Excoriations, severe pruritus and burning sensation common

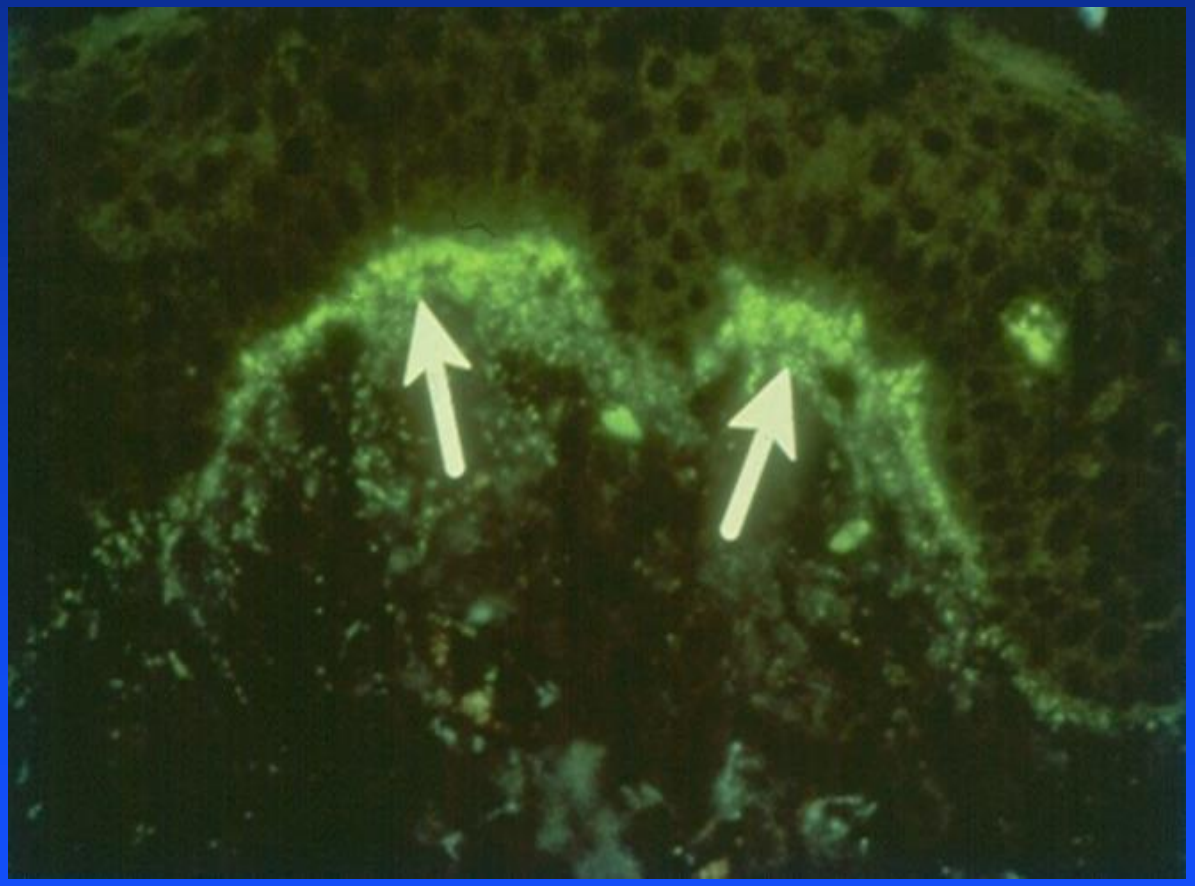
Dermatitis Herpetiformis

- Histology
  - Neutrophilic abscesses in dermal papillae
  - Fibrin with necrosis, acantholysis
  - Small lacunae
  - Then becomes multilocular subepidermal vesicle
  - Leukocytoclasis
  - Eosinophils seen in older lesions, may be confused with BP

Dermatitis Herpetiformis

- Immunofluorescence
  - Direct- Granular IgA deposition w/in dermal papillae (and other Ig's and C3)
    - Best to bx uninvolved skin, adjacent to area of inflammation
  - Indirect- Neg for circulating IgA ab's that bind to dermal papillae
    - Ab's to endomysium of smooth muscle correlate with dz activity and severity of GI path

Dermatitis herpetiformis Direct IgA

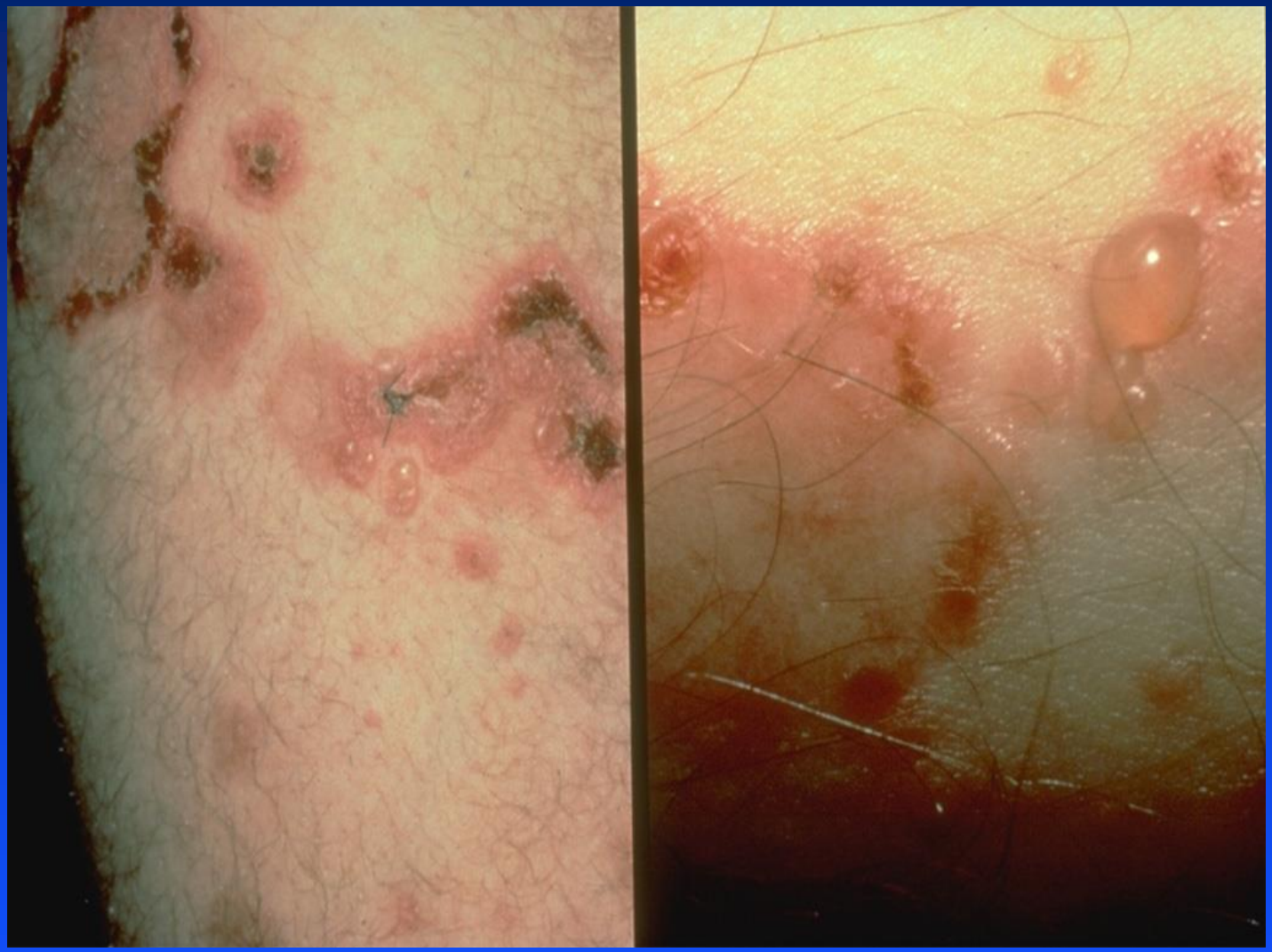


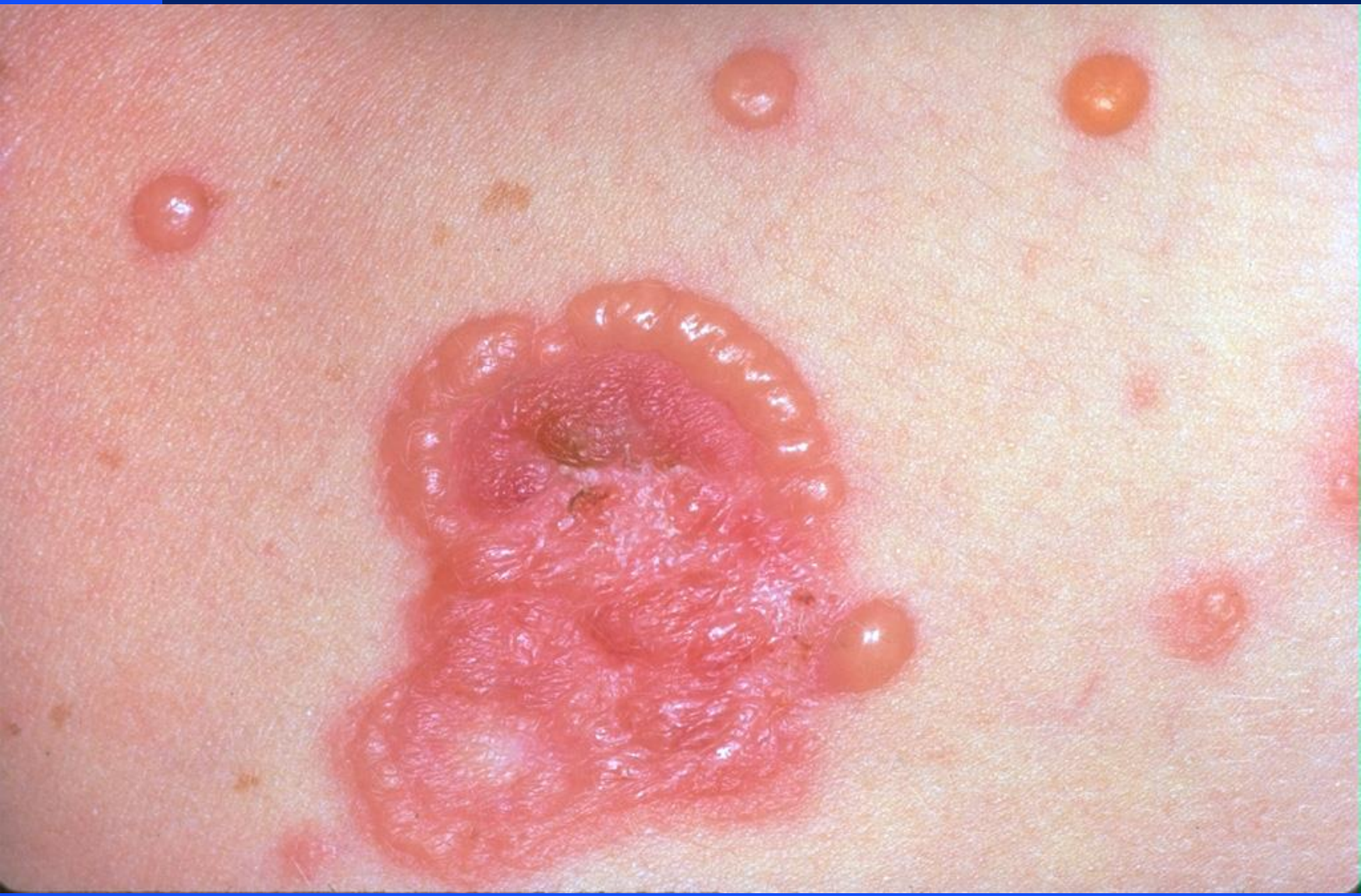
Dermatitis herepetiformis: Antigen

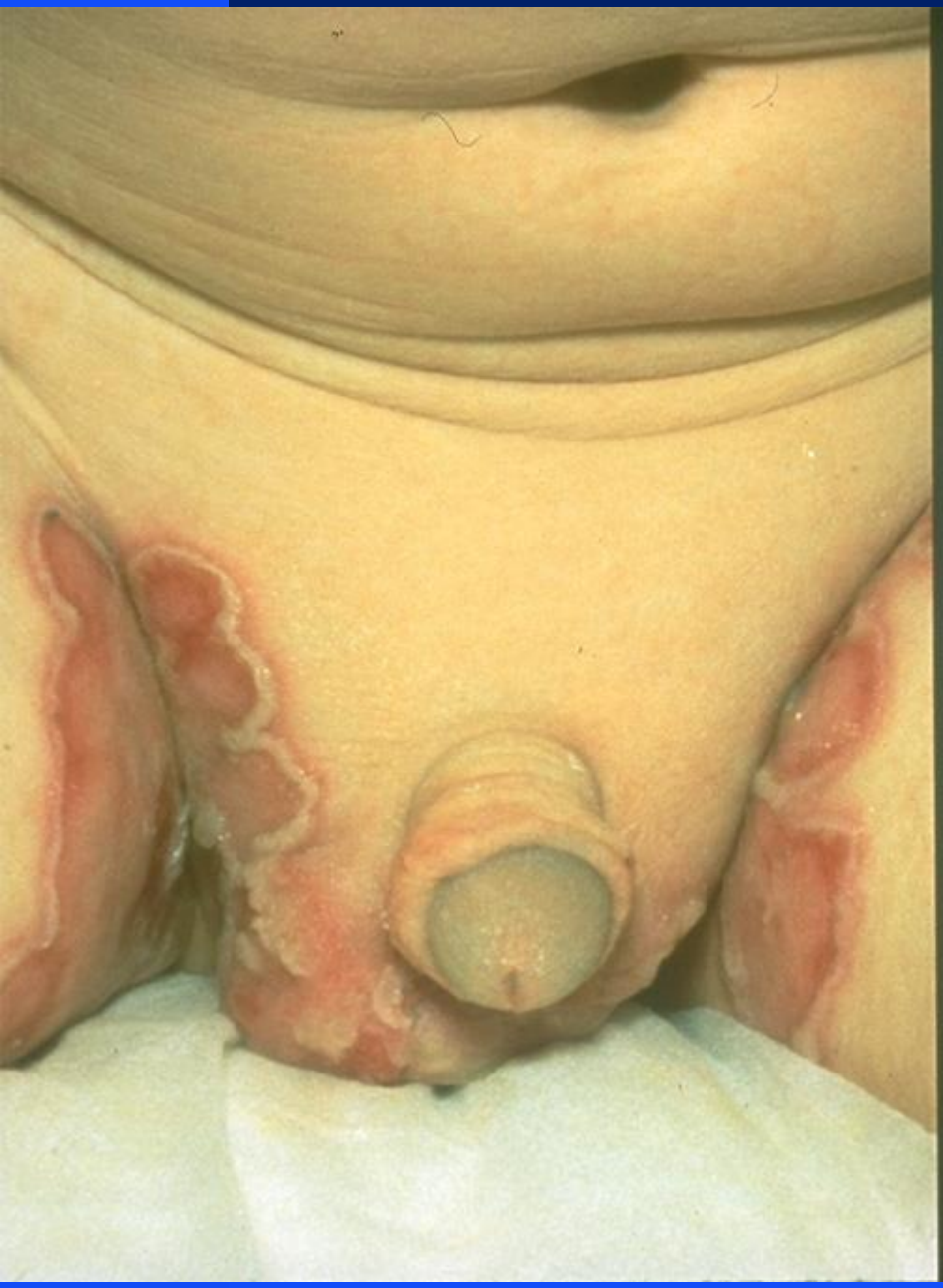
- Anti-tissue tranglutaminase

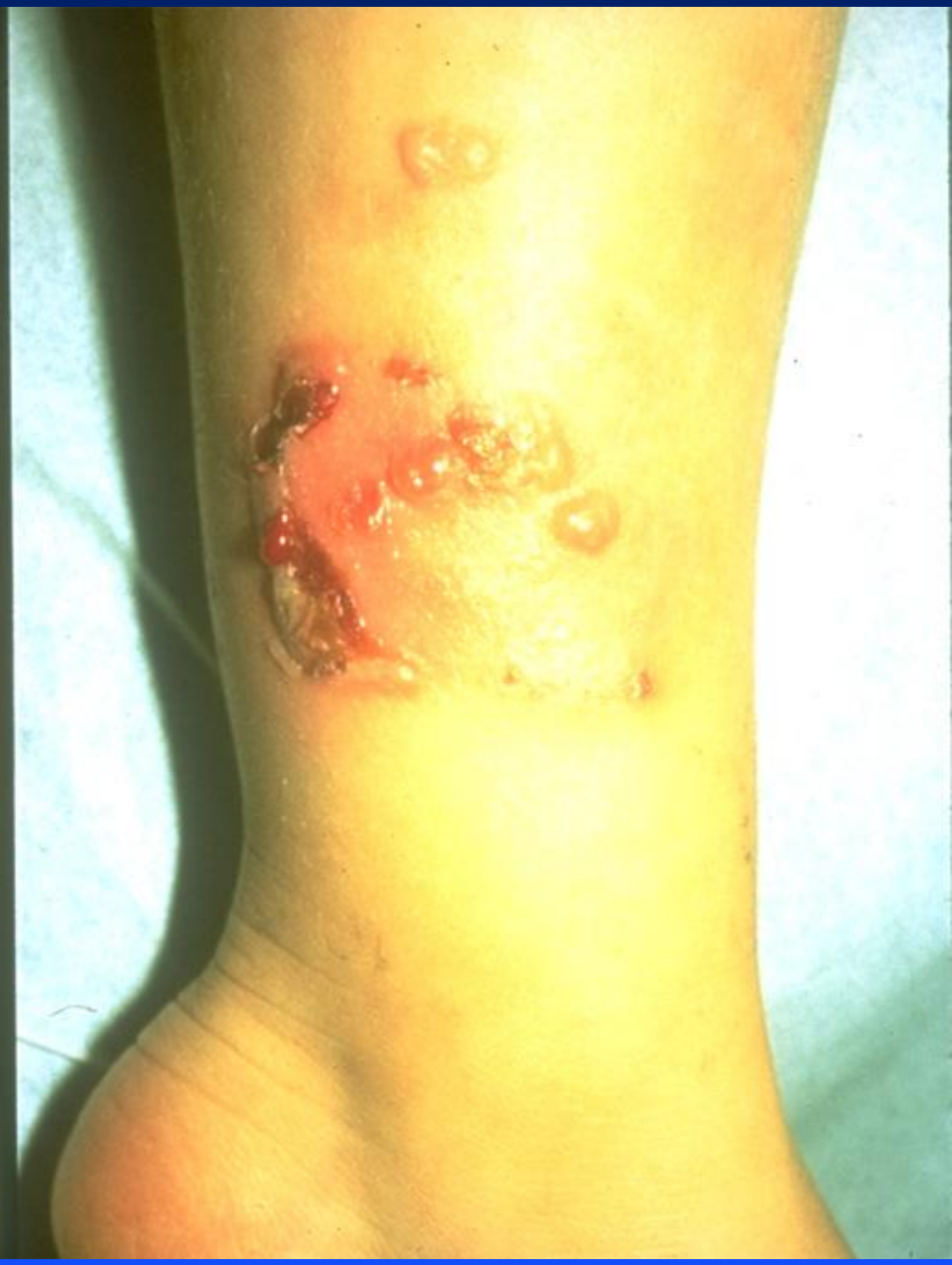
Differential diagnosis

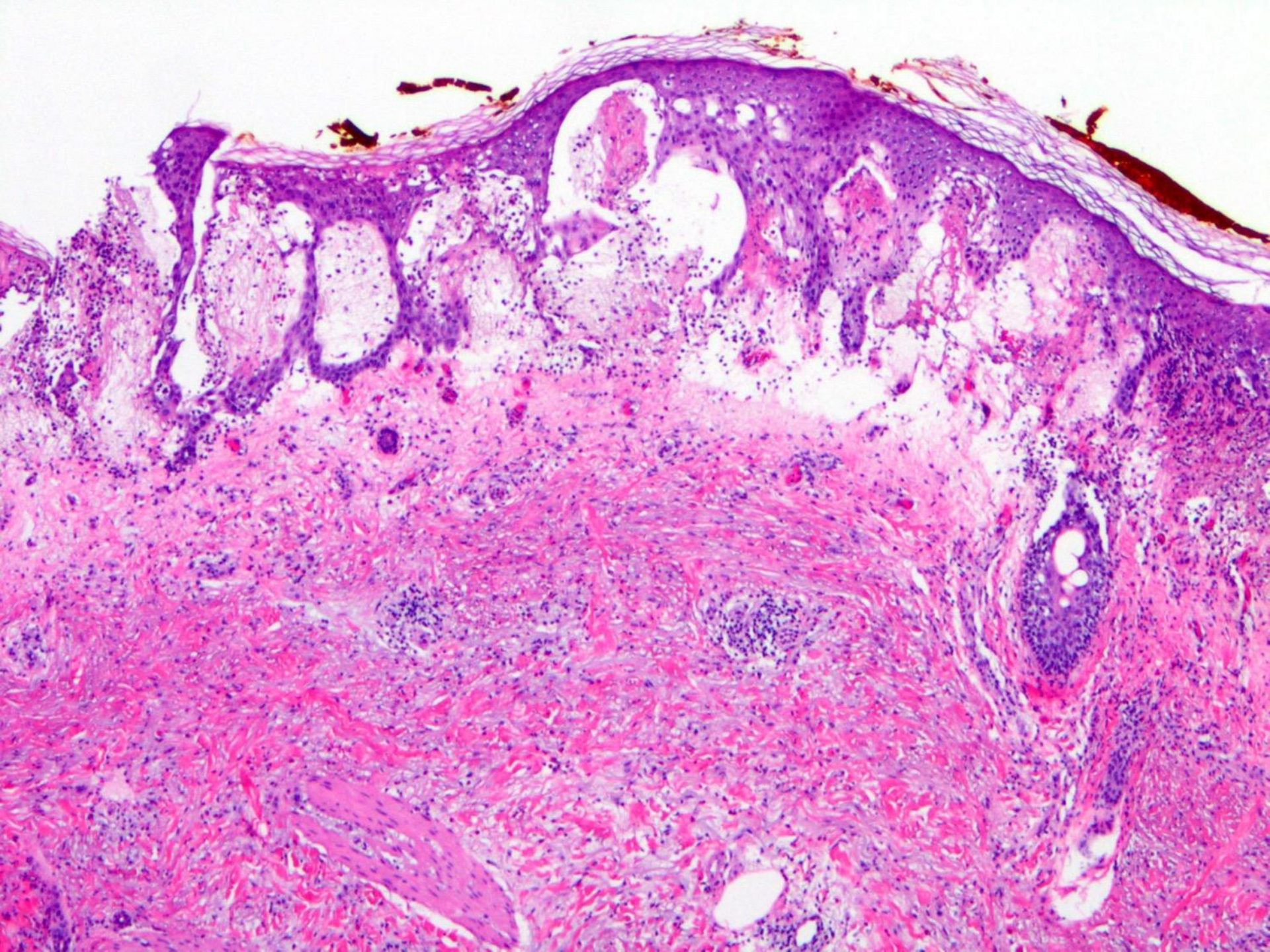
- Linear IgA disease
- Inflammatory type of EBA
- Bullous SLE
- Cicatricial pemphigoid

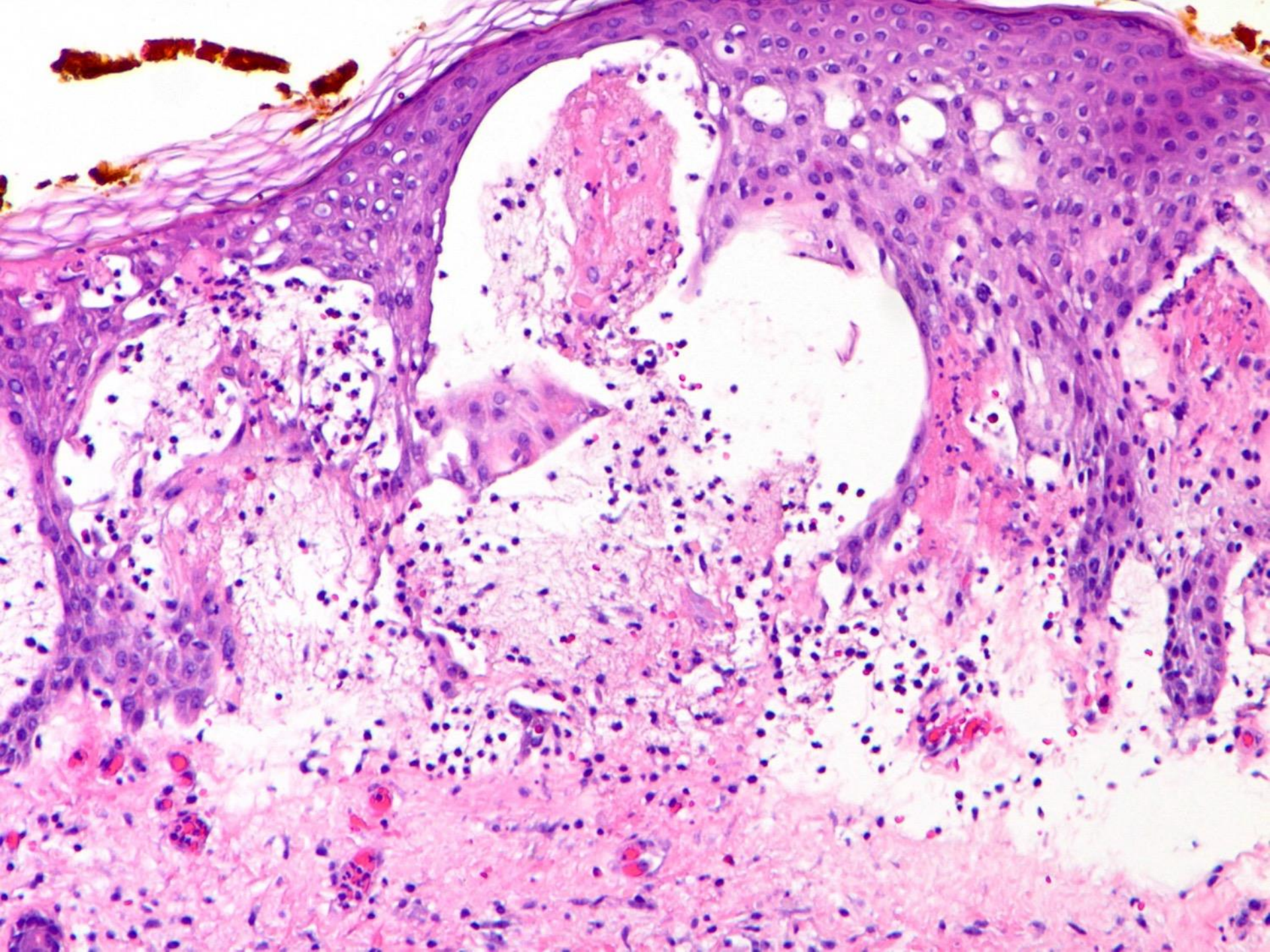


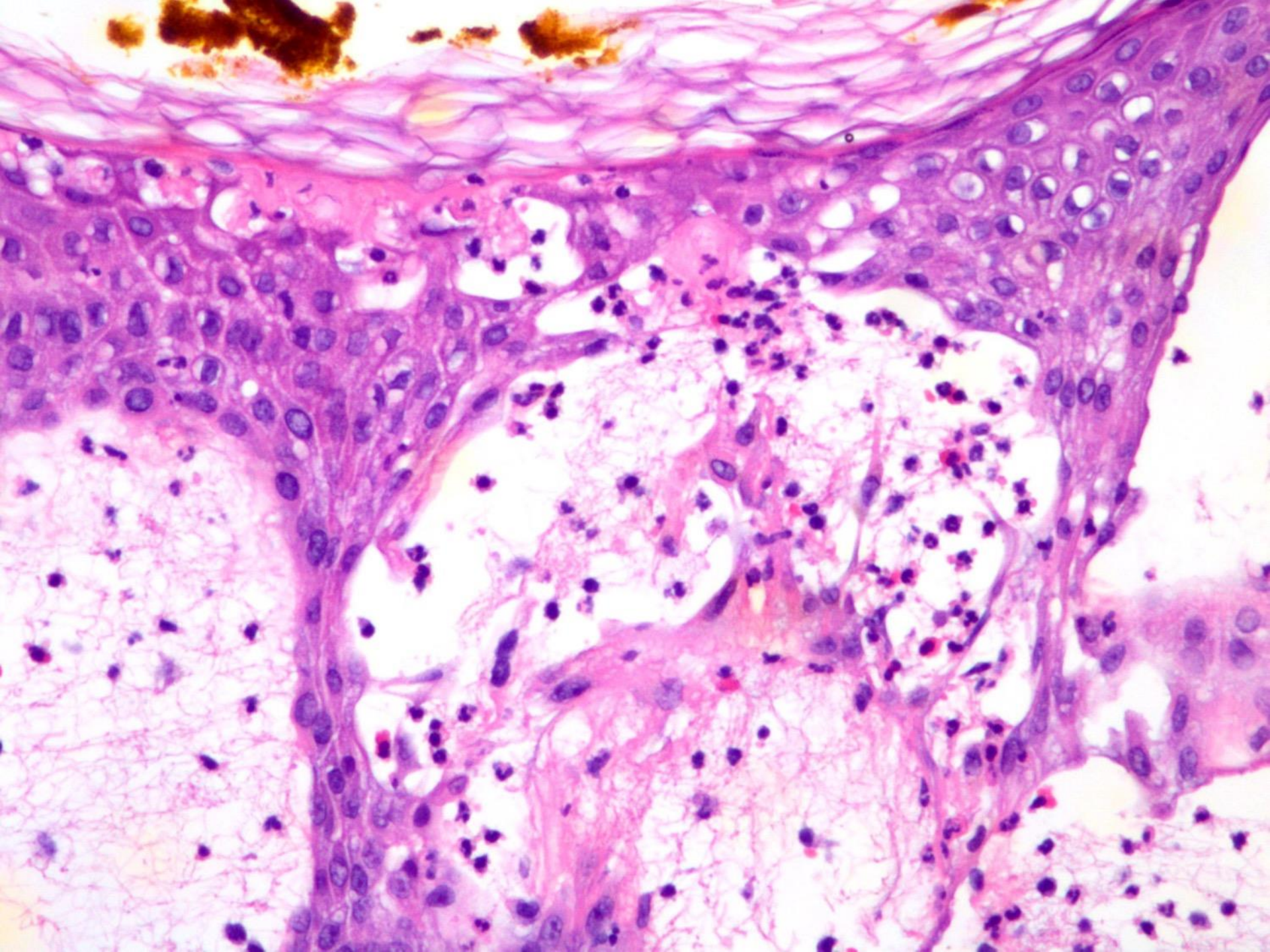












Linear IgA bullous dermatosis

Linear IgA Bullous Dermatosis: Clinical

- Age- Bimodal, children(Chronic Bullous Disease of Childhood) and adults age 60-65yrs
- Perioral, genital, thighs
- Tense bullae, polycyclic
- Cluster of jewels
- Clinical presentation in adults maybe heterogeneous TEN like

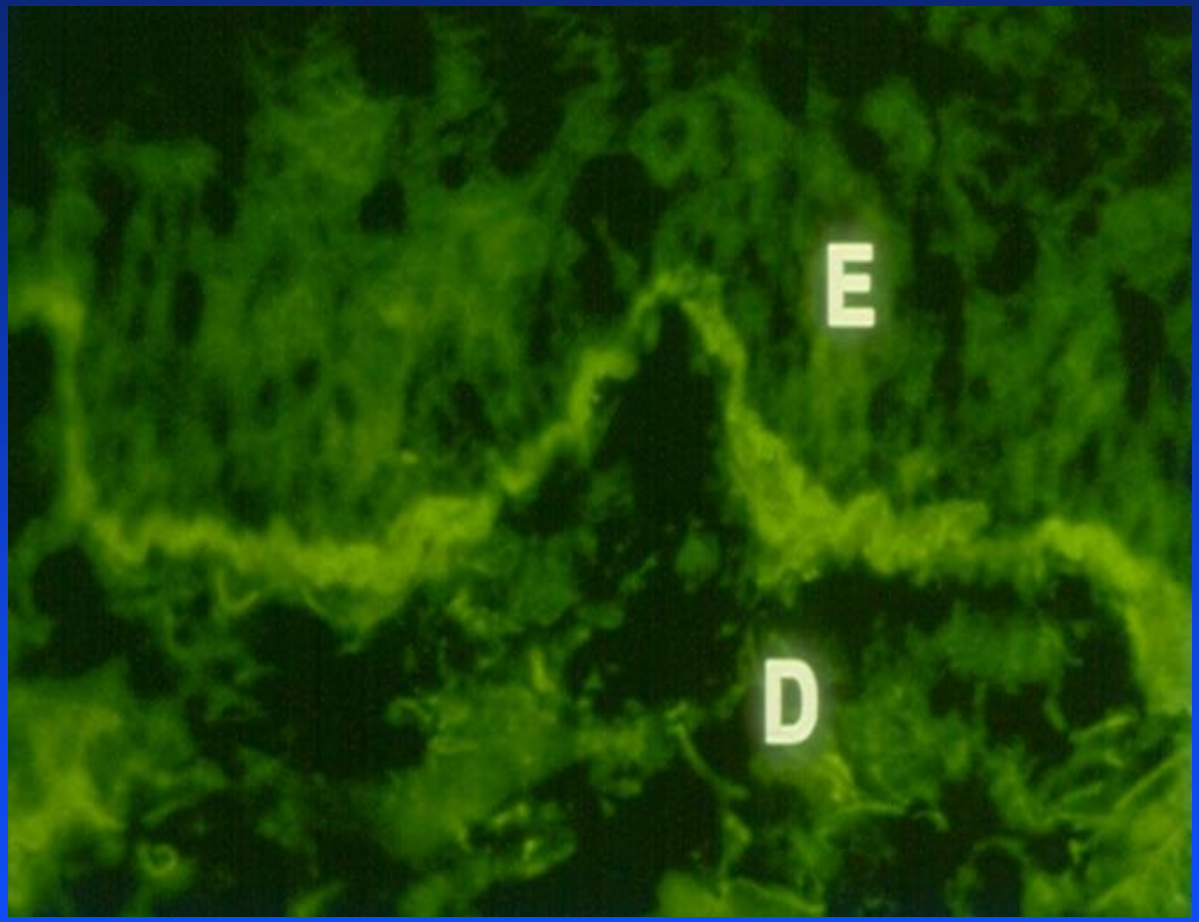
Linear IgA Bullous Dermatosis

- Histology
  - DH-like
    - Neutrophilic microabscesses in dermal papillae, but broader segments of BMZ involved-rete tips and between (vs DH)
  - BP-like
    - Subepidermal blister w mixed inflammatory infiltrate, eos, neuts (sometimes in drug induced cases)

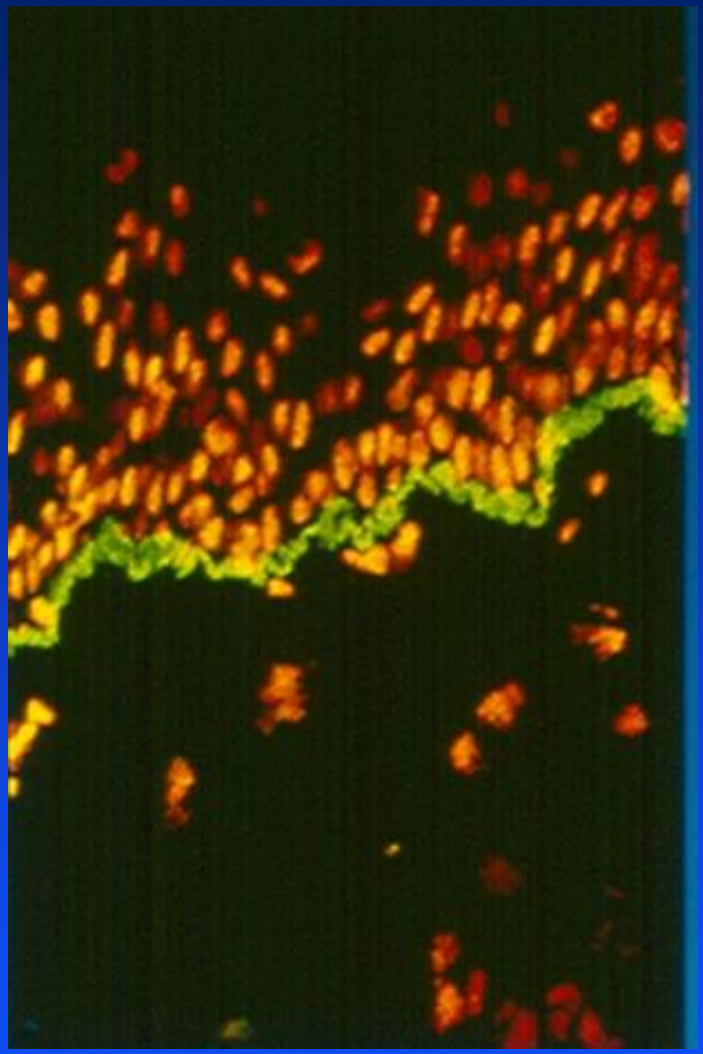
Linear IgA Bullous Dermatosis

- Immunofluorescence
  - Direct- Linear IgA +/- C3 BMZ, 25%IgG
  - Indirect- Intact skin-Circulating IgA, occ IgG 30-50%
    - Salt Split Skin-80-90% circulating ab's
    - Differing locations in BMZ LL LD

Linear IgA disease: DIF



Adult linear IgA disease Indirect

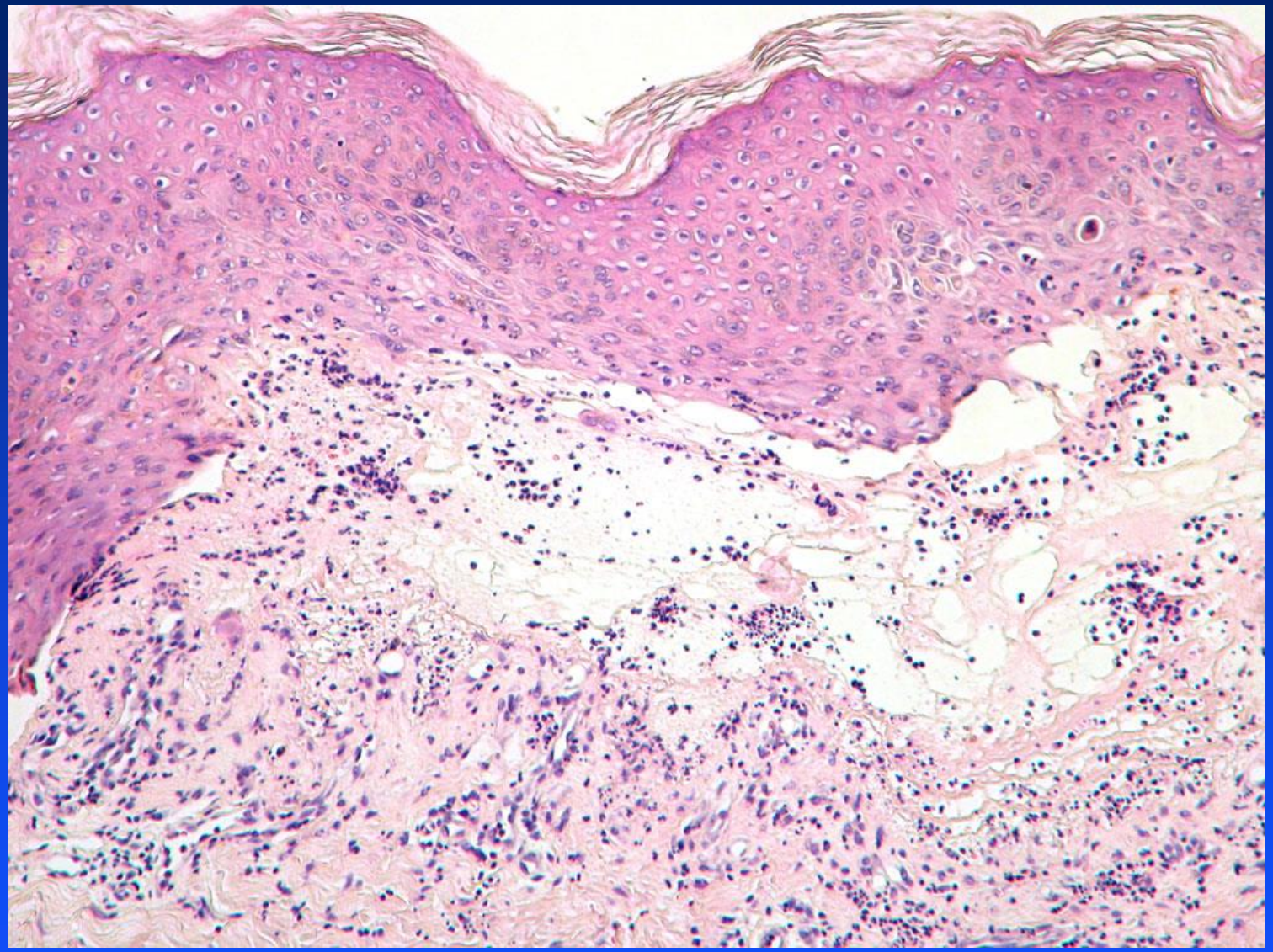


Linear IgA Bullous Dermatosis: Antigen

- Etiology- heterogenous
  - 97kD antigen (LABD97) or 120kd
    - The main antigen-in Upper Lamina Lucida degradation product of BPAg2
  - Type VII collagen
  - LAD285

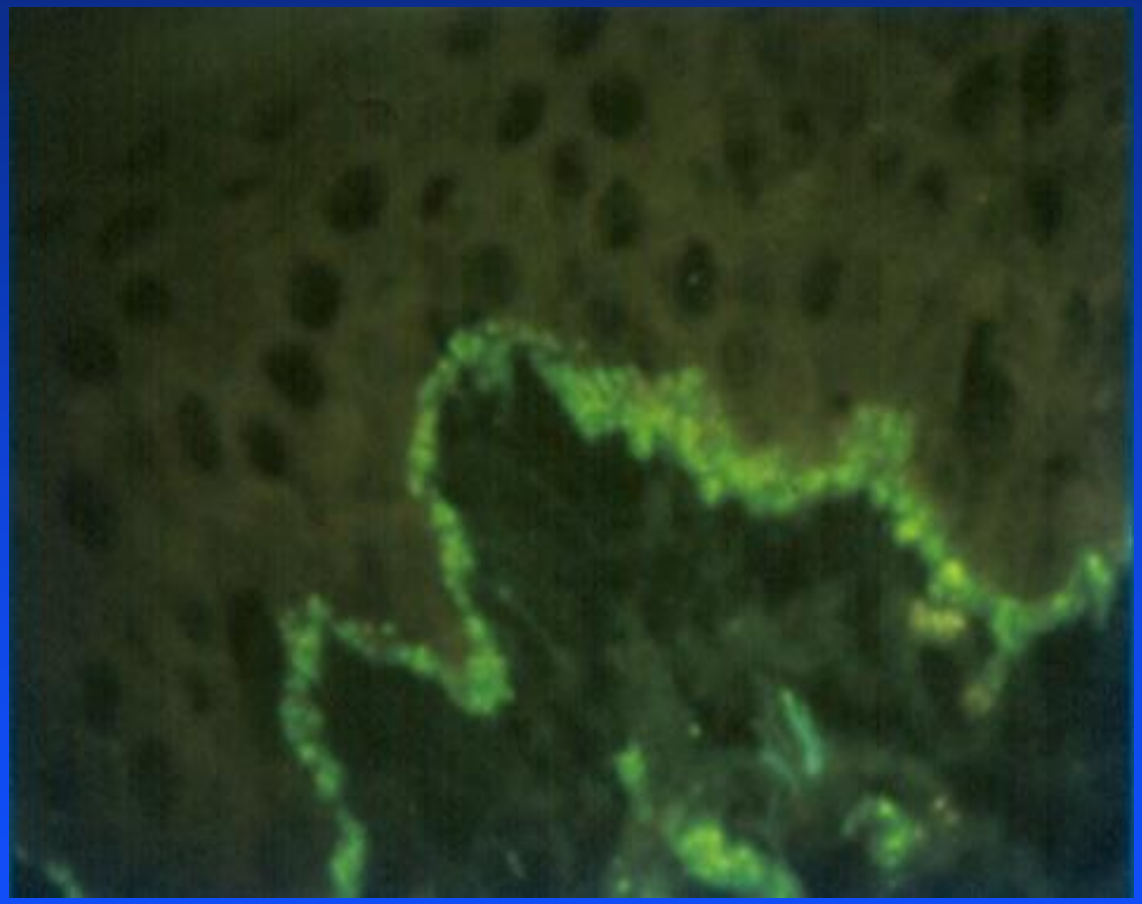
Differential diagnosis

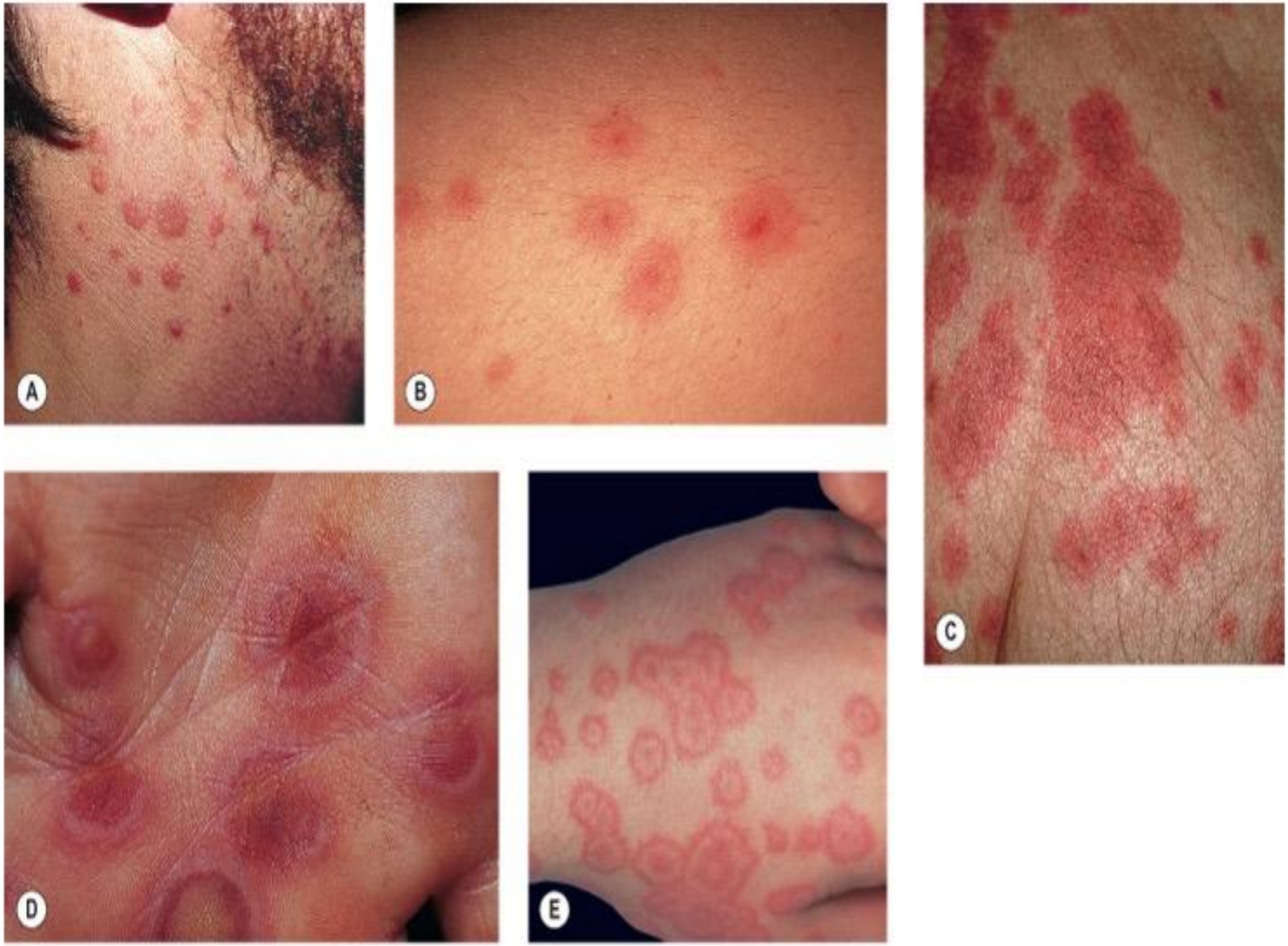
- Dermatitis herpetiformis
- Bullous SLE
- Inflammatory type of EBA



EBA

LE DIF:IgG

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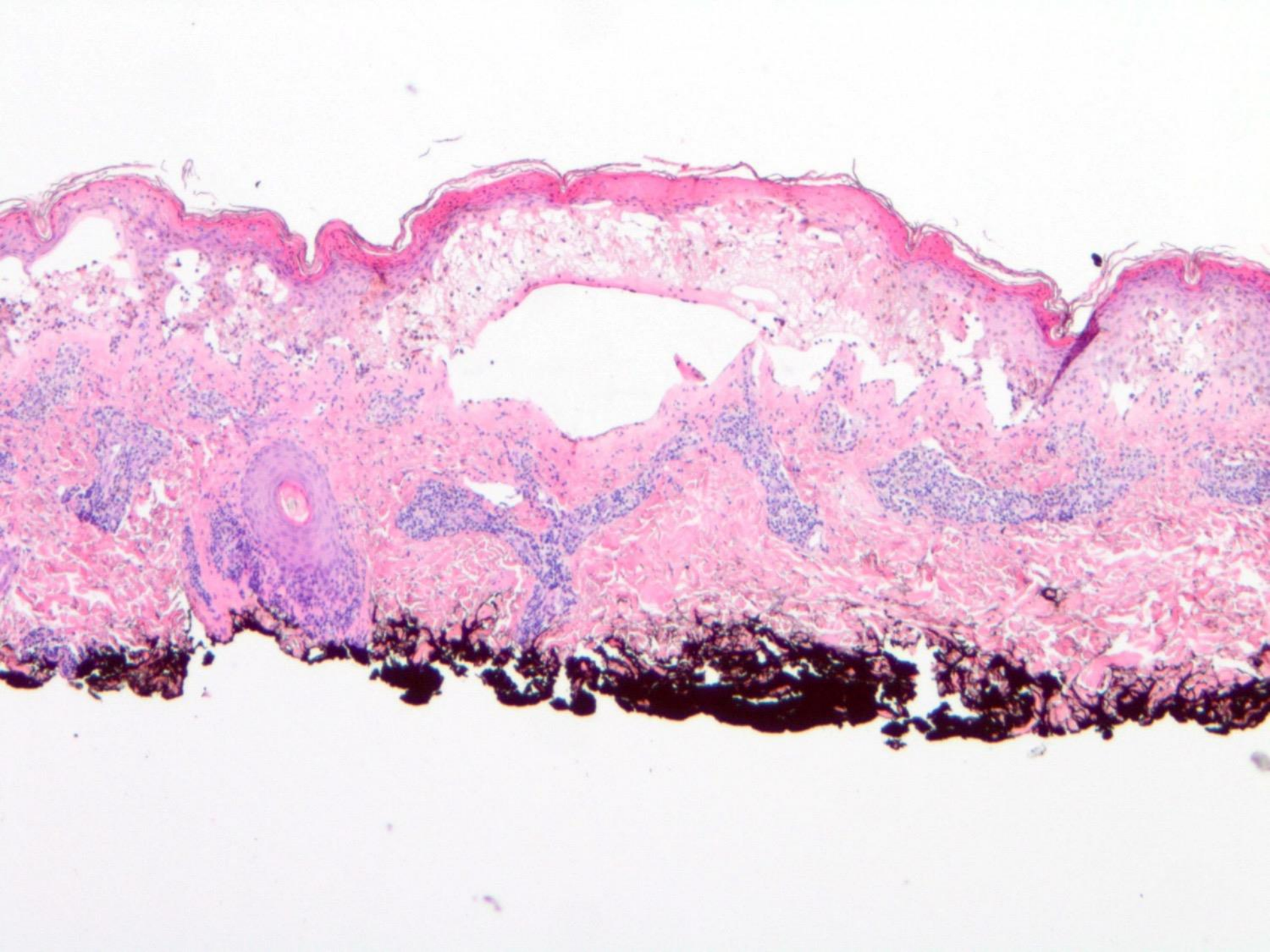
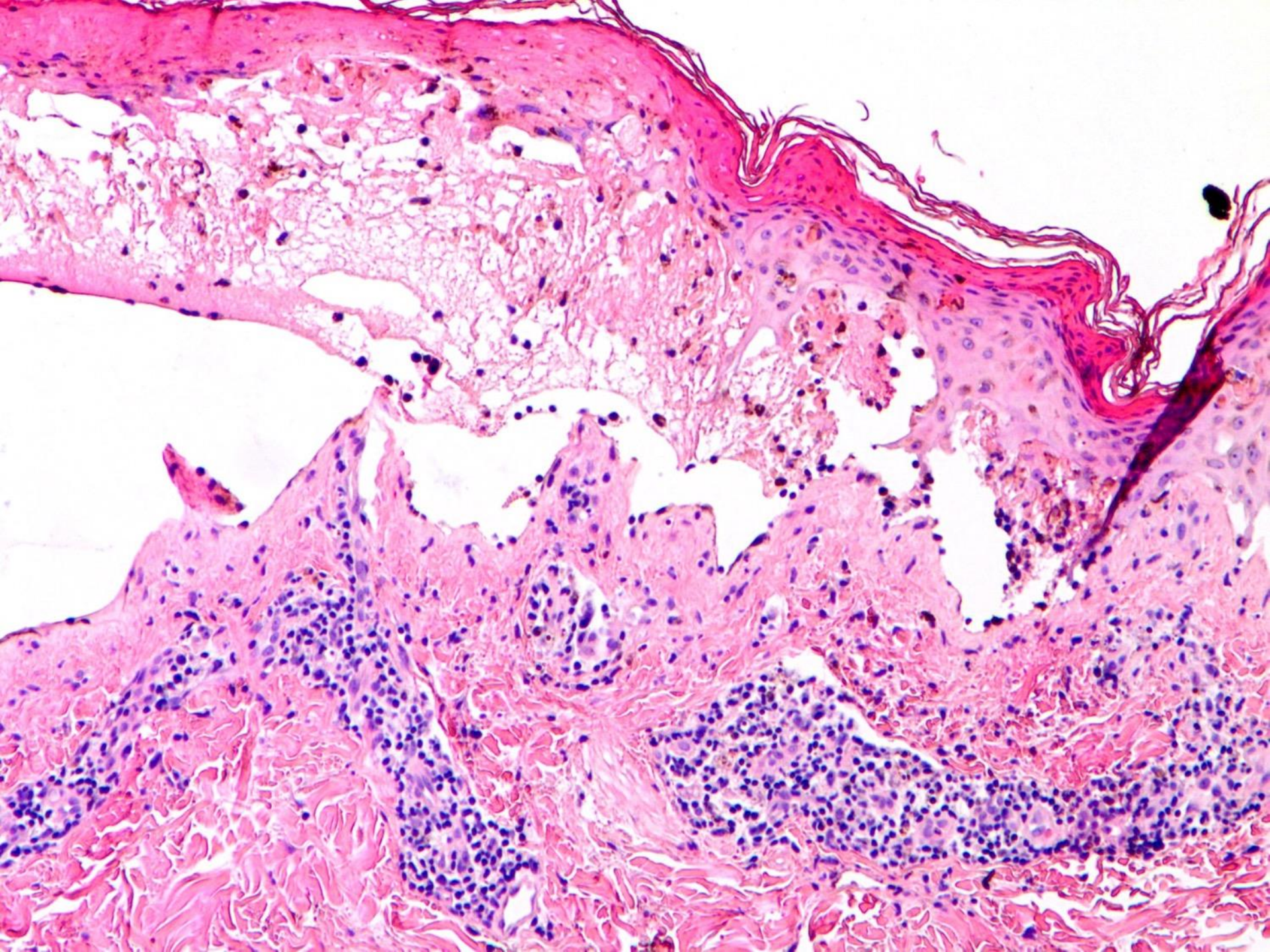
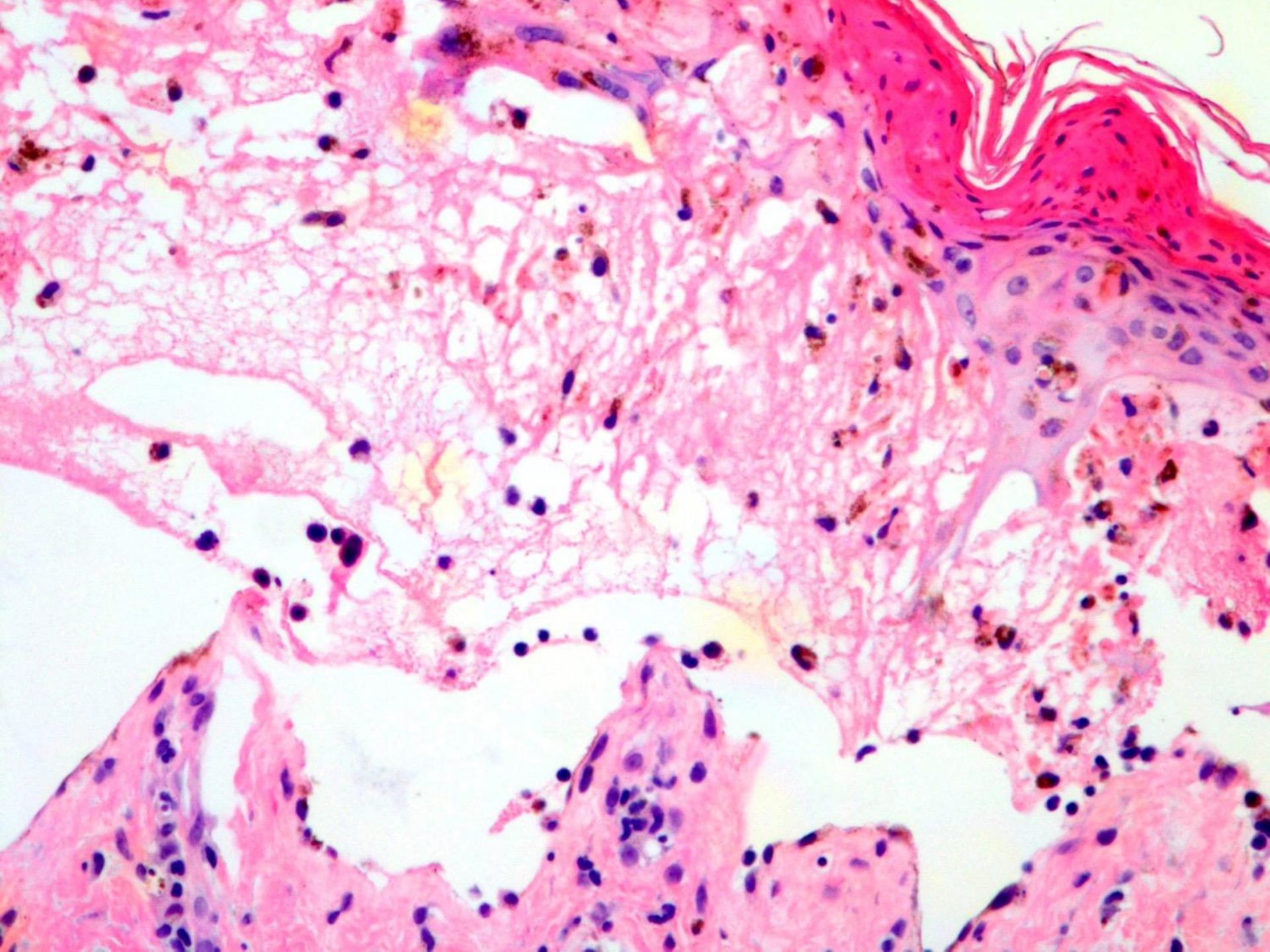
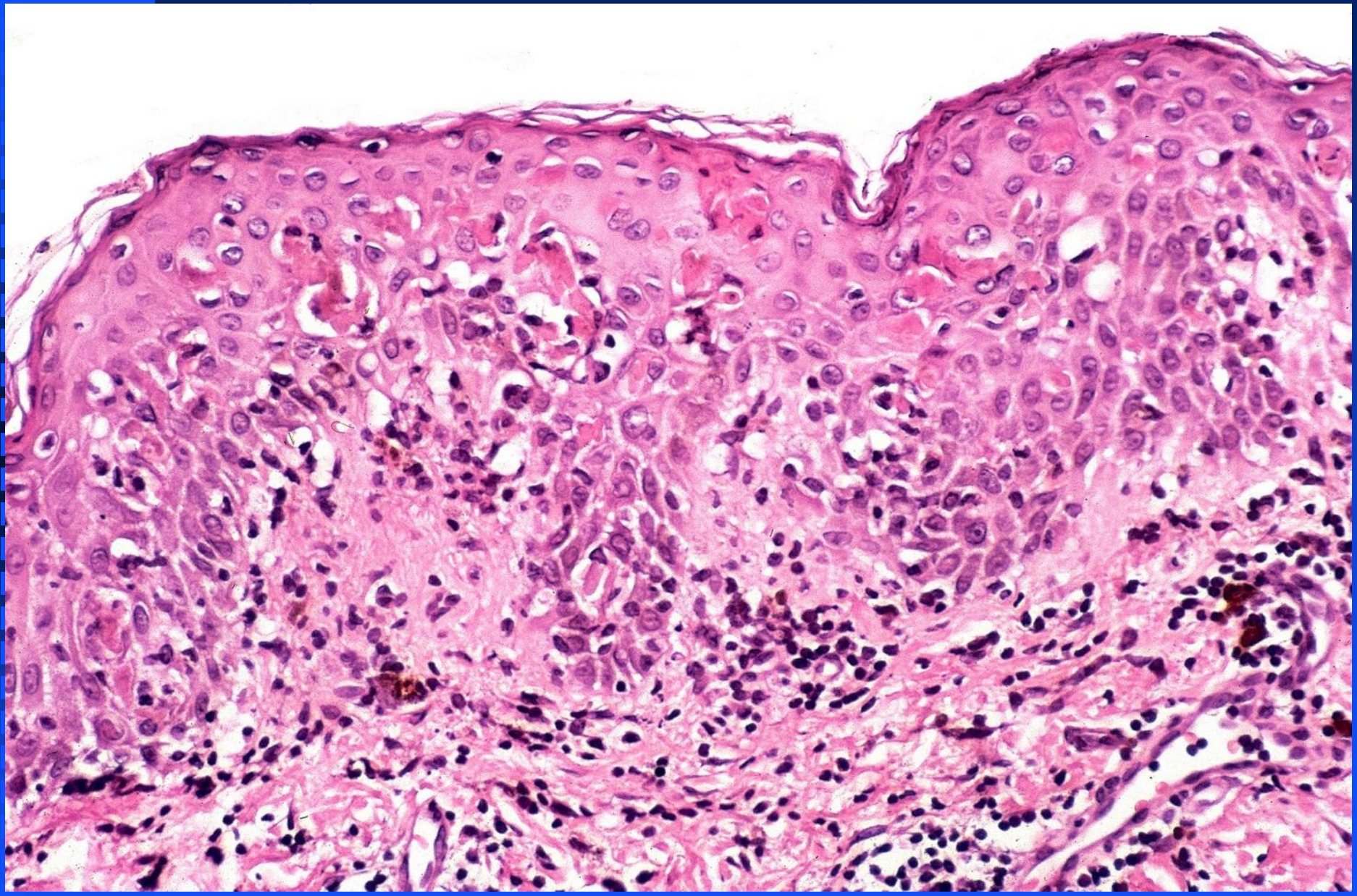








Erythema multiforme

Erythema multiforme

- Acute onset vesiculobullous dermatsosis (with numerous variants)
- Defined as without major mucous membrane or body surface area involved
- Occurs acutely following many antecedent stimuli-most commonly HSV but can beo ther infections and CVD
- Usually self limited

Pathology

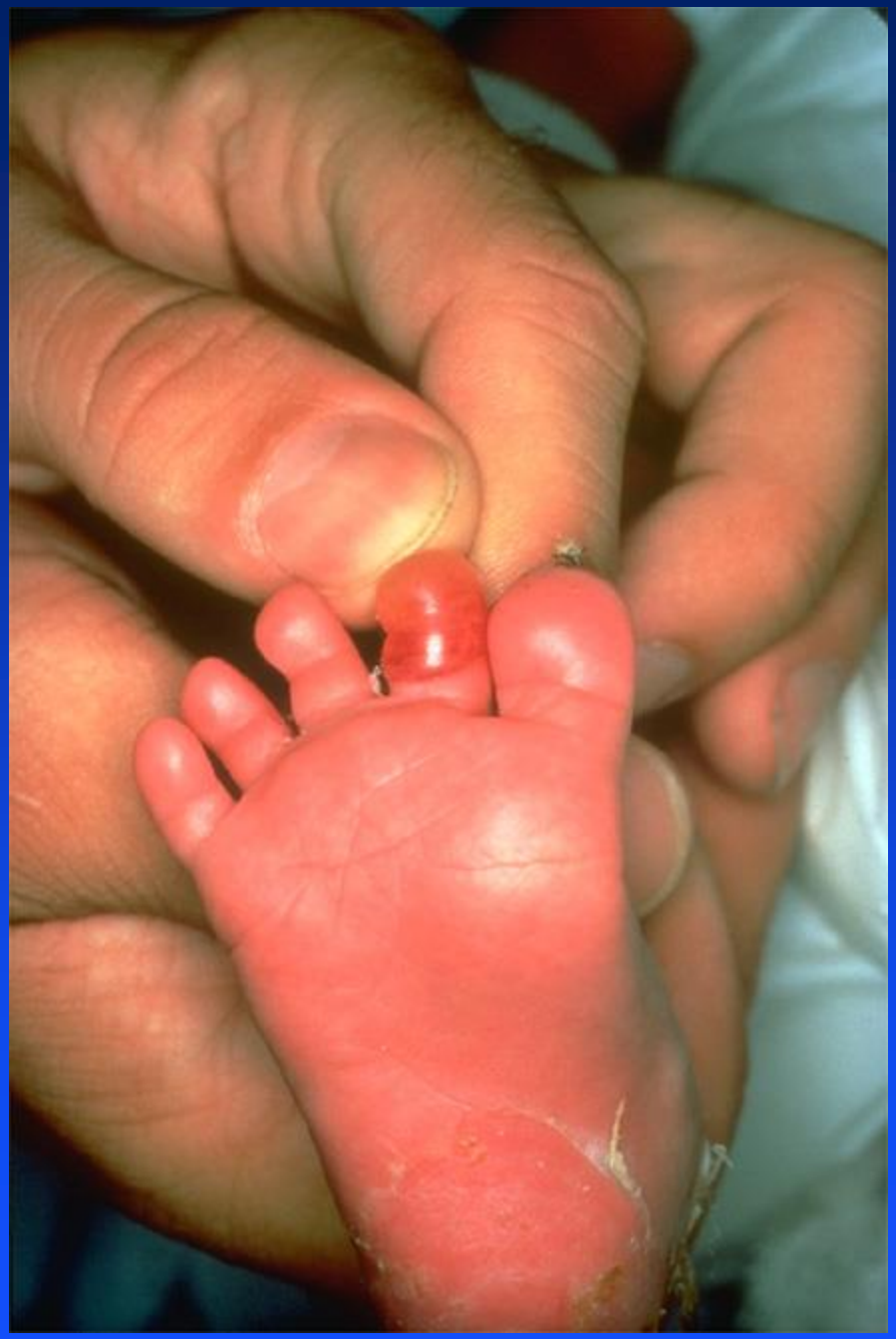
- Hydropic change at basal layer with some damage to basal keratinocytes
- Intraepidermal lymphocytes
- Necrotic (apoptotic) keratinocytes at all levels of the epidermis, possible confluent necrosis
- Subepidermla vesiculation
- Perivascular mononuclear or mixed infiltrate with some eosinophils

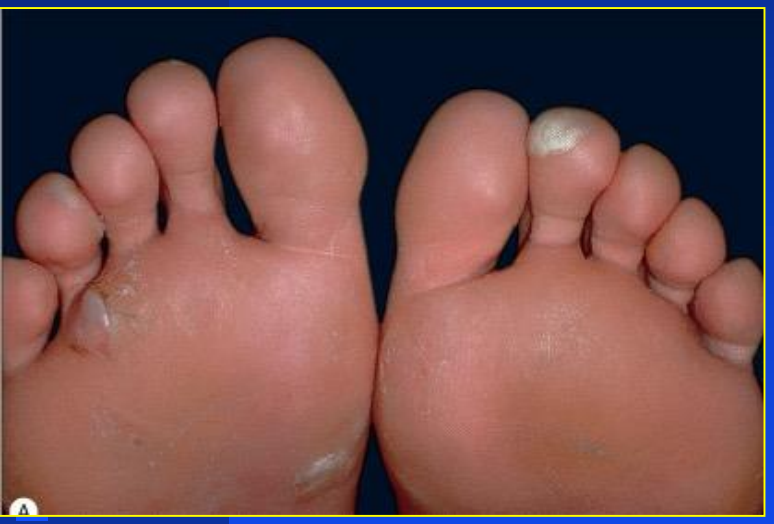
Immunofluorescence

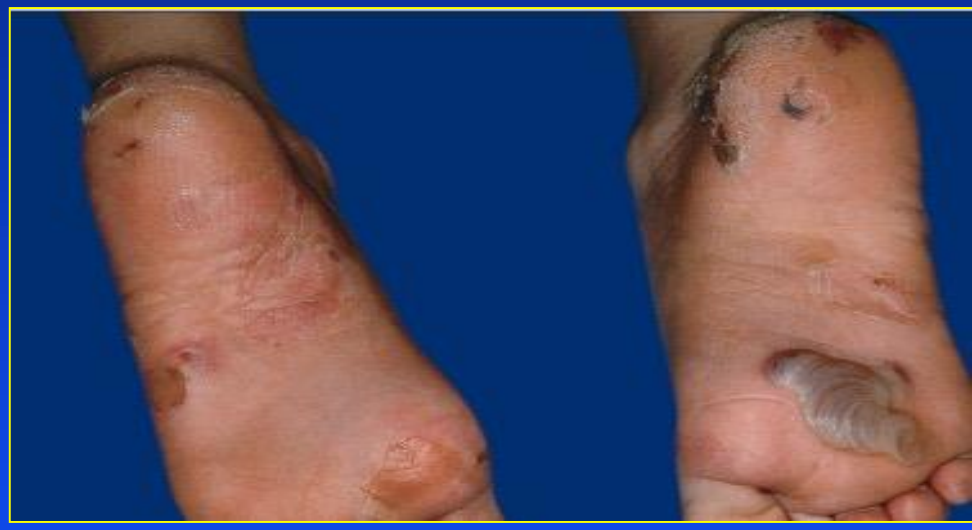
- C3 at DE junction and in blood vessels
- Staining of cytoid bodies with IgM

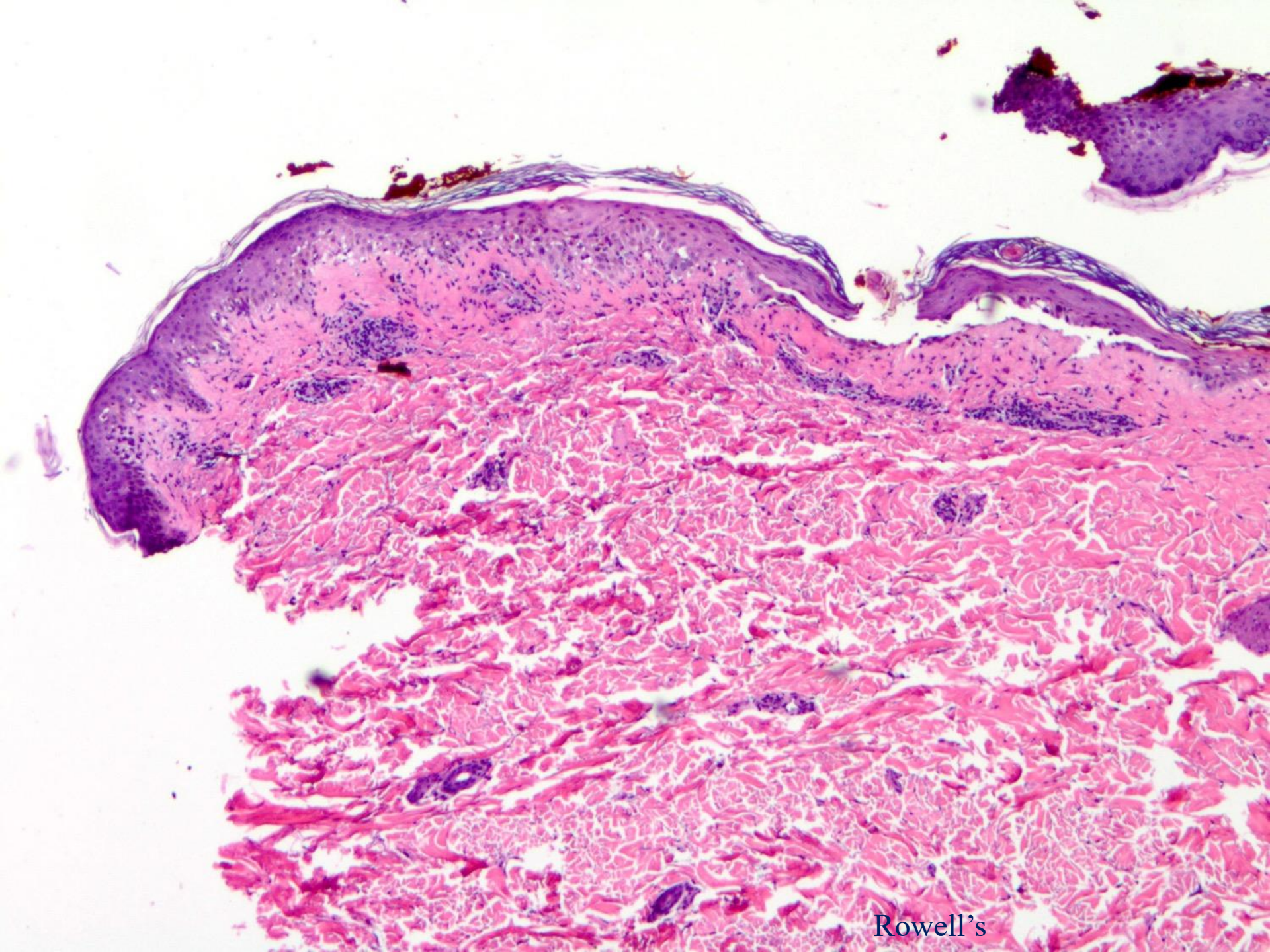
Differential diagnosis

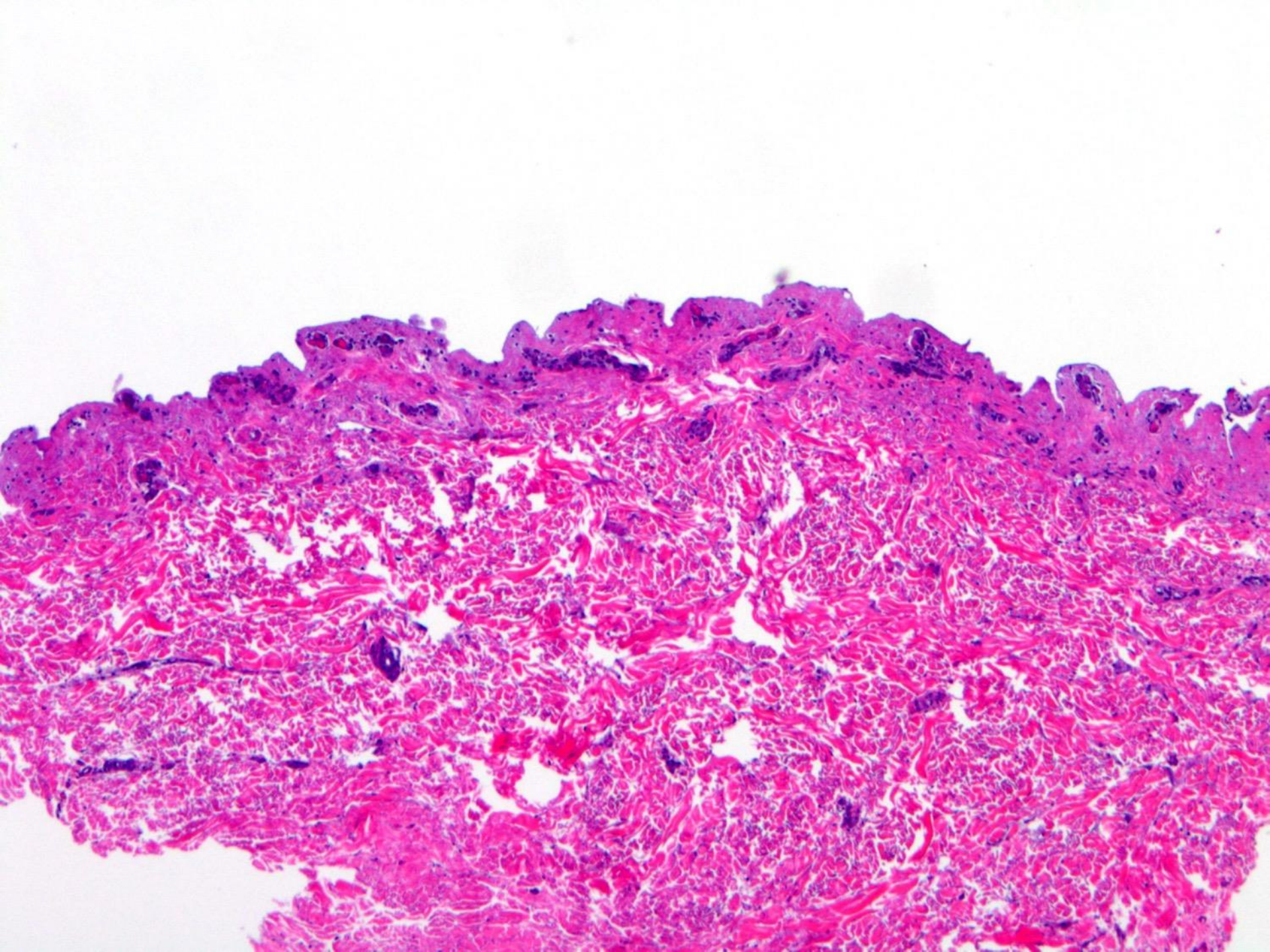
- Graft versus host disease
- Hand foot and mouth disease
- Paraneoplastic pemphigus
- Rowells syndrome

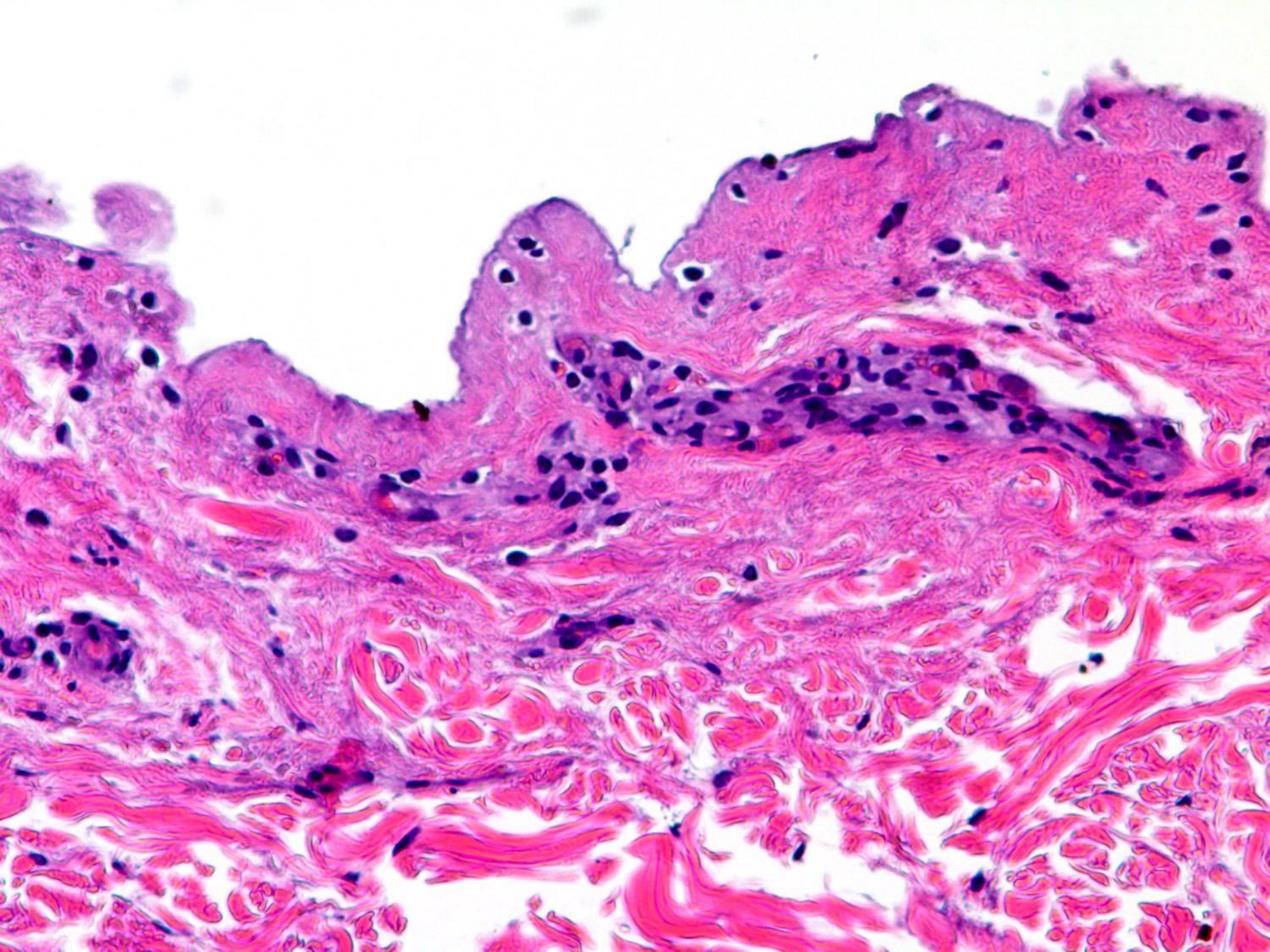


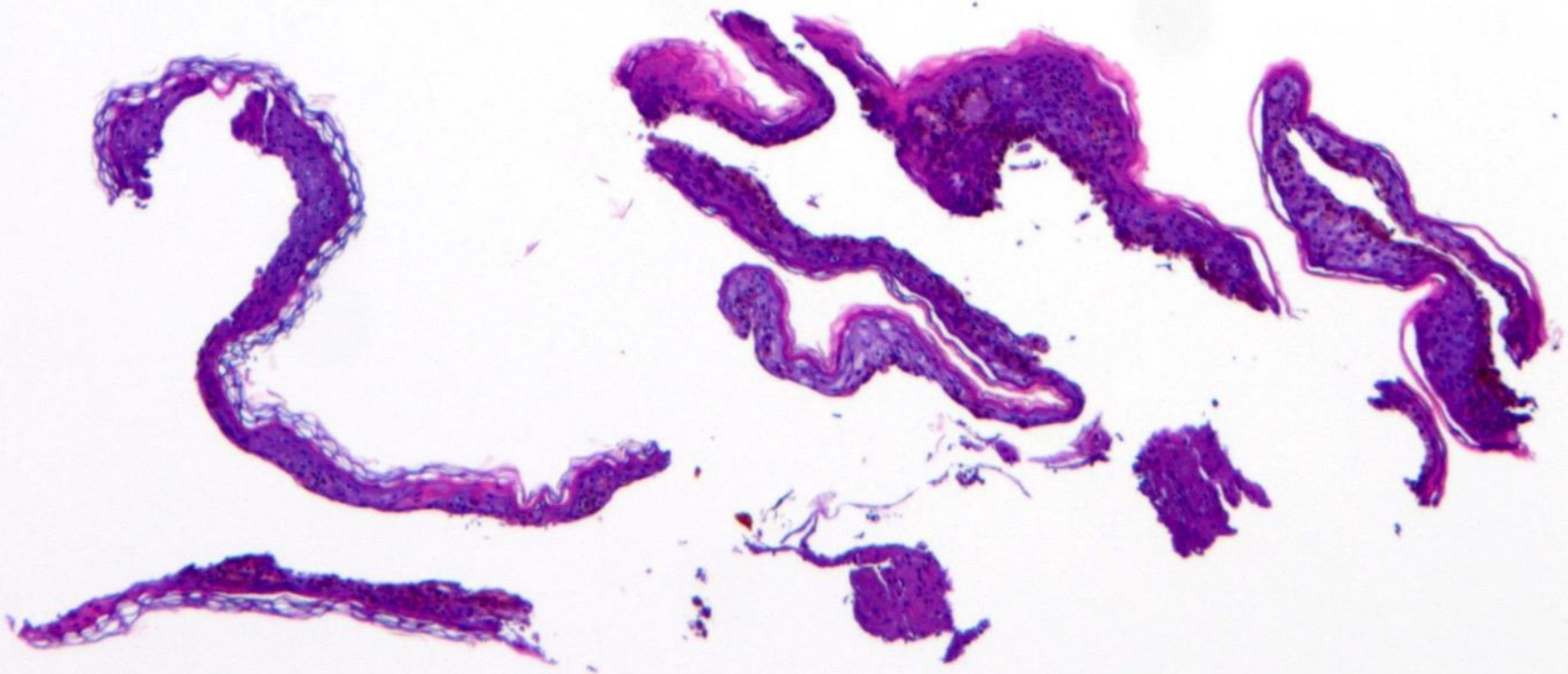


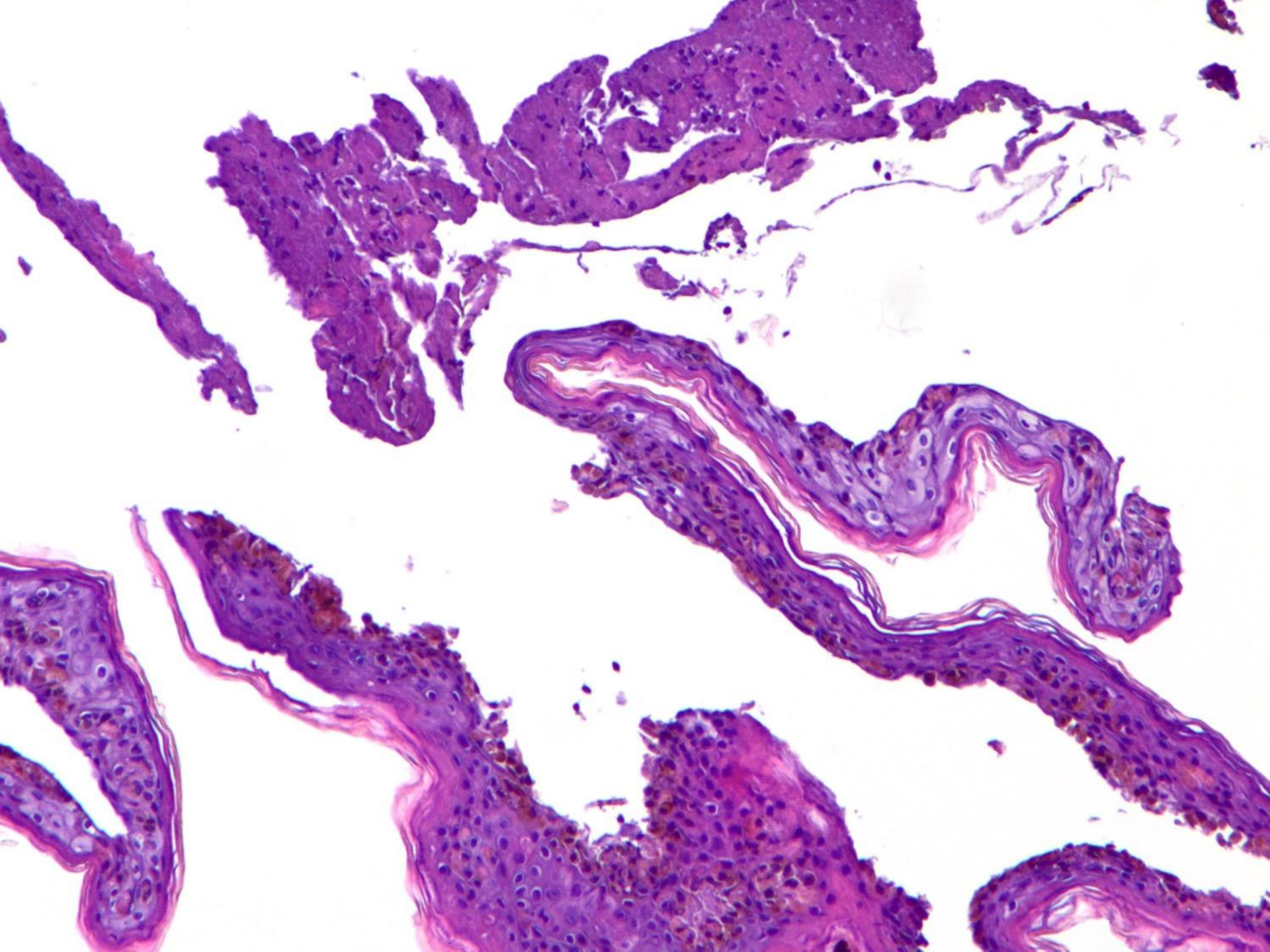



Rowell's









Epidermolysis bullosa (?simplex)

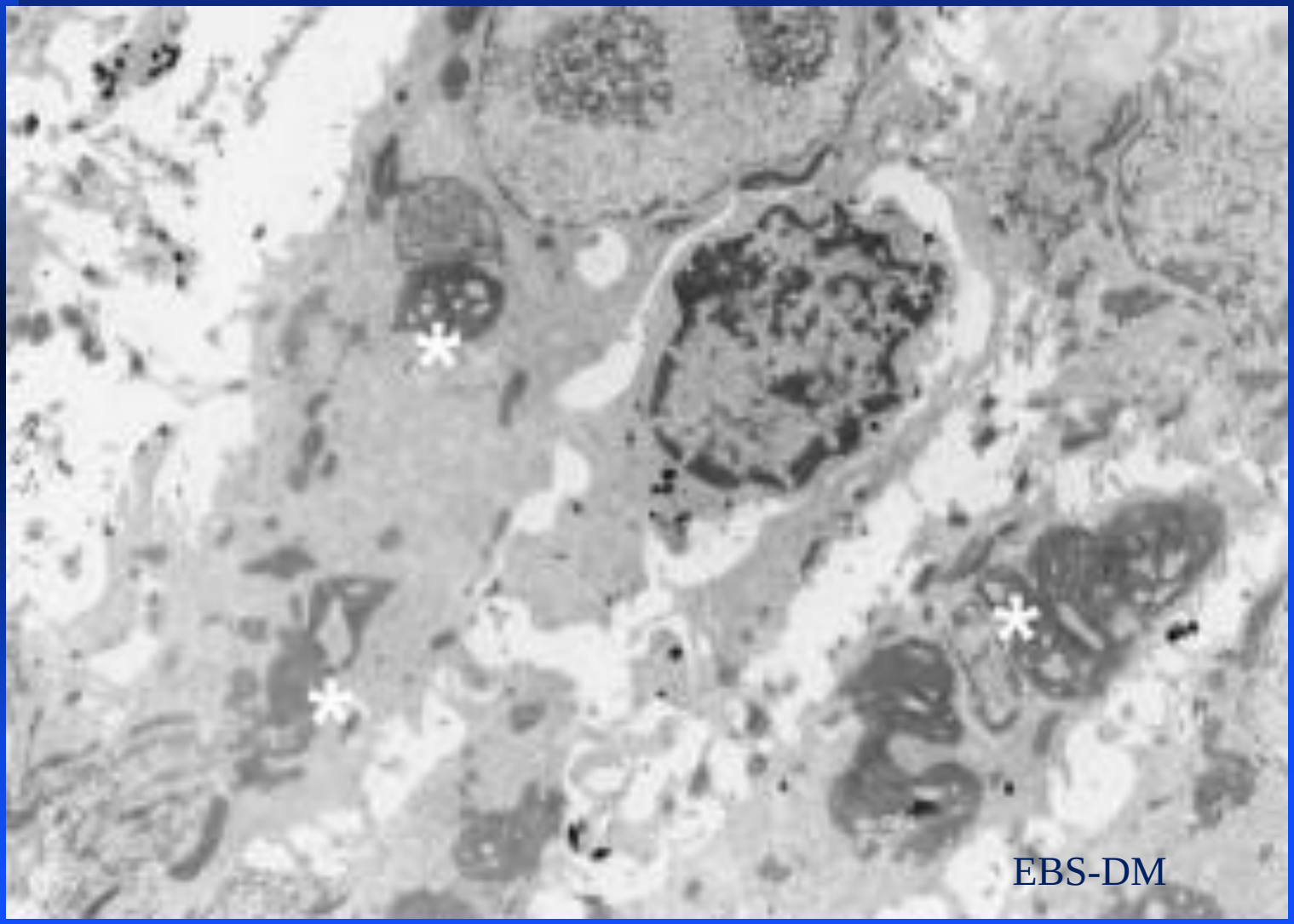
Pathology

- Non inflammatory subepidermal bullous disease (in most instances)
- Pathology can vary sometimes- Dowling Meara

Etiology

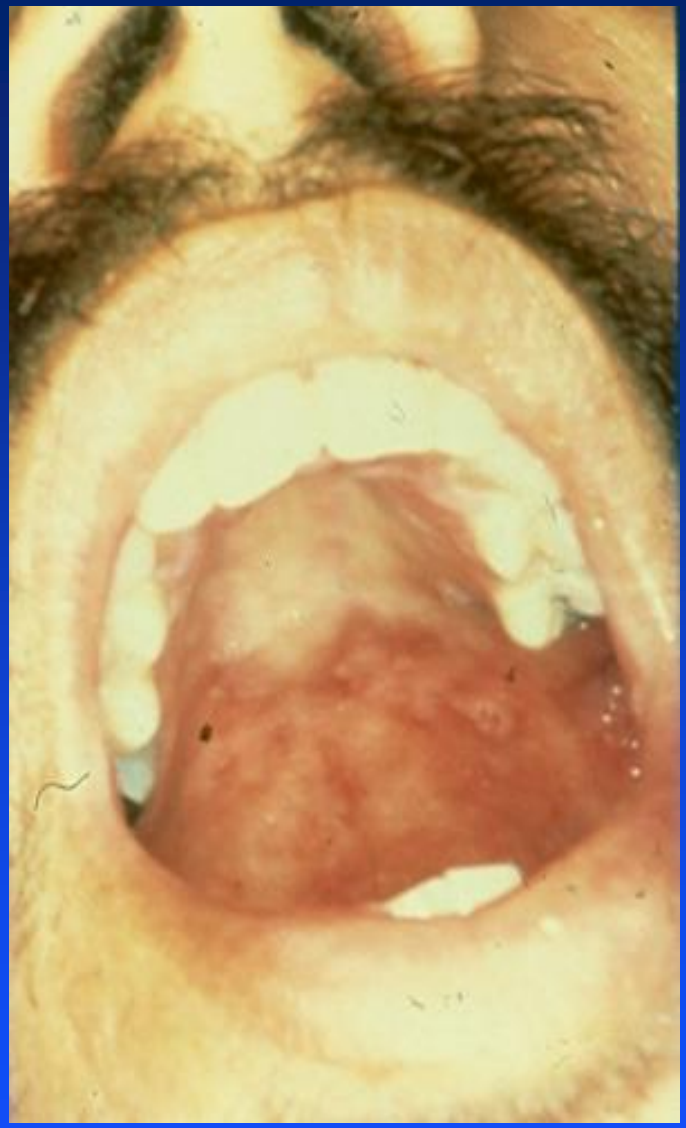
- Numerous variants
- Defects in keratins, cytoskeletal proteins, basement membrane proteins
- Can affect skin, mucous membranes, nails, teeth, hollow viscera, other organ systems depending on defect

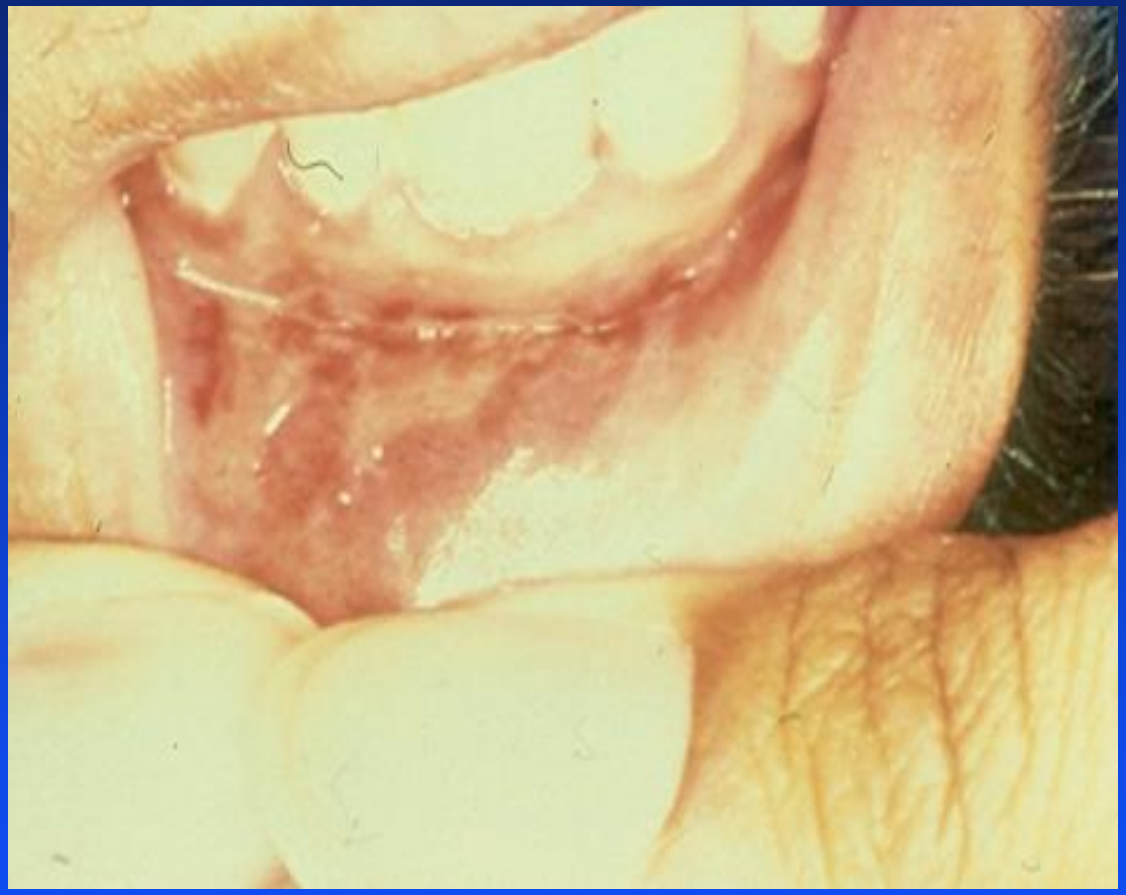
Electron microscopy

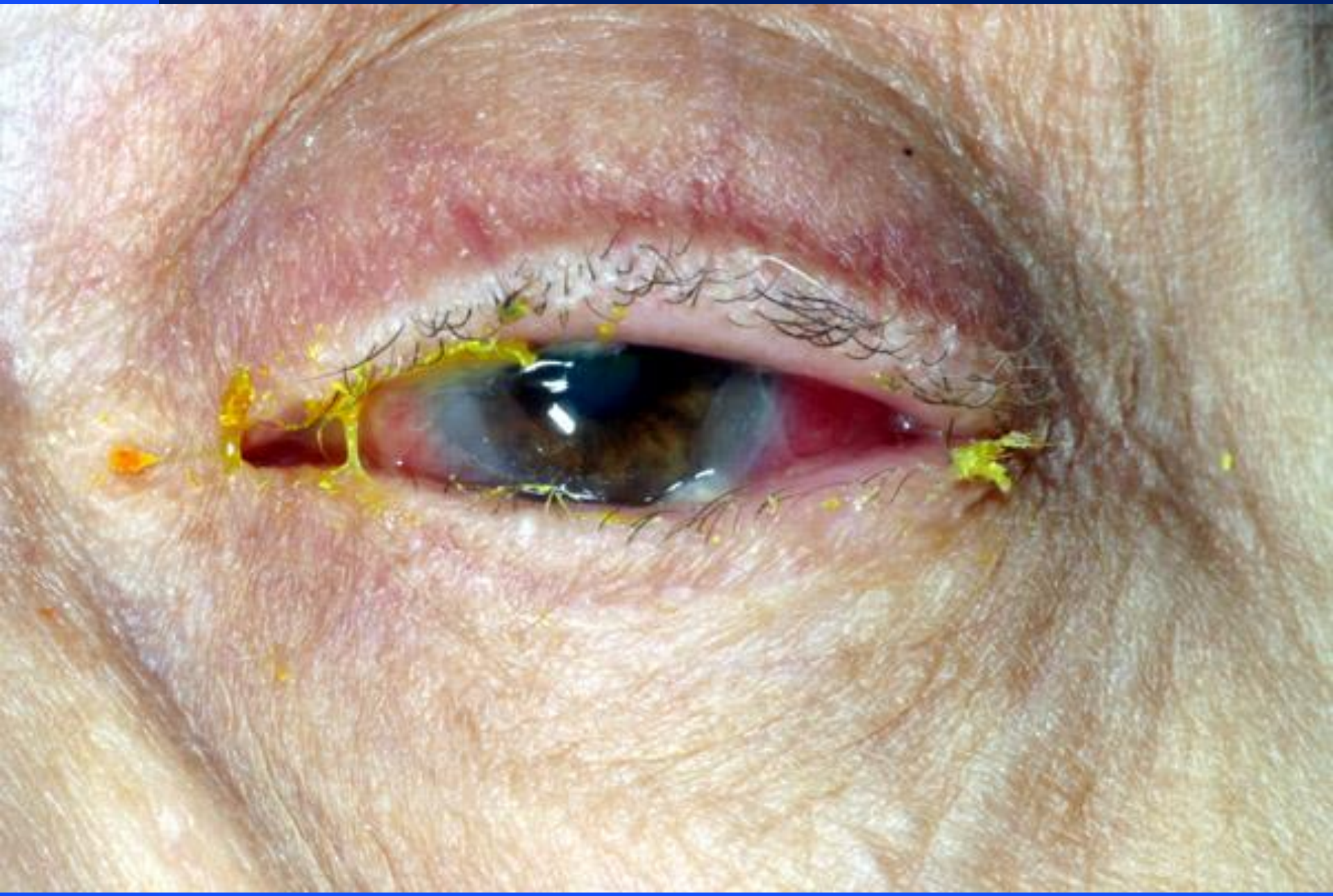


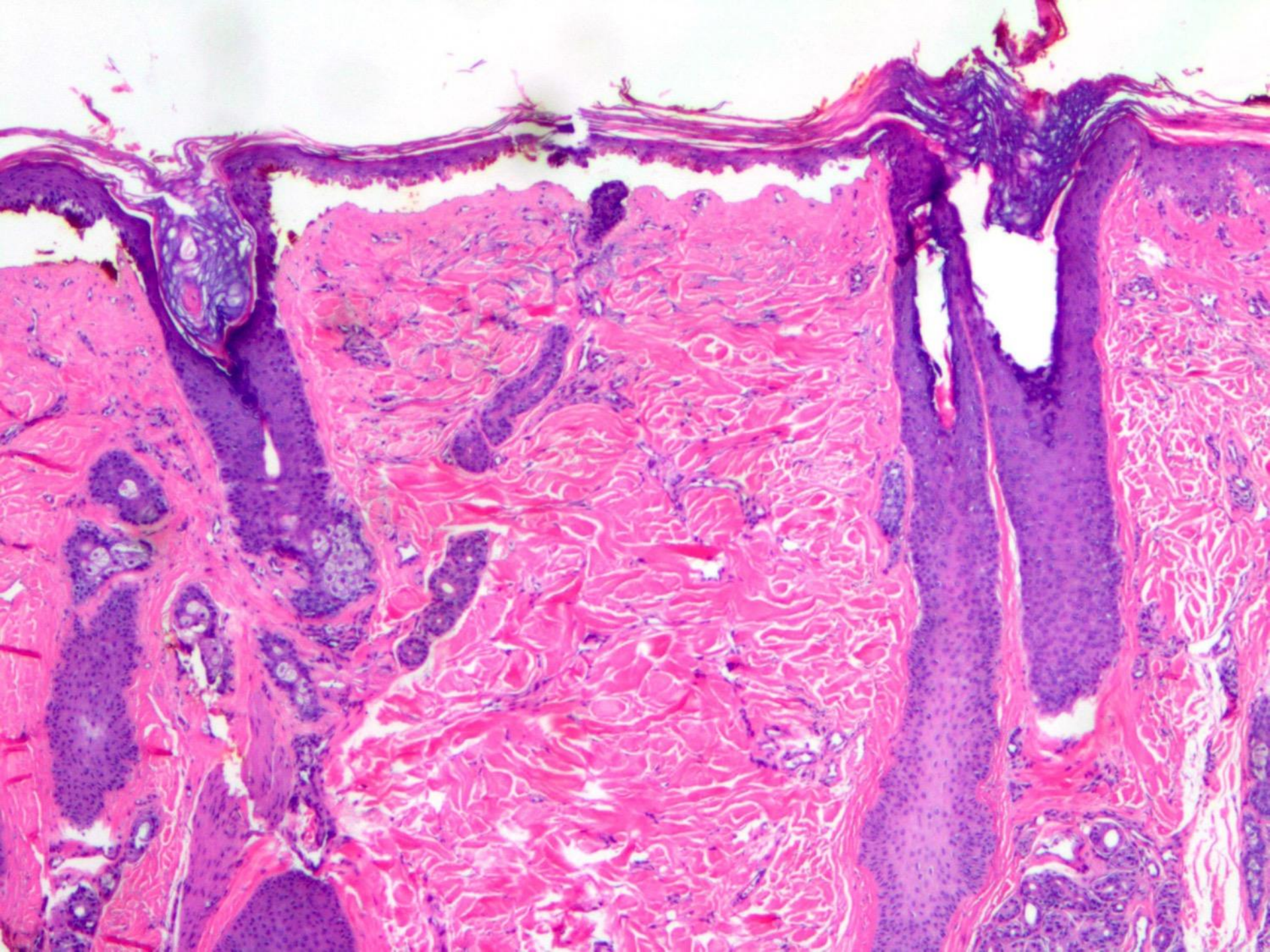
Differential diagnosis

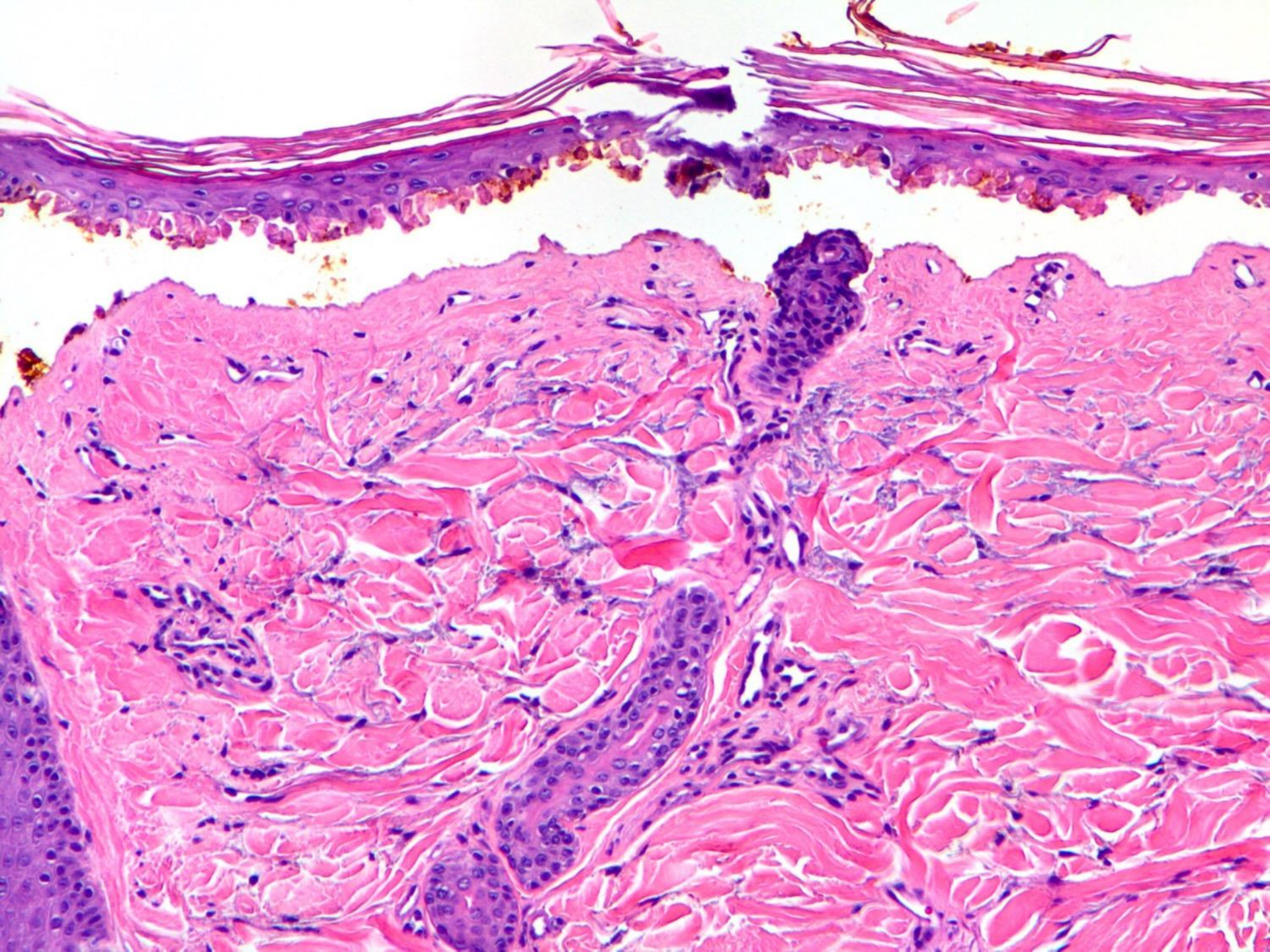
- Cell poor pemphigoid
- Noninflammatory EBA
- PCT

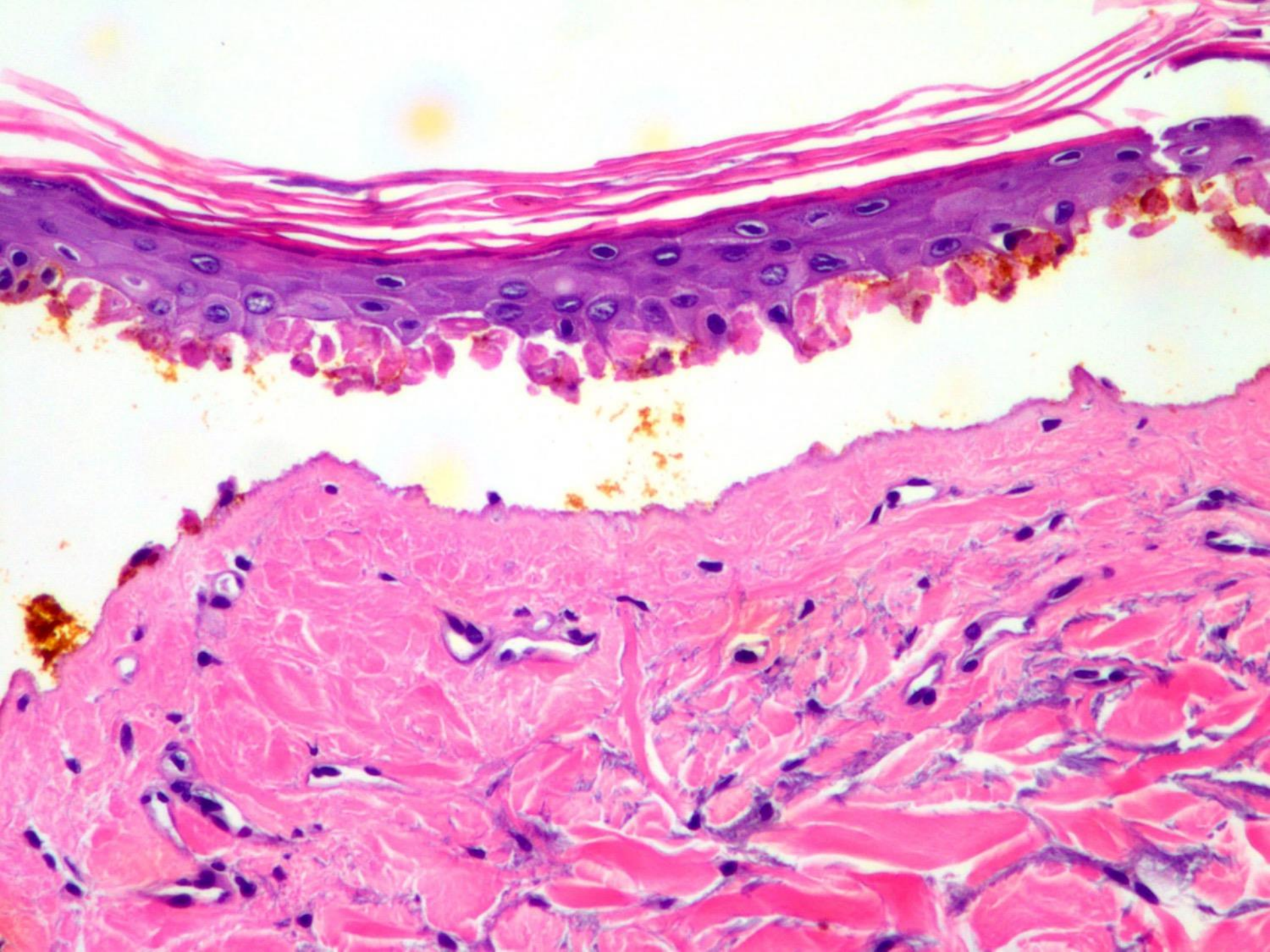












Cicatricial pemphigoid

Clinical presentaton

- Usually major involvement of mucous membranes
- Oral-gingiva, buccal, palate, tongue, alveolar ridge, lower lip
- Ocular-conjunctival mucosa
- Cutaneous 25%

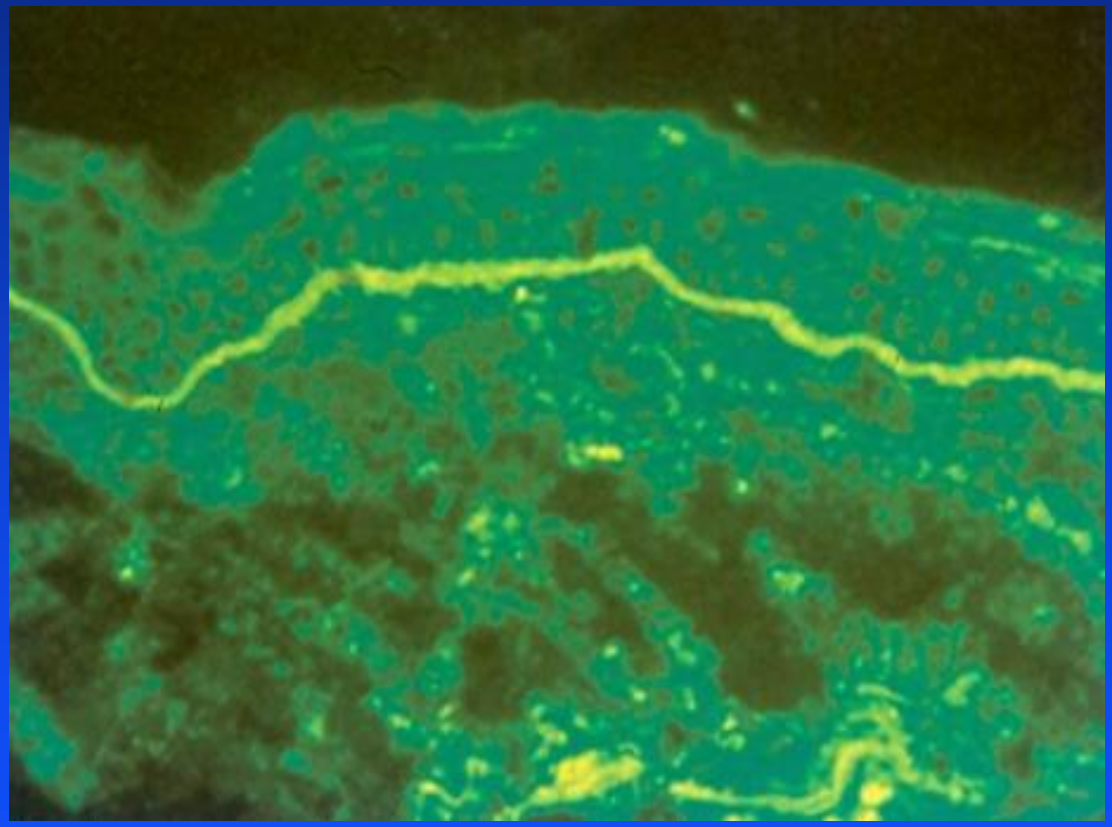
Pathology

- Non inflammatory subepidermal bullae with extension down adnexa
- Subepidermal blister w/ variable infiltrate of lymphs, eos, neuts depends on age of lesion
- Fibrosis

Immunofluorescence

- Varies according to type
- Most often linear C3

Cicatricial Pemphigoid: Linear C3

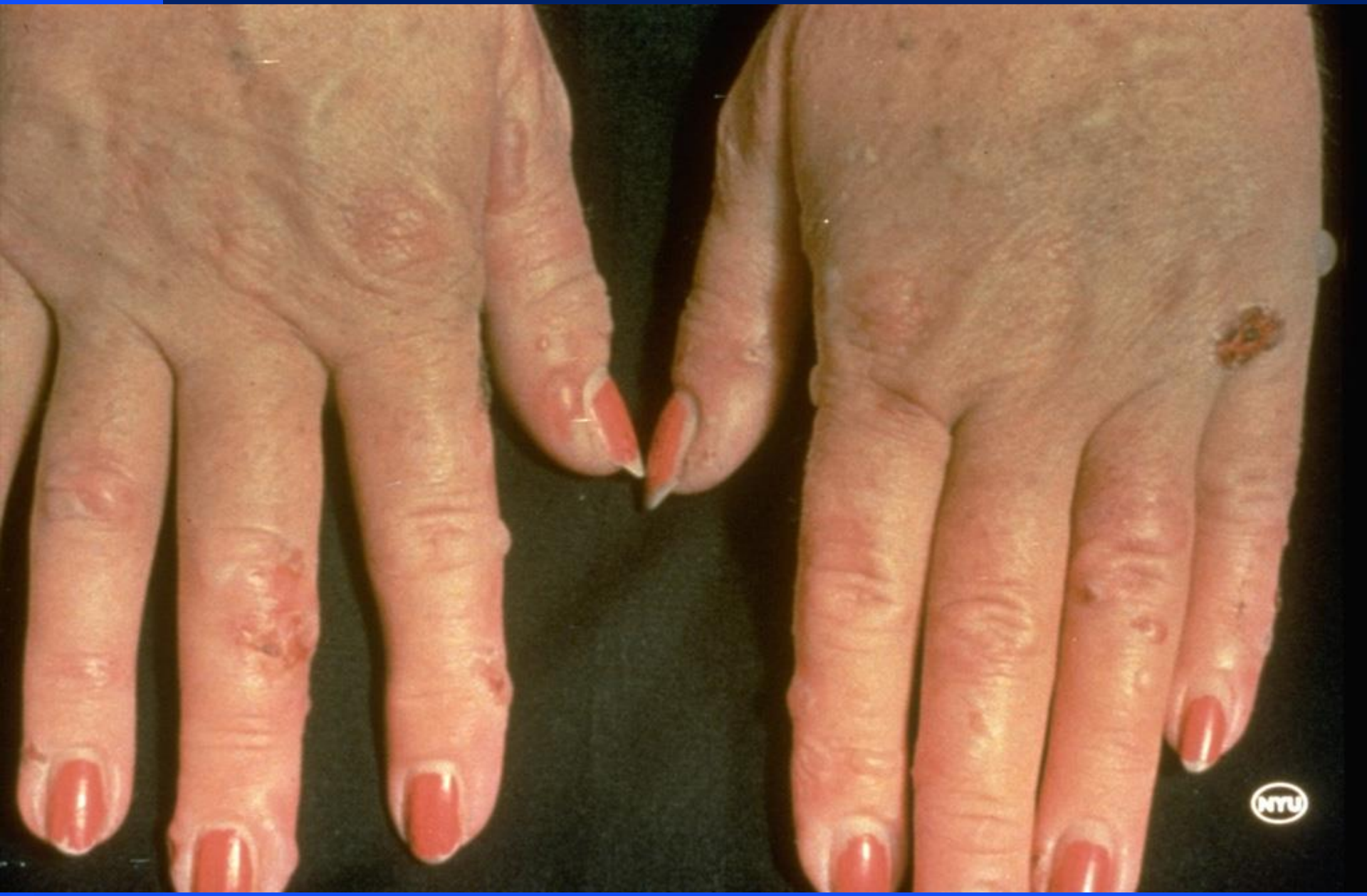


Cicatricial Pemphigoid

- Etiology: heterogenous
  - Variety of antigens: a disease phenotype
    - BP180(BPAG2)-most frequent in CP, target epitope on BPAG2 is more distal at the NC 16 C-terminus domain
    - Laminin 5 332 (aka epiligrin, kalinin, BM600, nicein) A3 chain, oral lesions predominant and severe
    - 205kD B4 integrin, ocular CP
    - Type VII (collagen(EBA)

Differential diagnosis

- PCT
- EBA (inflammatory and noninflammatory type)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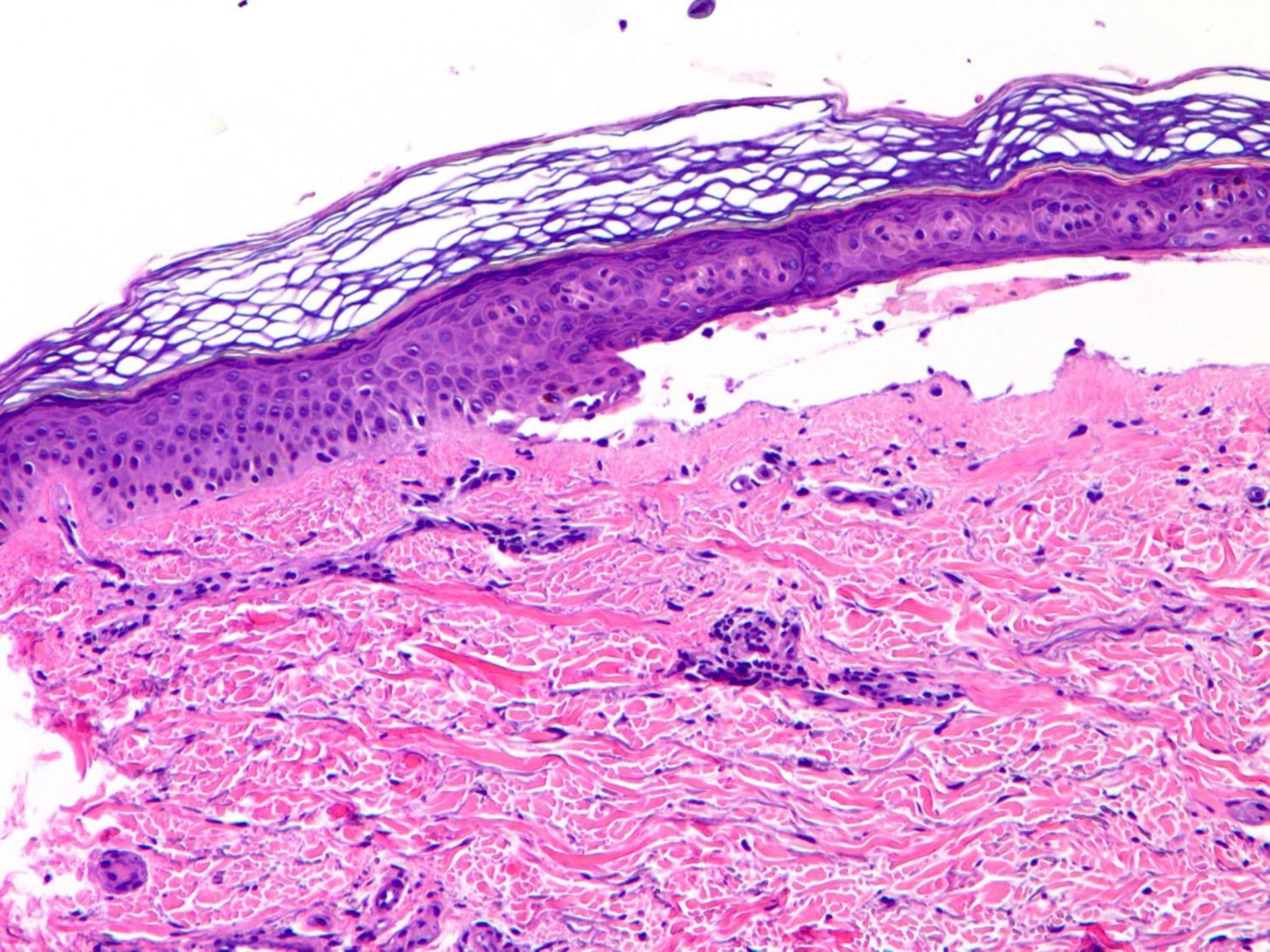
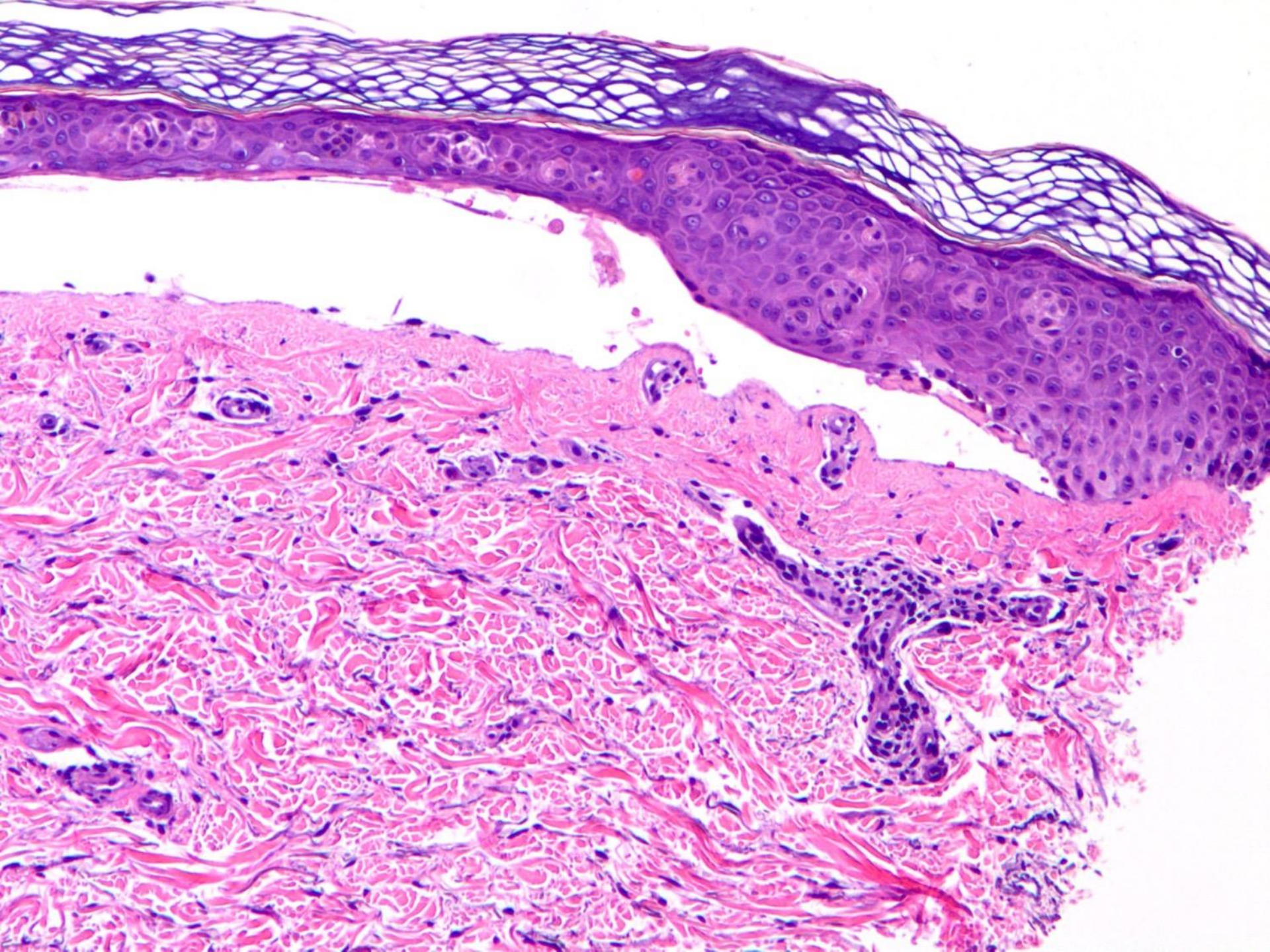
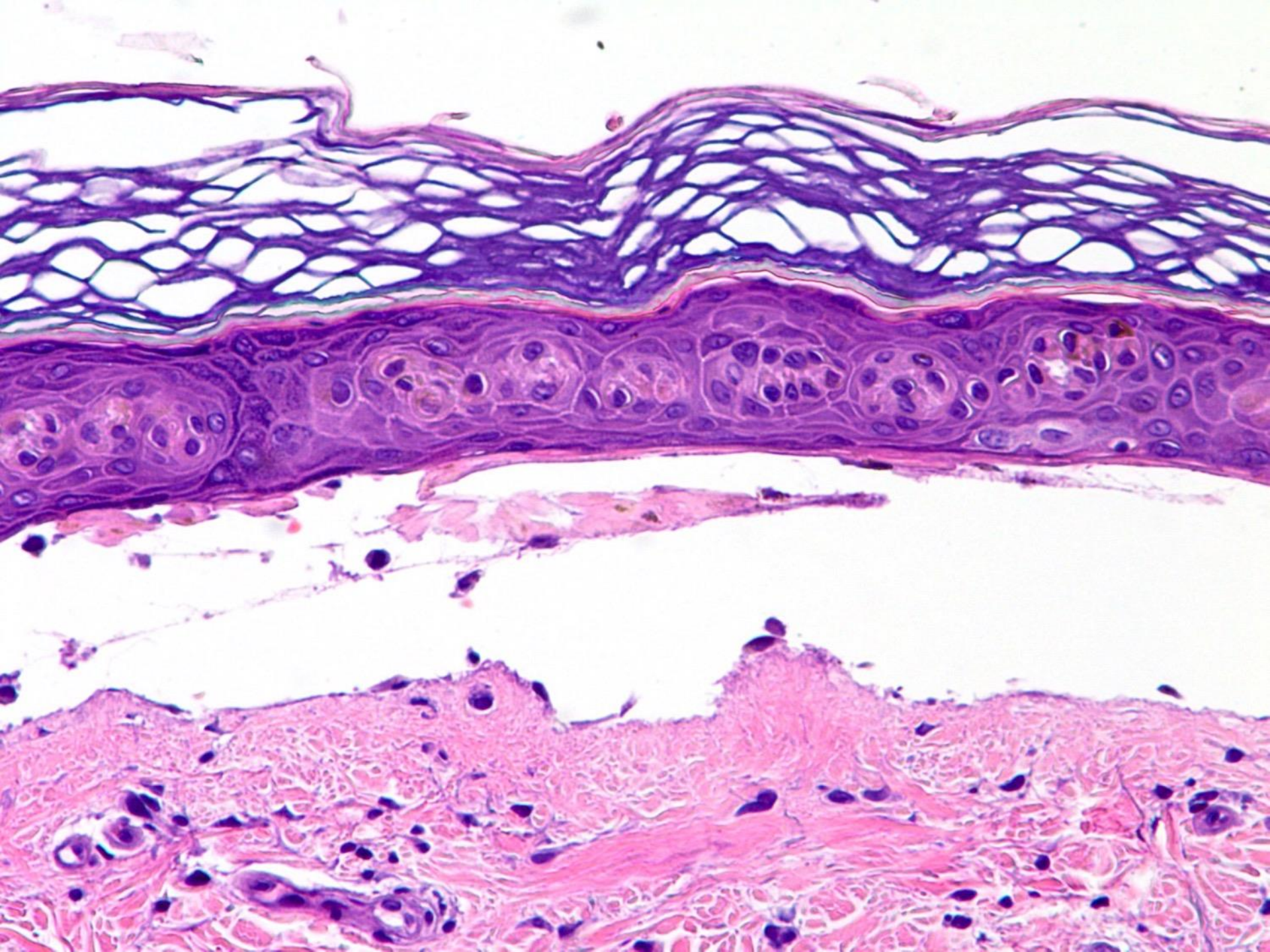
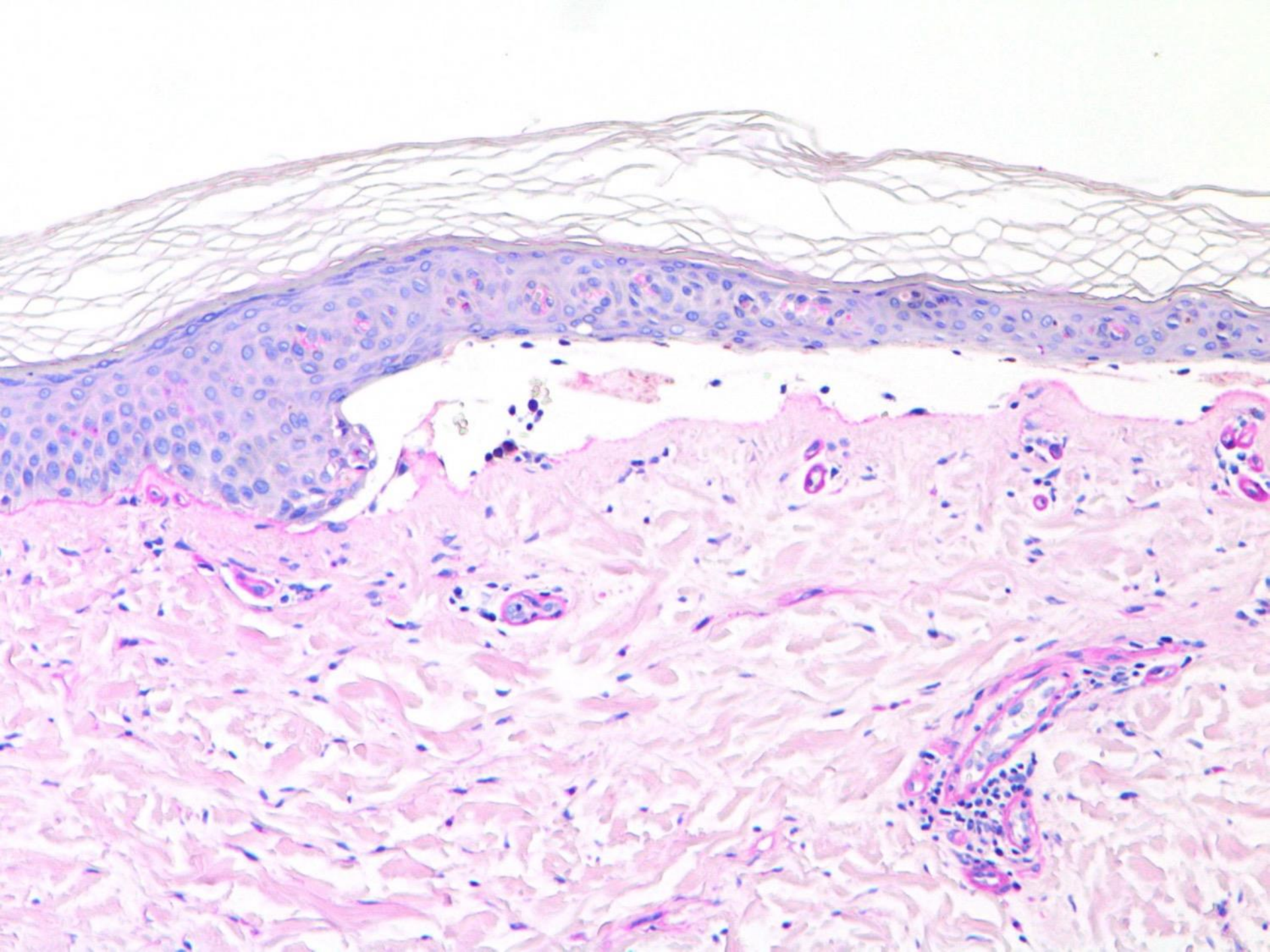








Porphyria cutanea tarda

Clinical features

- Many different genetic types
- Not all types have skin manifestations
- Skin fragility followed by blisters and scarring
- Usually photosensitive
- Porphyria cutanea tarda by far the most common type, can be acquired and sporadic

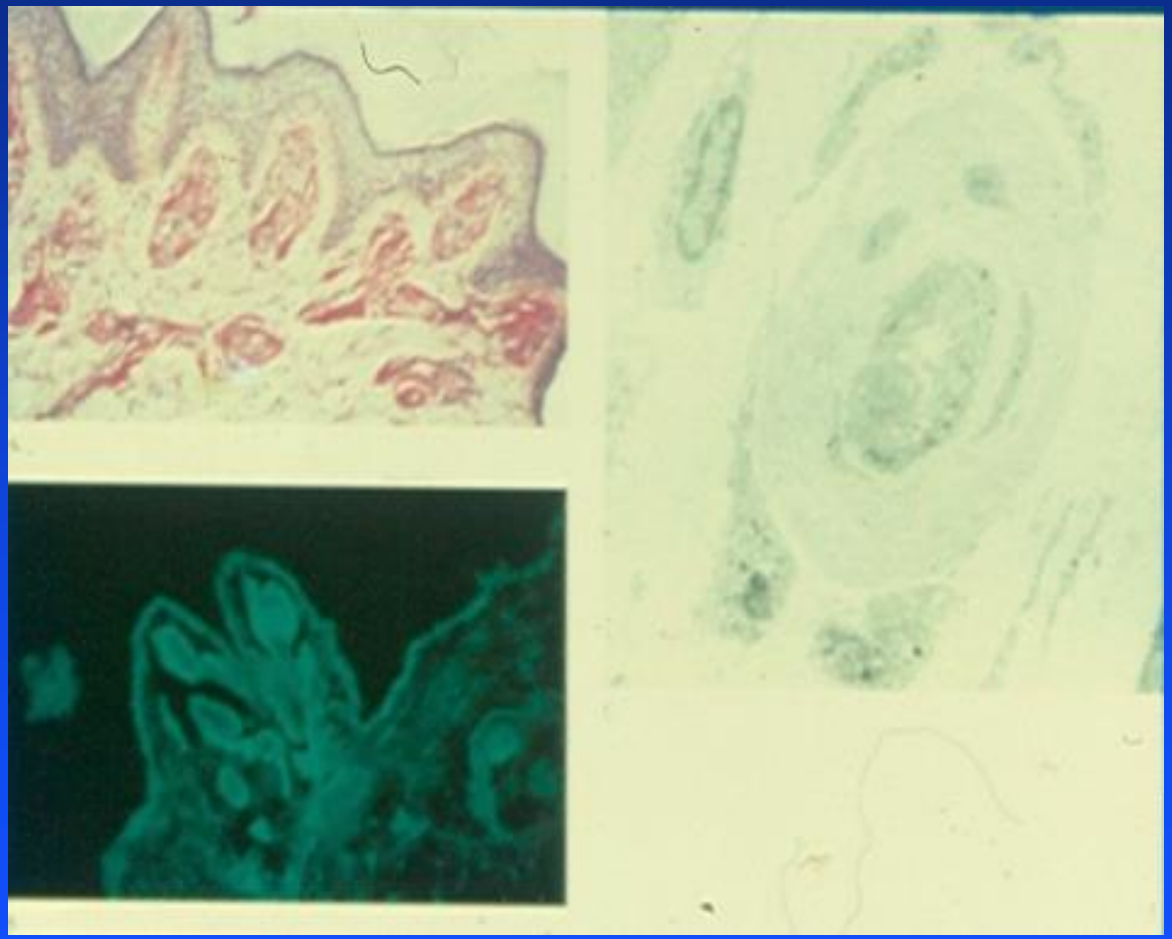
Pathology

- Non inflammatory subpepidermal bulla
- Acral sites
- Prominent dermal papillae
- Thickened capillaries
- Reduplication of basement membrane in epidermis-caterpillar bodies

Immunofluorescence

- Linear fluorescence in basement membrane and epidermis

Porphyria (skin types)



Differential diagnosis

- EBA
- EB (most types)
- Cell poor pemphigoid

Immunofluorescence review

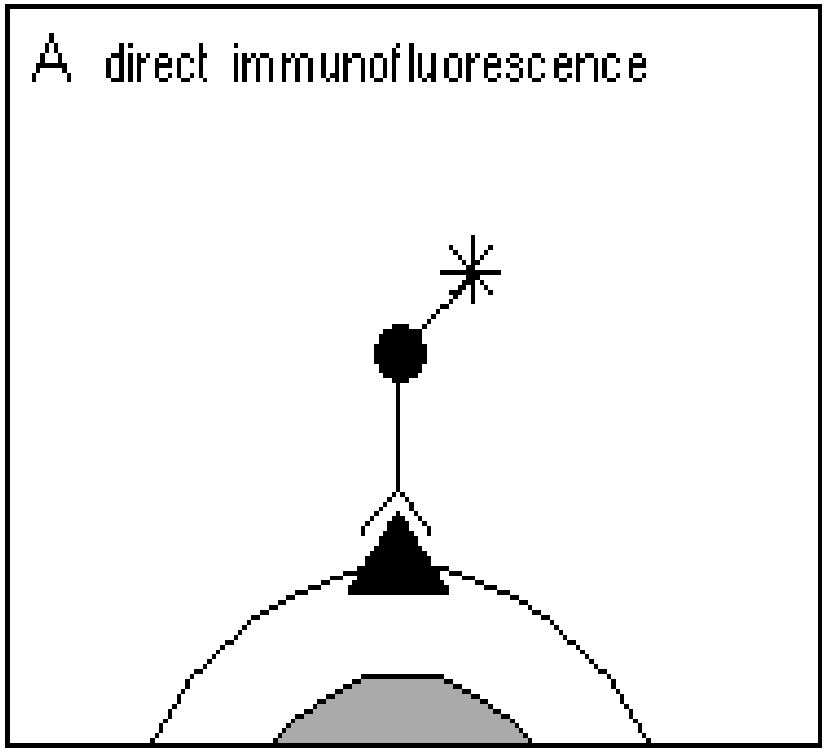
- Where to biopsy
  - Lesional- for H&E
  - Perilesional for IF
- Target antigen (s)
- Pattern on direct immunofluorescence
- Pattern on indirect immunofluorescence

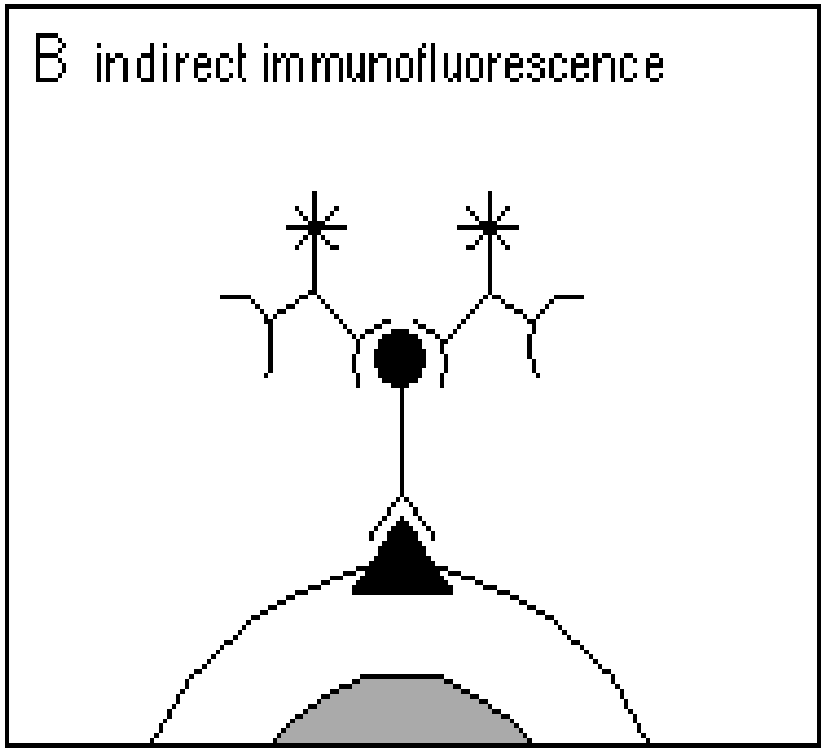
Direct Immunofluorescence

- Purpose- to detect deposited immunoglobulins, complement and fibrin in the skin
- One-step procedure
  - 3-4mm punch bx, Michel's solution
  - 4micron section on slide
  - Overlaid with specific fluoresceinated ab's
  - Examined under fluorescence microscope

Indirect Immunofluorescence

- Detects circulating ab's in bullous and connective tissue diseases
  - 10 fold more sensitive than DIF
- Two-step procedure
  - Frozen sections of monkey or guinea pig or human esophagus
  - Incubated with pt's serum(primary ab)
  - Overlaid w/ fluoresceinated ab agst primary ab
- Diagnostic importance
  - Titrations can be done. Titers correlate w dz(PV)
  - ANA-different patterns of nuclear fluorescence


A direct immunofluorescence


B indirect immunofluorescence

Salt-Split Skin

- Indirect IF method
  - Thin 0.4mm sections of normal skin, cut parallel to skin
  - Incubated in 1 M NaCl
  - Cleft produced in lamina lucida
- Stains either roof(epidermal) or base(dermal)

Patterns of direct immunofluorescence

- Epidermis
  - Intercellular linear meshwork(PV)
  - Intercelluar punctate(anti-RO)
  - Nuclear(anti-RNP)
- BMZ
  - Linear (tubular)(EBA,BP-BMZ)
  - Linear granular (DH,LE-ag/ab collections)
  - Shaggy broad(LE-immune complexes)

Patterns of direct Immunofluorescence

- Dermis
  - Vascular
    - granular
    - homogenized
    - linear
  - Globular
  - Dermal papillae granular
  - Diffuse
  - Circumscribed
  - Autofluorescence and background

New Techniques

- For most antigens ELISA
  - Specific epitopes characterized
  - Titers can be determined
  - Useful to distinguish minor differences which may affect clinical presentation

Definitions

- Nikolsky-top layers of skin slip away when slightly rubbed
- Asboe-Hansen-extension of blister in adjacent unblistered skin when pressure is placed on top of the bulla