Cutaneous Immunopathology

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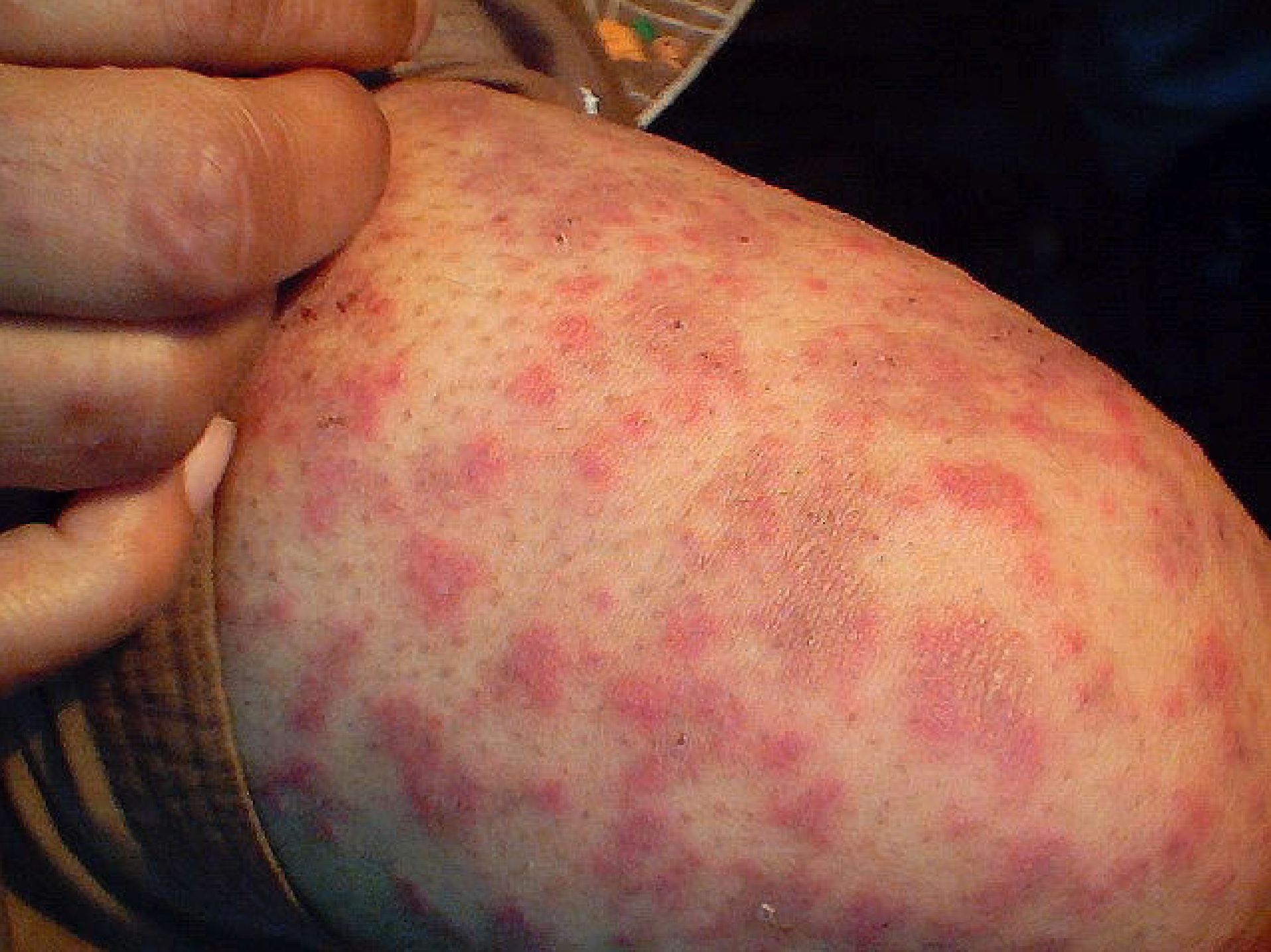
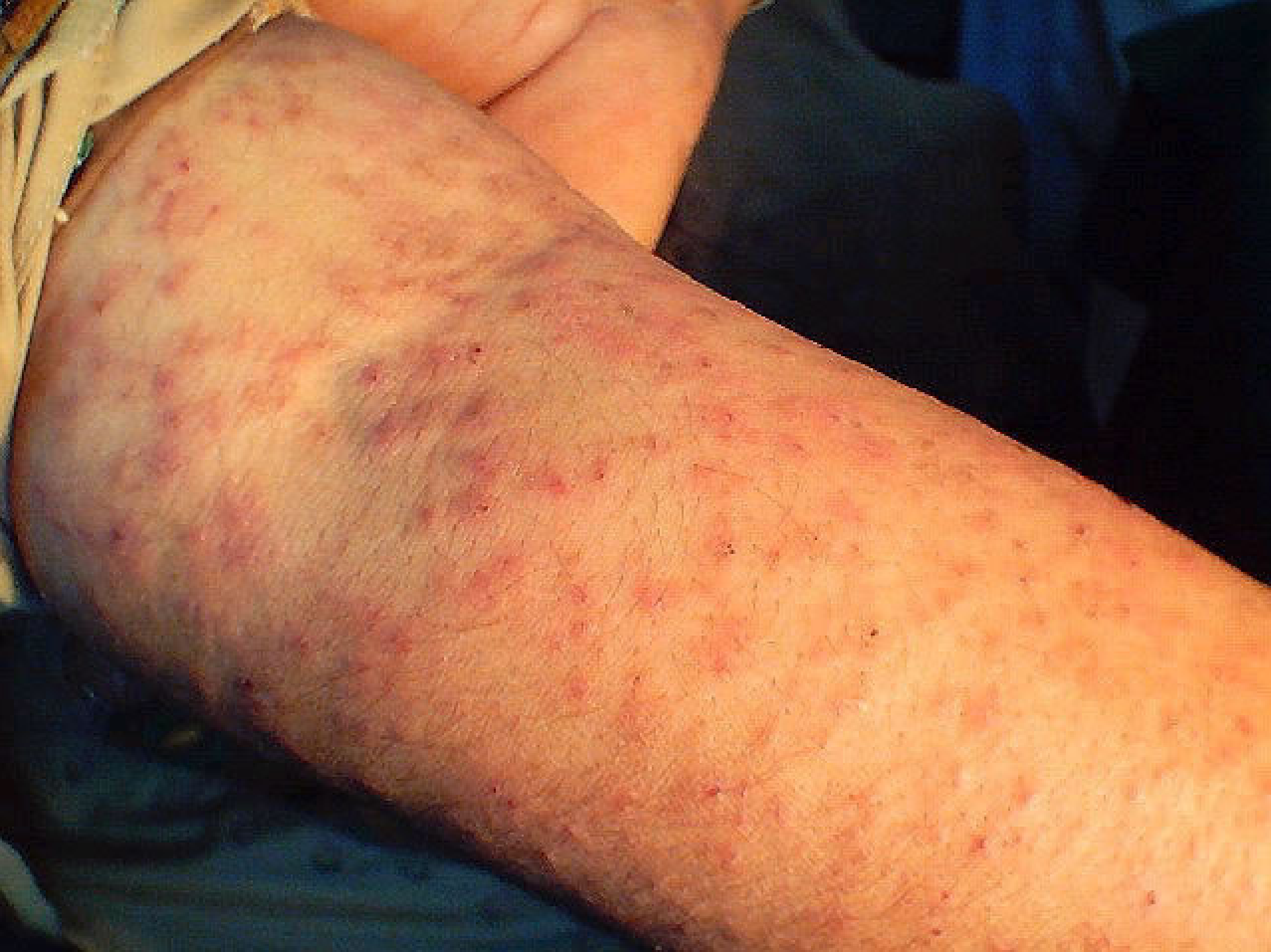
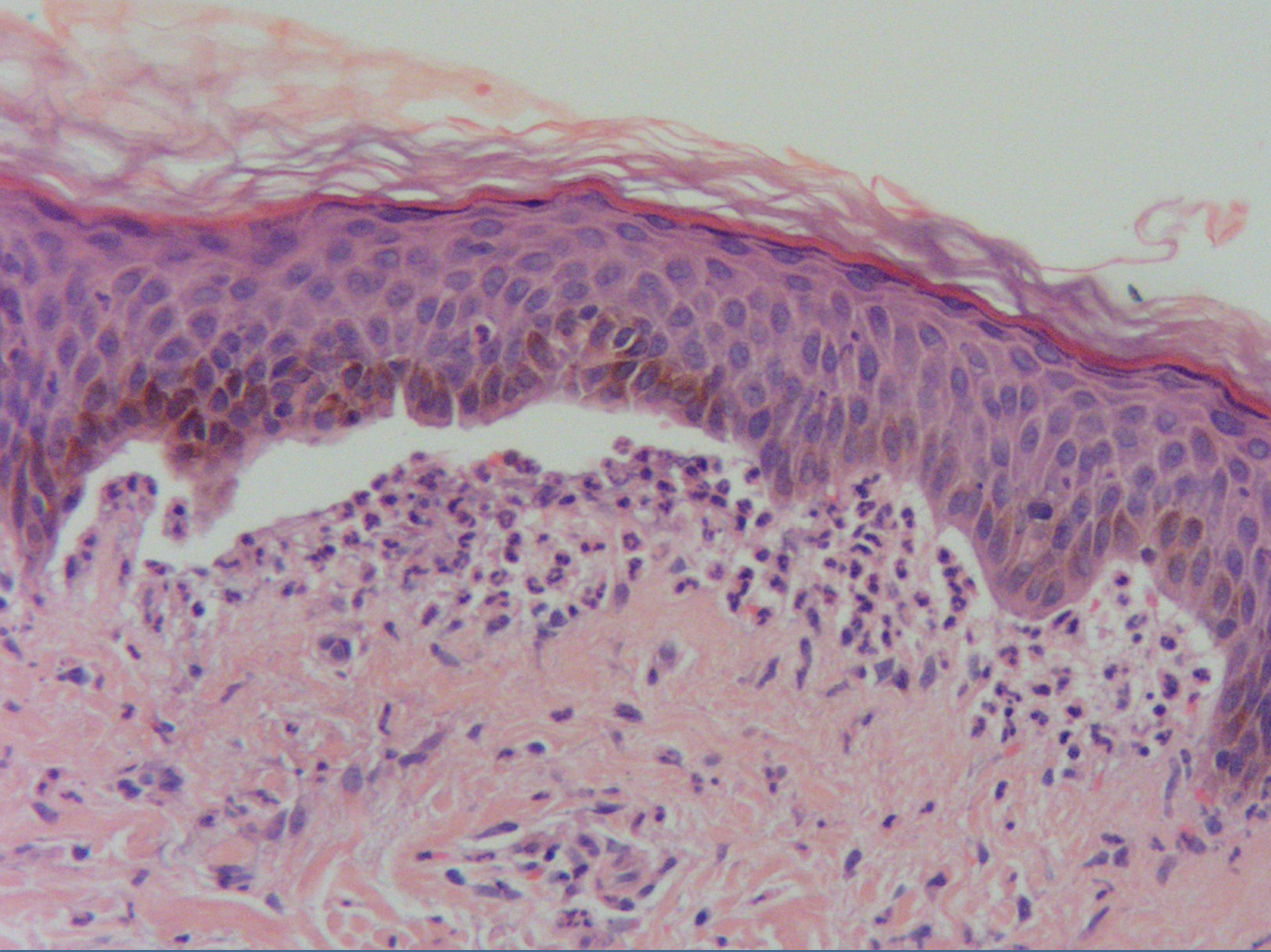
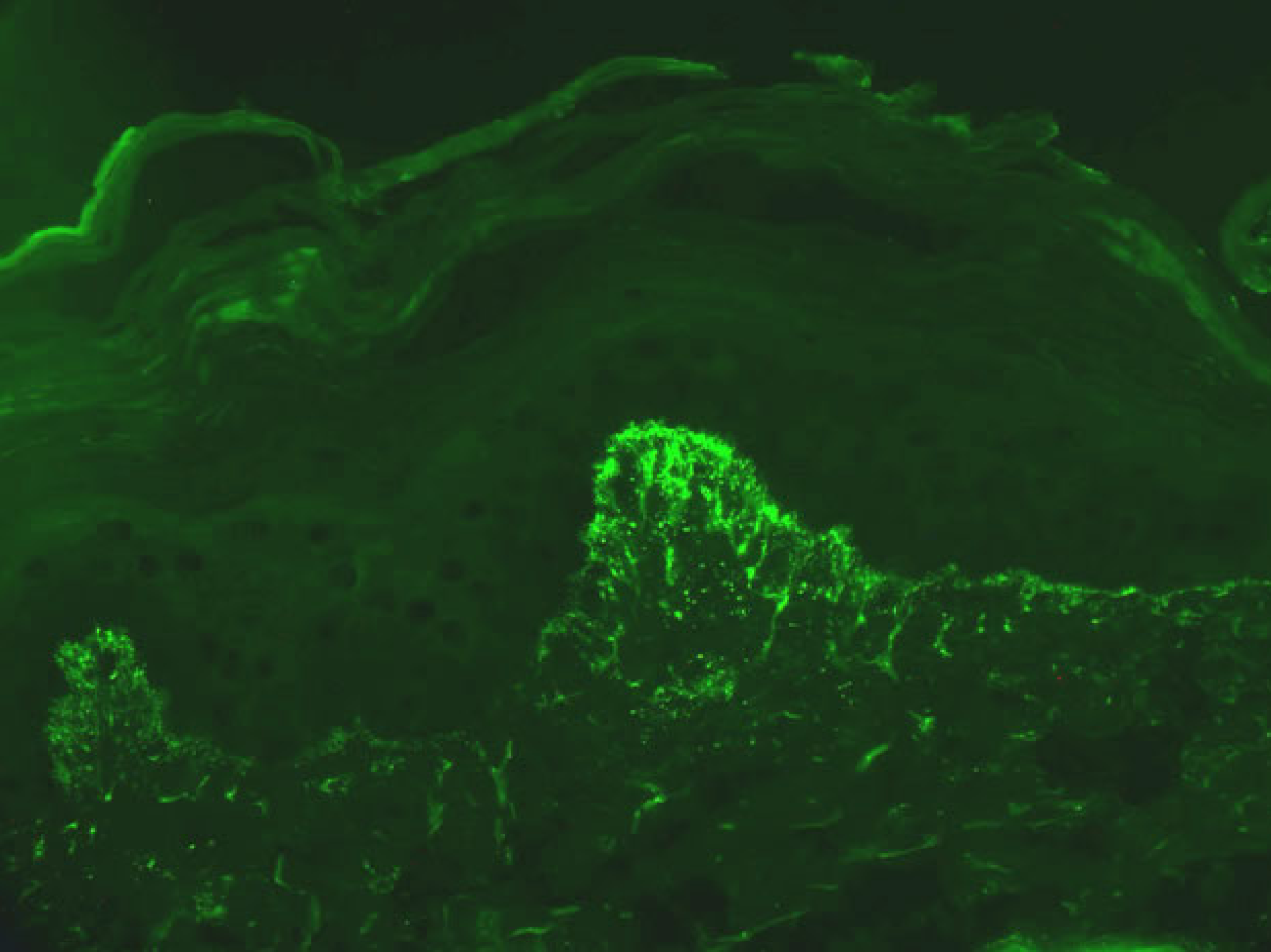








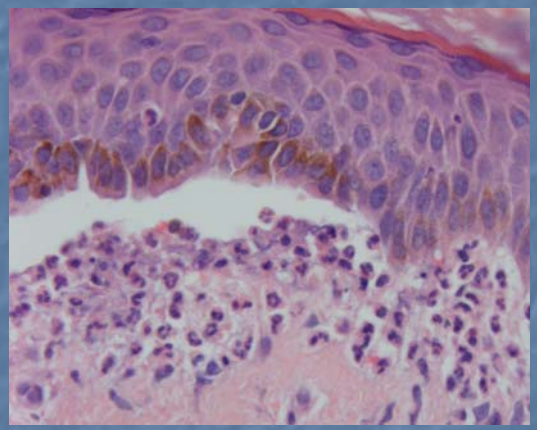
Dermatitis Herpetiformis

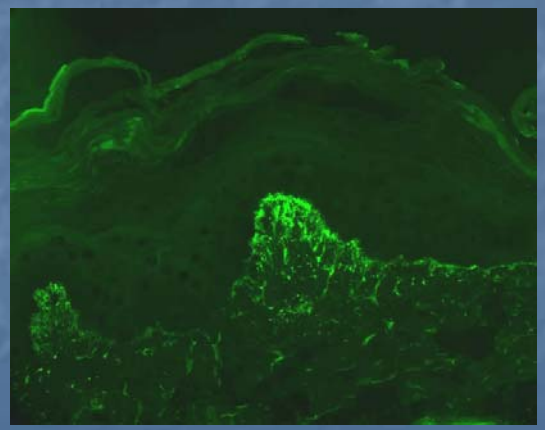
- Flesh-colored–to–erythematous vesicles appear in a herpetiform pattern
  - Symmetrically distributed over extensor surfaces including elbows, knees, buttocks, shoulders, and the posterior (nuchal) scalp
  - Erythematous papules and urticarialike plaques occur less frequently, bullae rare
  - Erosions and crusts
  - Burning, stinging, and intense pruritus, often precede new lesions
  - Oral mucosa lesions rare
  - Palms and soles usually spared

Dermatitis Herpetiformis and Sprue

- Majority have some degree of gluten sensitive enteropathy although usually asymptomatic
  - Fewer than 10% of patients have bloating, diarrhea, or symptomatic malabsorption
  - Mild steatorrhea or other signs of mild malabsorption in 20-30%
  - Patients with DH and no apparent gastrointestinal disease can be induced by increased gluten intake
- Gluten-free diet results in normalization of mucosal and skin lesions
  - Resumption of a gluten-containing diet results in recurrence of skin lesions
- Serum tests of IgA endomysial Ab
  - 80% of DH and all of atypical DH
  - Gluten free diet leads to decreased levels

Dermatitis Herpetiformis Histopathology





- Biopsy from normal skin about 3 mm. from the lesion
- Neutrophils may degrade IgA
- DIF necessary, rule out Linear IgA disease and subepidermal bullous dermatoses

Clues in a monkey's gut!

- Anti-endomysial Ab bind to reticular structures in smooth muscle in primate esophagus
  - 99% specific for gluten sensitive enteropathy
  - Occur in >80% of DH cases
    - >95% of DH cases with villous atrophy
  - Titers not affected by dapsone but decreased with gluten free diet
  - If gluten reintroduced, skin lesions precede AEmA and AEmA reappears before villous atrophy

Location of Biopsy

Skin blister	3 mm biopsy with both the edge of a fresh lesion and some adjacent normal skin
Mucosa	Perilesional with normal intact mucosa
Screen	Edge of fresh skin and include scale, if possible

Specific Diseases

Pemphigus or pemphigoid, skin	1st biopsy edge of lesion 2nd 3 mm from lesion
Pemphigus or pemphigoid, oral	1st biopsy 3mm from lesion 2nd at edge
Purpura/ vasculitis	10 mm from lesion
Stasis	Edge of lesion

Specific Diseases

Dermatitis herpetiformis	Biopsy normal skin 3mm from lesion
Porphyria/ Pseudoporphyria	Biopsy from edge of a fresh lesion with edge of normal skin

Disorders Excluded With Negative IF

- IgA pemphigus
- Pemphigus
- Bullous pemphigoid
- DLE
- SLE
- IgA vasculitis/Henoch-Schonlein Purpura

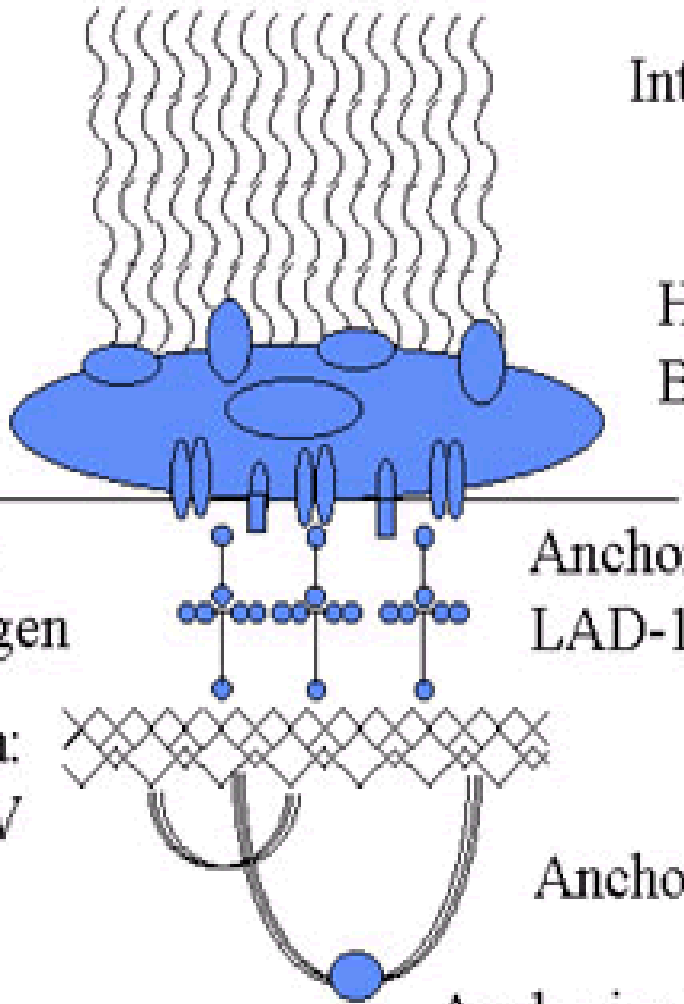
Disorders with Negative/Nonspecific IF

- Subcorneal pustulosis
- Hailey-Hailey disease
- Bullous impetigo
- Grover's disease
- Acantholytic PR
- Bullous insect bite
- Bullous drug eruption
- Lichen planopilaris
- Drug induced lichenoid photodermatitis
- Non-IgA associated vasculitis

Basement Membrane Components

- Bullous pemphigoid antigens (BP 220/BP180)
- Epiligrin (Laminin 5)
- Uncein
- Ladinin (LAD-1)
- EBA antigen (Noncollagenous domain of type VII collagen)

The dermal-epidermal basement membrane



Intermediate filaments: keratins 4, 15

Hemidesmosome: 200 kD protein, BP180, $\alpha 6\beta 4$ integrin, BP230, HD1

Plasma Membrane

Lamina Lucida: laminin-1, nidogen

Anchoring filaments: laminin-5, laminin-6, LAD-1. uncein, LH39 antigen

Lamina Densa: HSPG, type IV collagen

Anchoring fibrils: type VII collagen

Anchoring plaques: type IV collagen

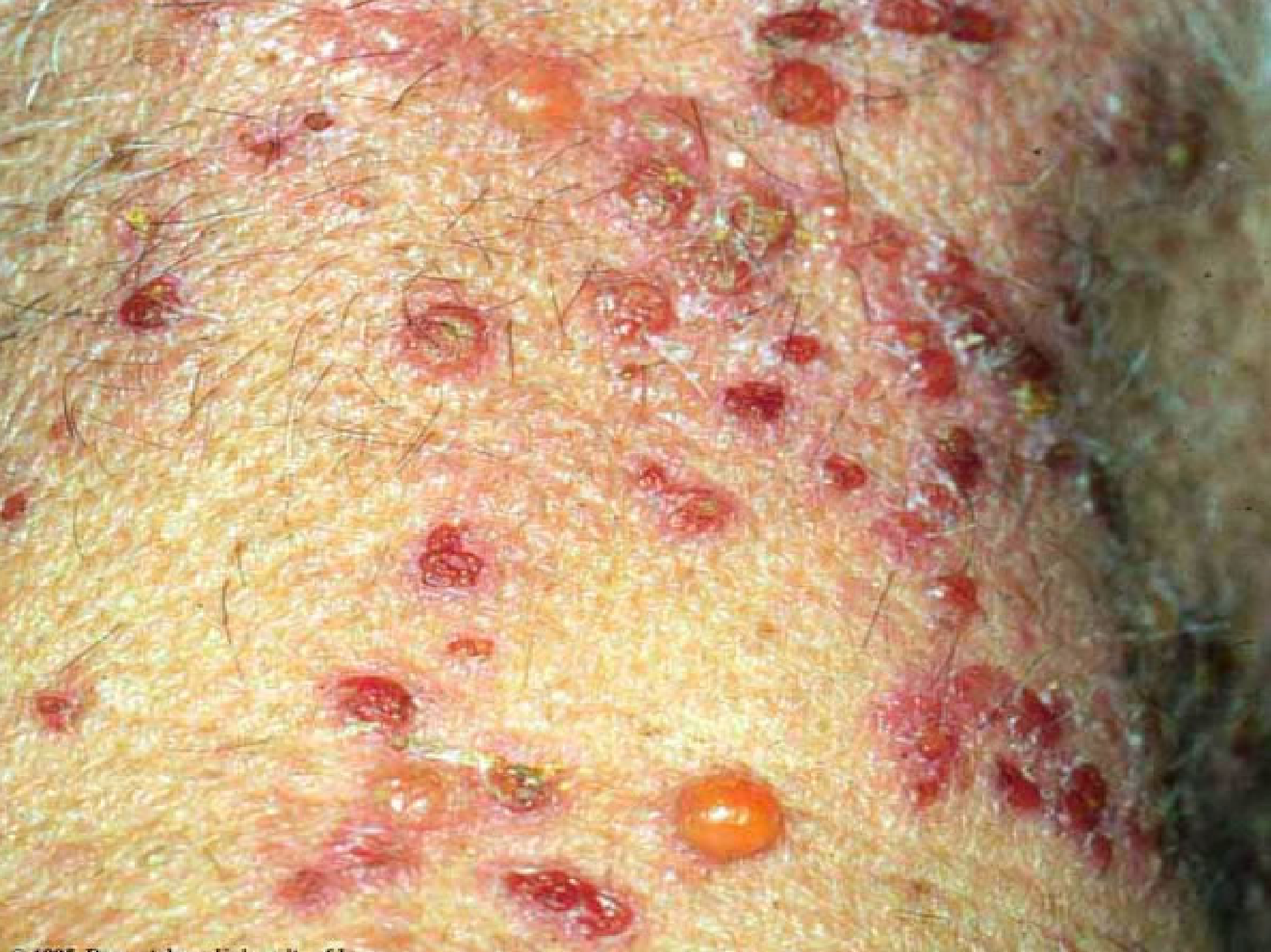
Location of Components

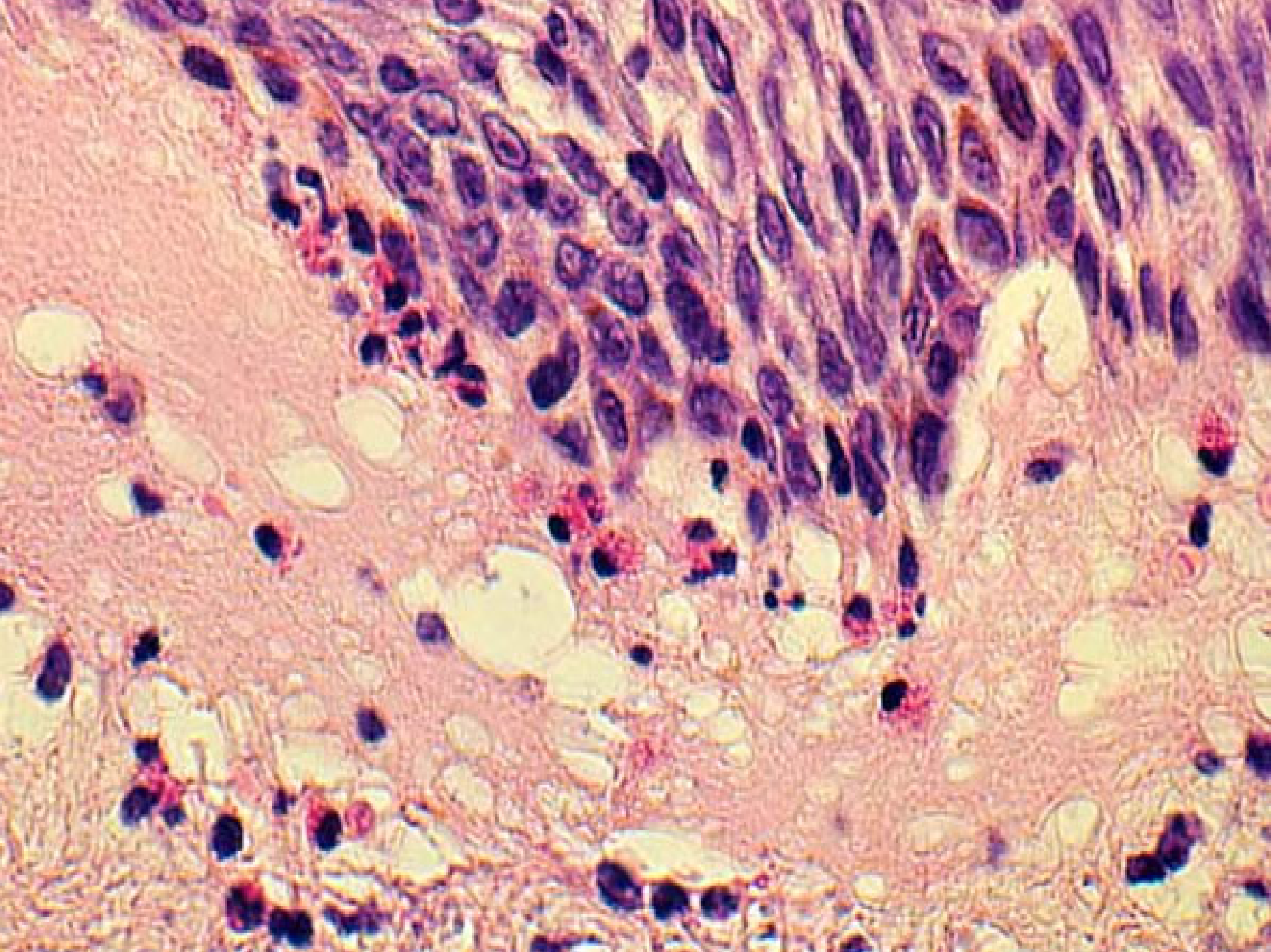
Plasma membrane	BP antigen
Lamina lucida	Laminin
Lamina densa	Type IV collagen EBA antigen Heparin sulfate

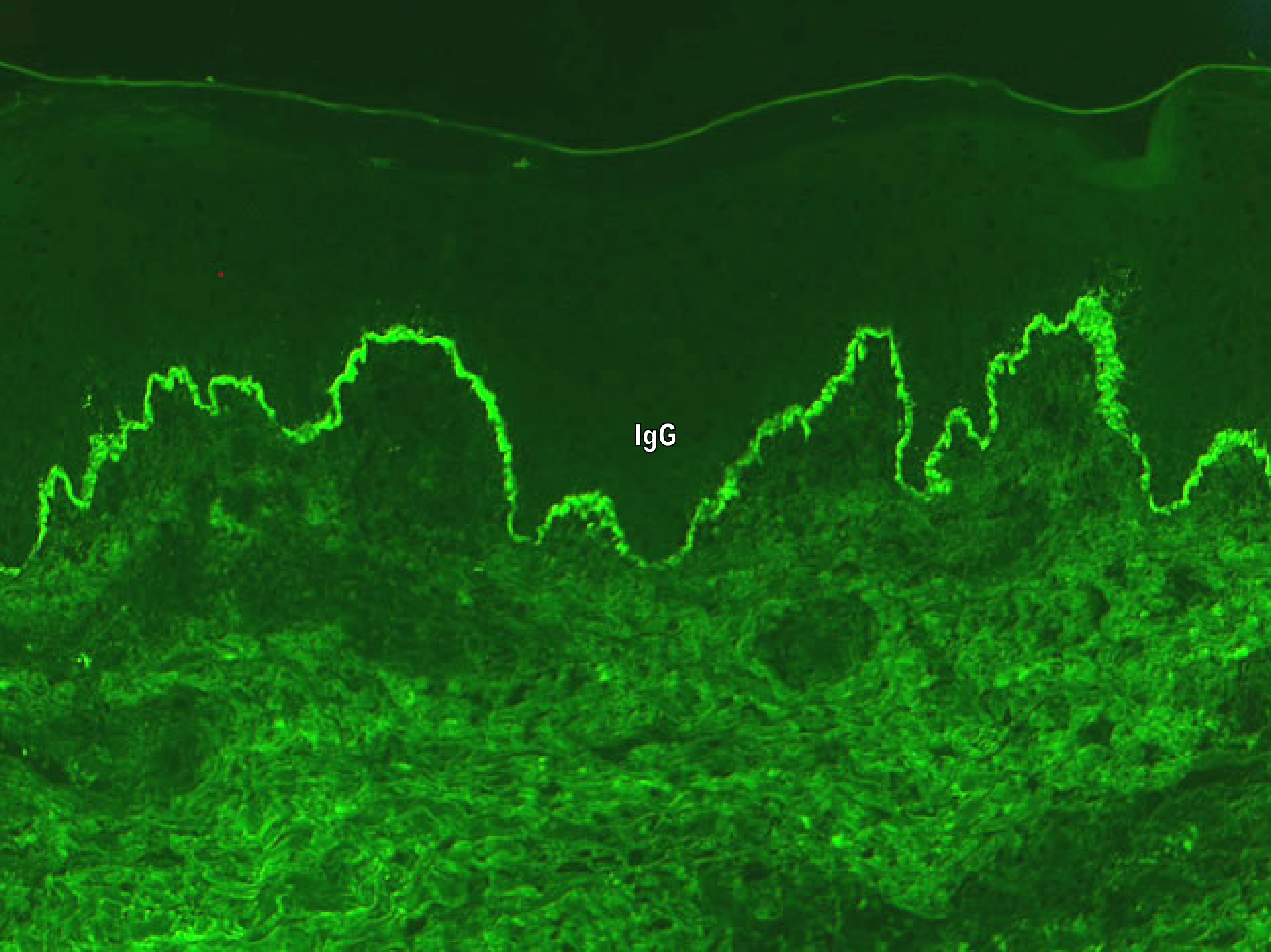
Component	Disease
Epiligrin	Anti-epiligrin cicatricial pemphigoid Some junctional EB
Uncein	Overlap syndrome with features of CP and EBA
Ladinin (LAD1)	Chronic bullous disease of childhood Linear IgA disease
EBA antigen	EBA

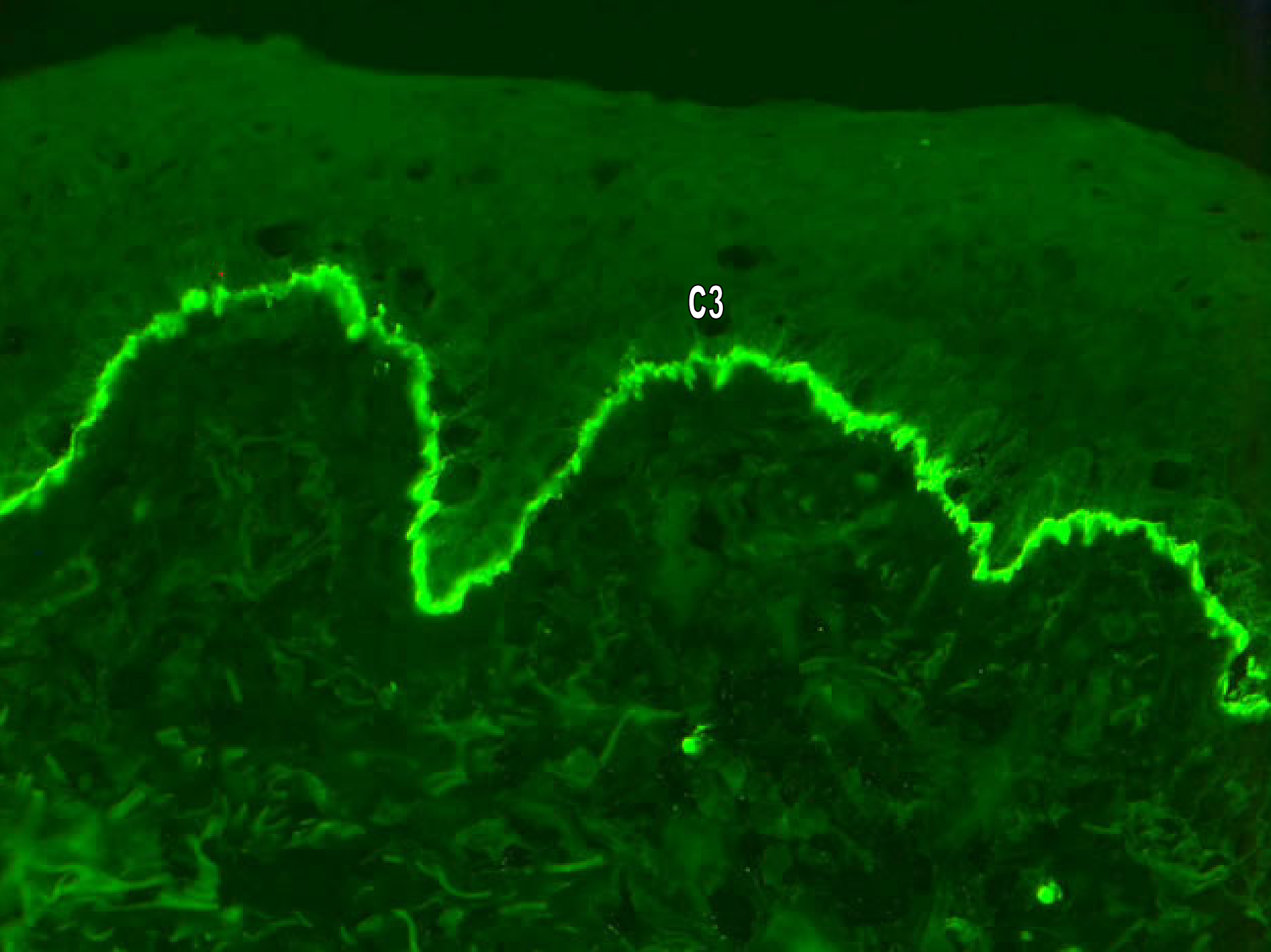
Technical Considerations

- Storage of slides at room temperature <11 months
  - Storage with antifading agent-2 years
- Biopsy should be placed in Michel's or Zeus solution and kept from light

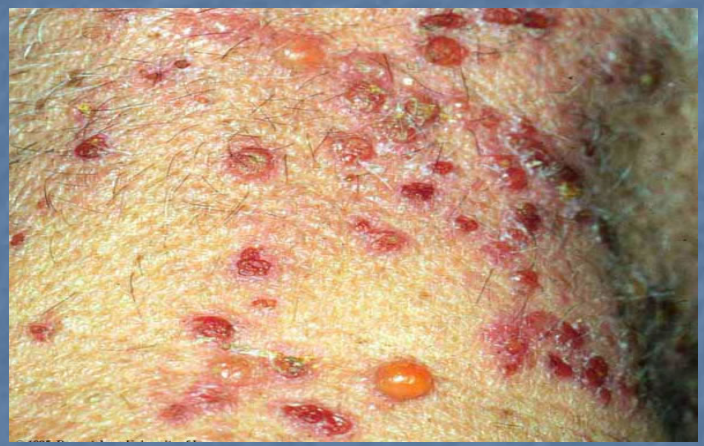


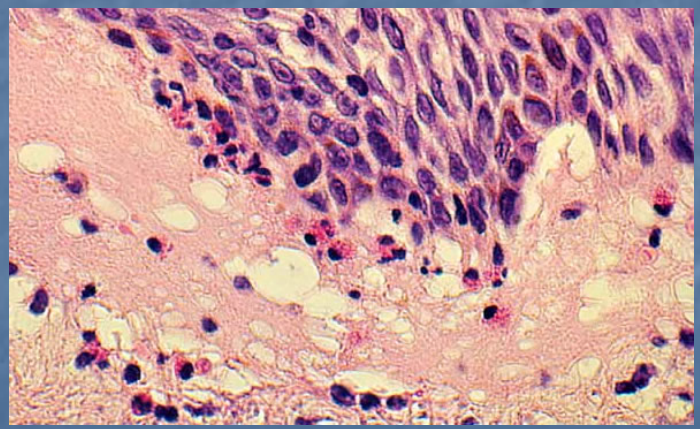



IgG


C3

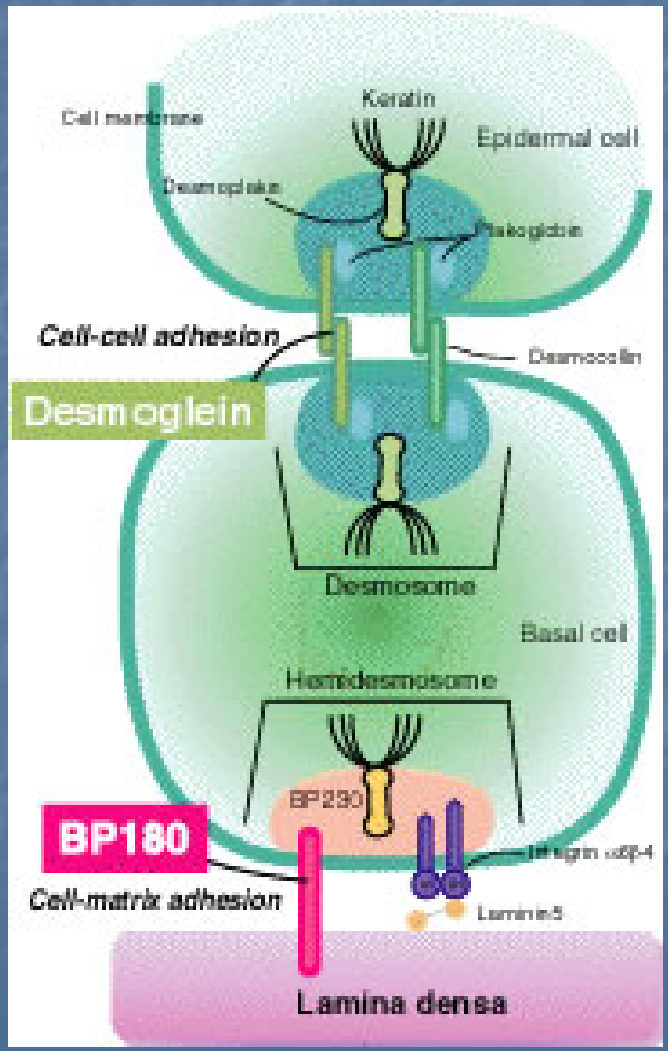
Bullous Pemphigoid





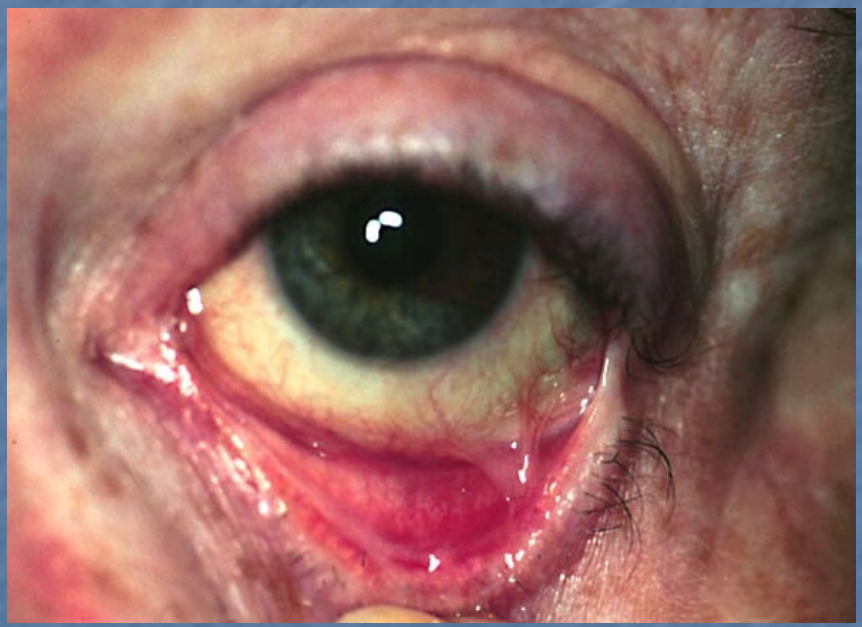
- Tense bullae on erythematous base
- Negative Nikolsky
- Subepidermal bullous dermatosis with eosinophils
- DDX: Herpes gestationis, Bullous LE, Cicatricial pemphigoid

Bullous Pemphigoid Antigen



- BPAg1 (220kd)
  - Intracellular associated with hemidesmosomes
  - Homology with desmoplakin
  - 70% of BP pts have circulating Ab to this
- BPAg2 (180kd)
  - Intra and extracellular with collagen-like domains
  - Also called collagen XVII
  - Extramembranous protion is antigenic epitope site for BP and HG

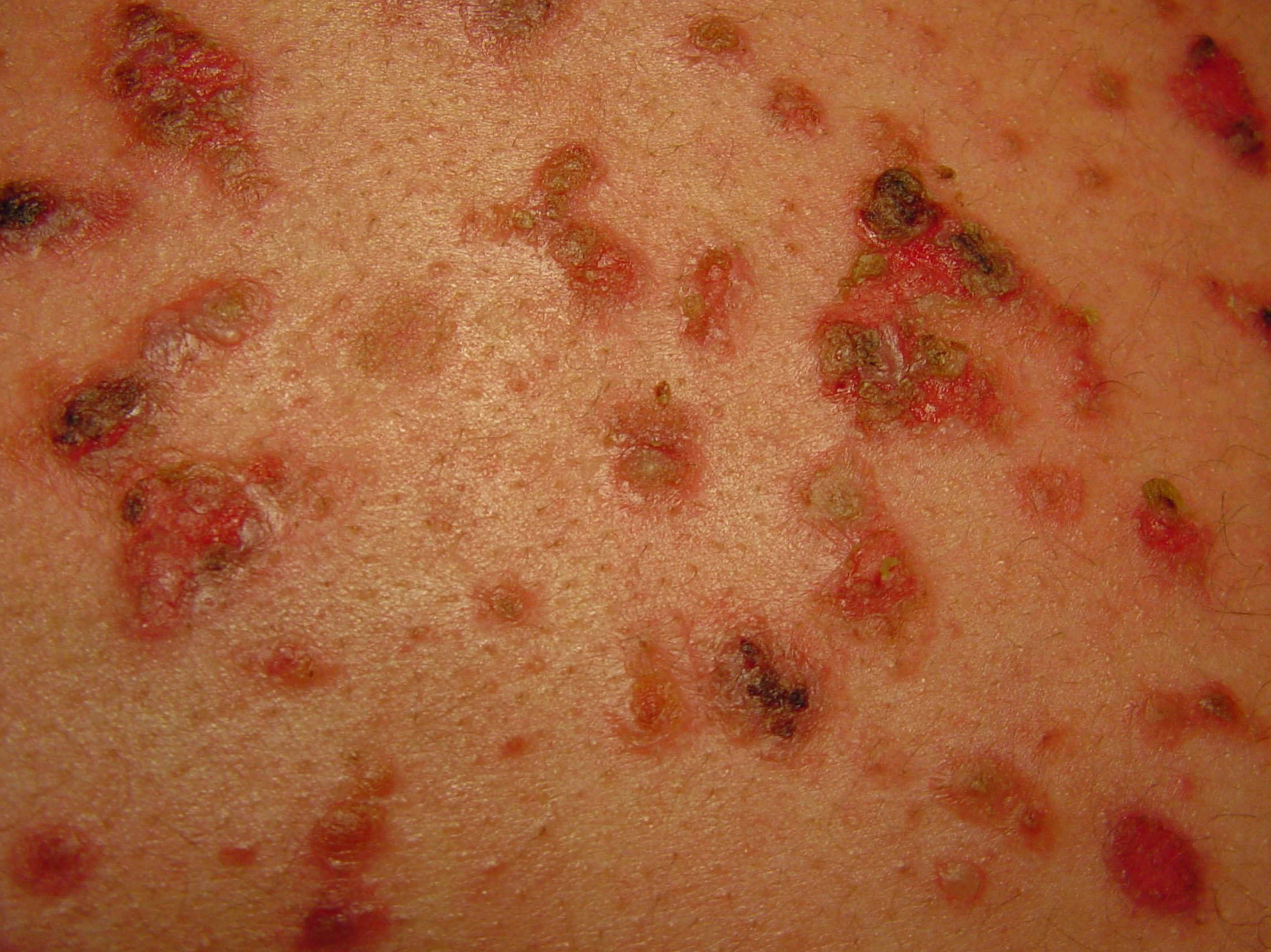
Cicatricial Pemphigoid

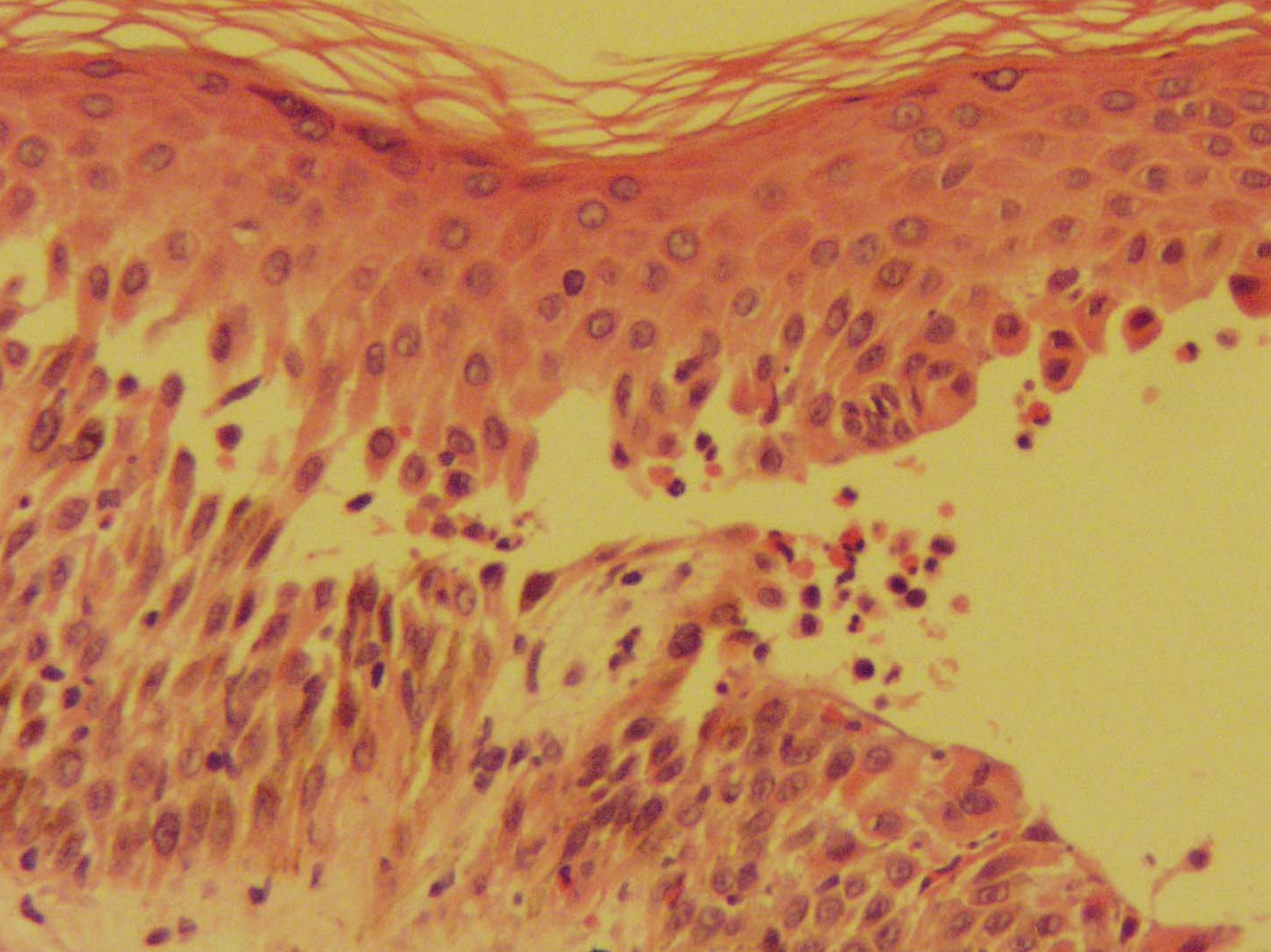


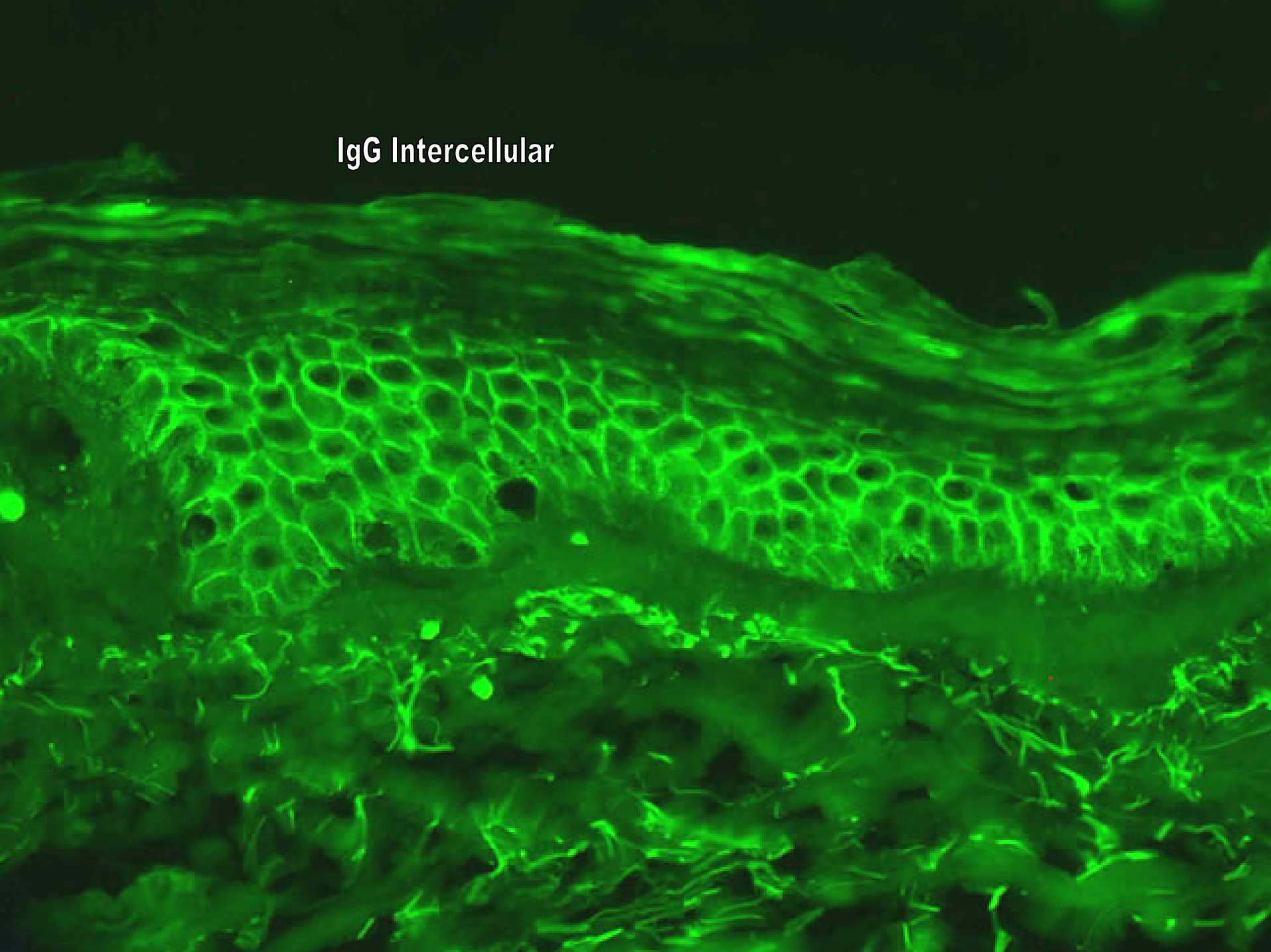
- Brunstig-Perry variant
  - Scarring blisters on head and neck
  - Mucosa rare
- Antiepiligrin variant
  - Associated with malignancy including endometrial, lung, and stomach
  - May be paraneoplastic blistering disease

Cicatricial Pemphigoid-Histopath/IF

- Subepithelial blister with mixed inflammatory cells
- Perilesional epithelium shows linear IgG and complement
  - Technically difficult
  - 70% have circulating Ab to BMZ material



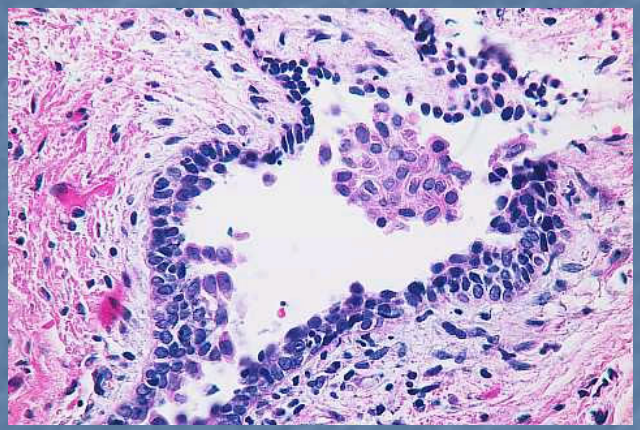


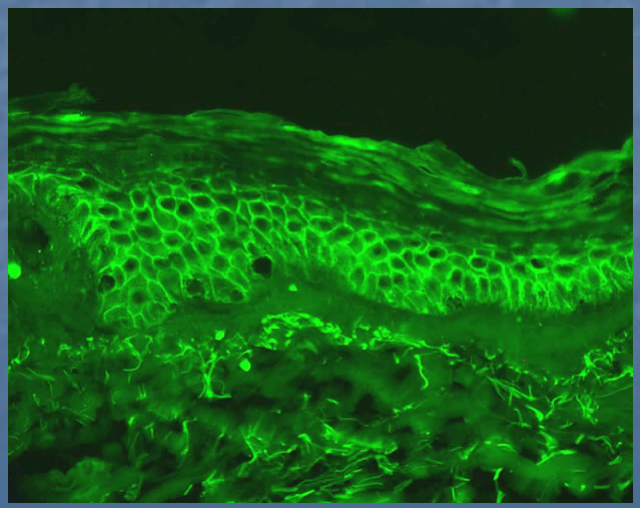

IgG Intercellular

Pemphigus Vulgaris

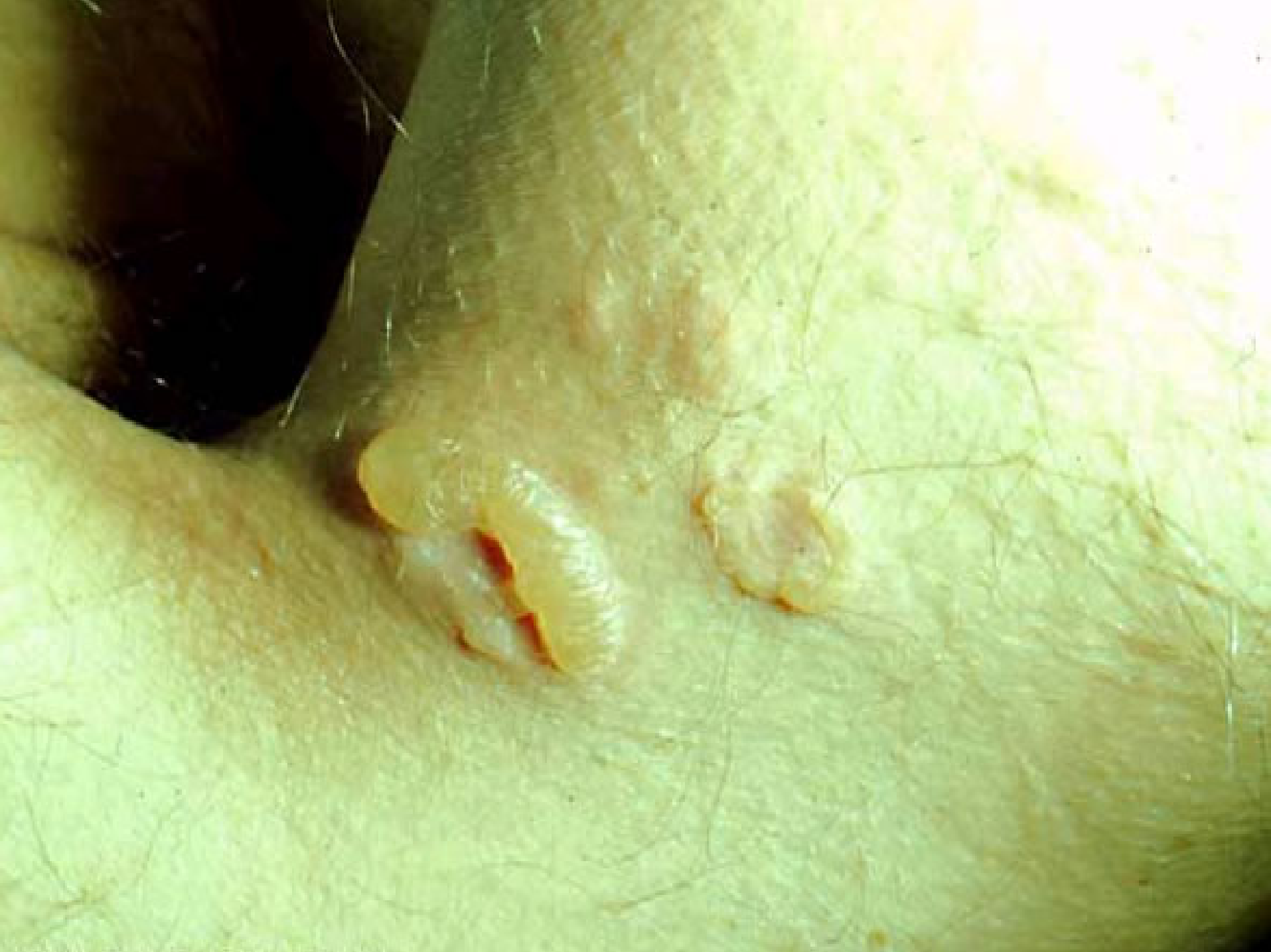
- Mucous membranes, usually oral cavity with erosions
- Flaccid and fragile skin blister filled with clear fluid that arises on normal skin or erythematous base
- Vegetating PV frequently in intertriginous areas and scalp or face
- Nikolsky sign
  - Firm sliding pressure with a finger separates normal-appearing epidermis, producing an erosion
- Asboe-Hansen sign
  - Lateral pressure on the edge of a blister may spread the blister into clinically unaffected skin

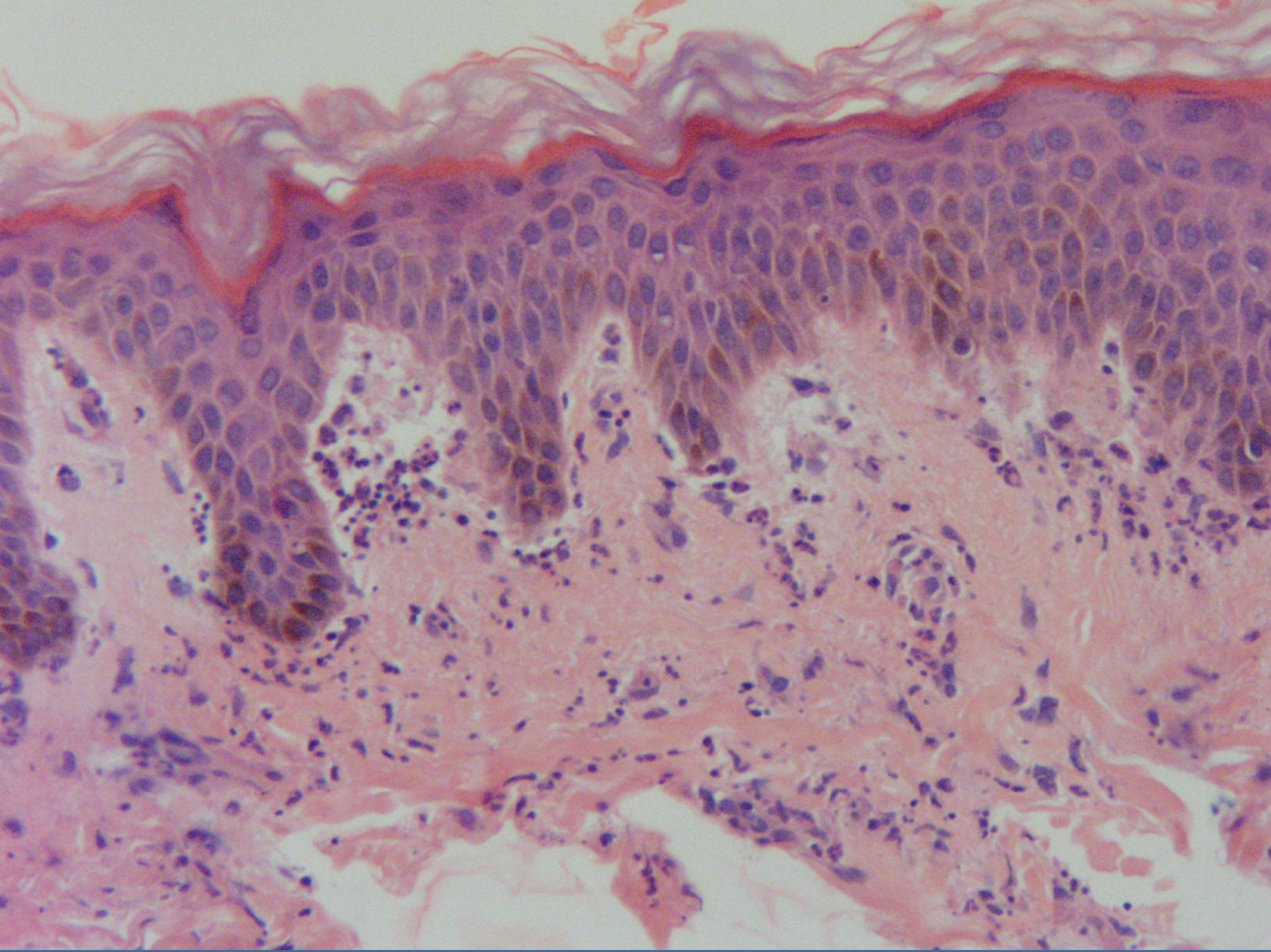
Pemphigus Vulgaris Histopathology

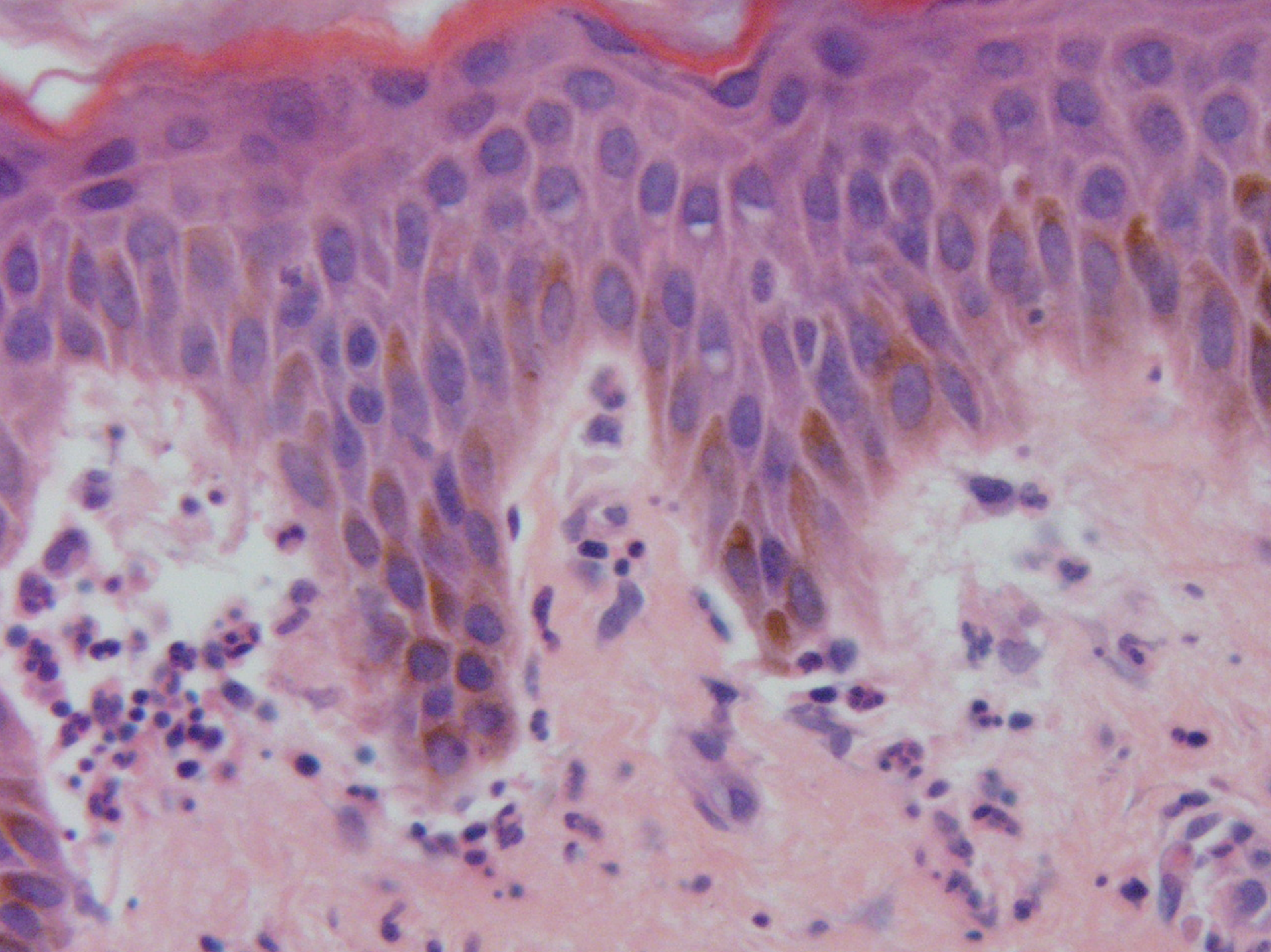


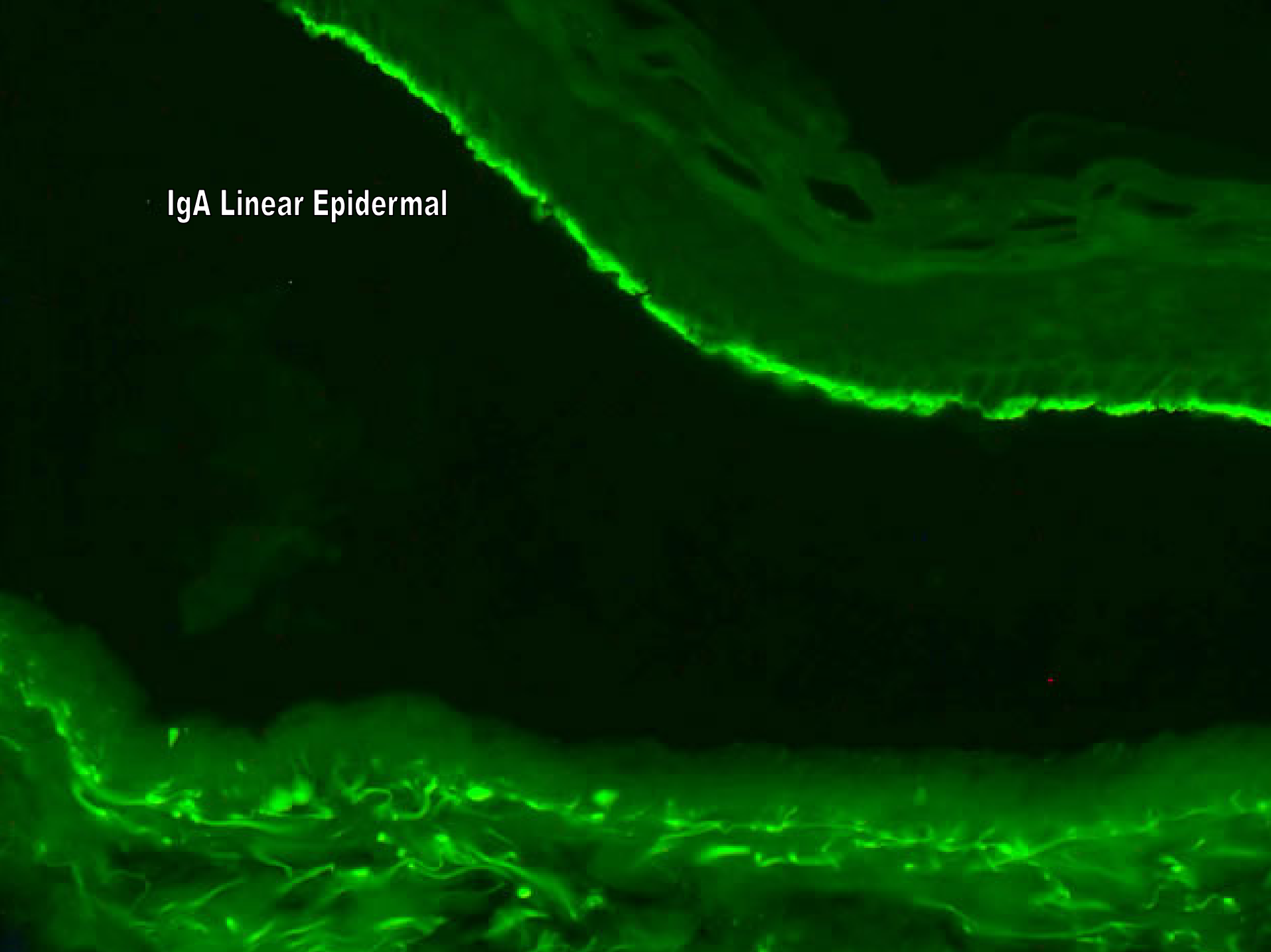


- Intradermal blister with suprabasal clefting and acantholysis
- May have preceding eosinophilic spongiosis
- DIF intercellular IgG
  - IgG1 and IgG4 subclasses
  - C3 and IgM less frequent
- IIF circulating IgG autoantibodies that bind to epidermis
  - 80-90% of patients
  - Titer of antibody correlates with disease course








IgA Linear Epidermal

Linear IgA Disease

- Vesiculobullous eruption on trunk, inner thigh, and pelvic region
  - Not symmetrical unlike DH
  - No association with gluten sensitivity
  - May involve mucosa with scarring
  - Bullae may be discrete or arranged in a herpetiform pattern (Cluster of jewels sign)
  - Lesions may be seen at the edge of annular or polycyclic lesions (String of beads sign)

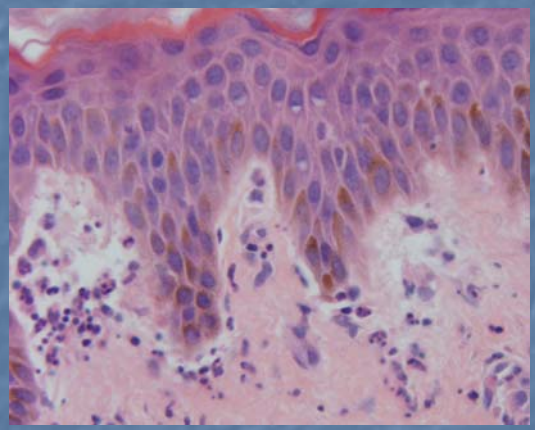
Linear IgA Disease

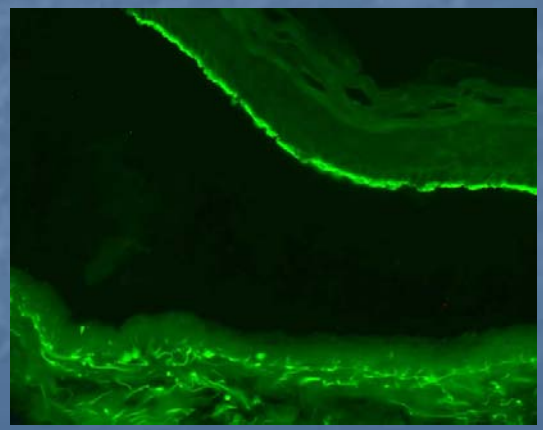
- Childhood lesions (Chronic bullous disease of childhood)
  - Localized to the lower abdomen and anogenital areas with frequent involvement of the perineum
  - Other sites of involvement include the feet, the hands, and the face, particularly the perioral area
- Adults
  - Trunk and the limbs are most commonly affected
  - Perineum and the perioral area is less frequent
- Both
  - Distribution may be symmetric or asymmetric
  - Dermatitis herpetiformis–like involvement of the extensor surfaces of the knees and the elbows infrequently
  - Oral manifestations vesicles, ulcerations, erythematous patches, erosions, desquamative gingivitis, or erosive cheilitis
  - Ocular symptoms, such as grittiness, burning, or discharge

Linear IgA Disease-Clinical

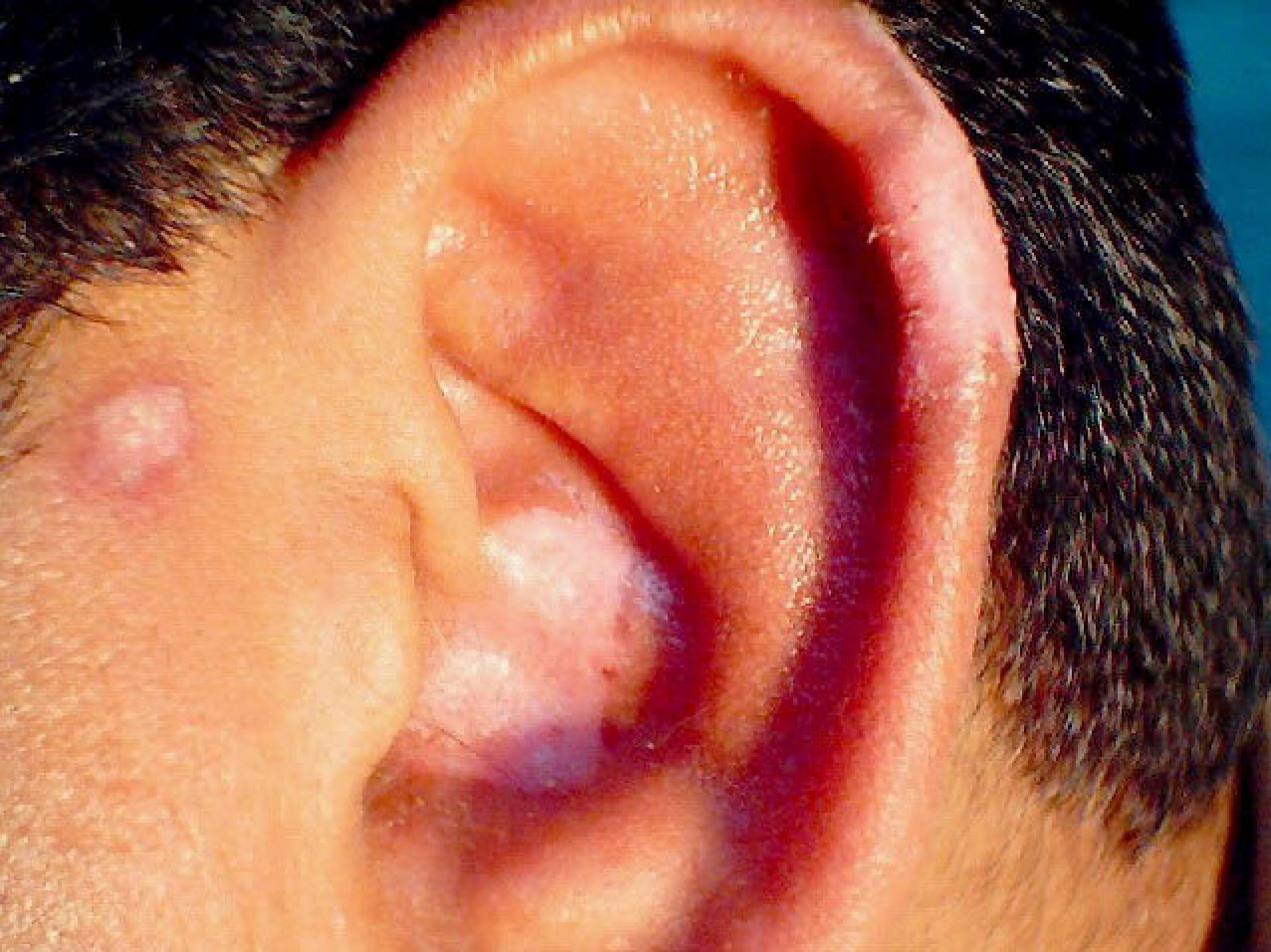
- Drug related
  - Vancomycin
  - Penicillin
  - Lithium
  - Dilantin
  - Diclophenac
- Lesions clear after cessation
- Rechallenge may have more severe changes

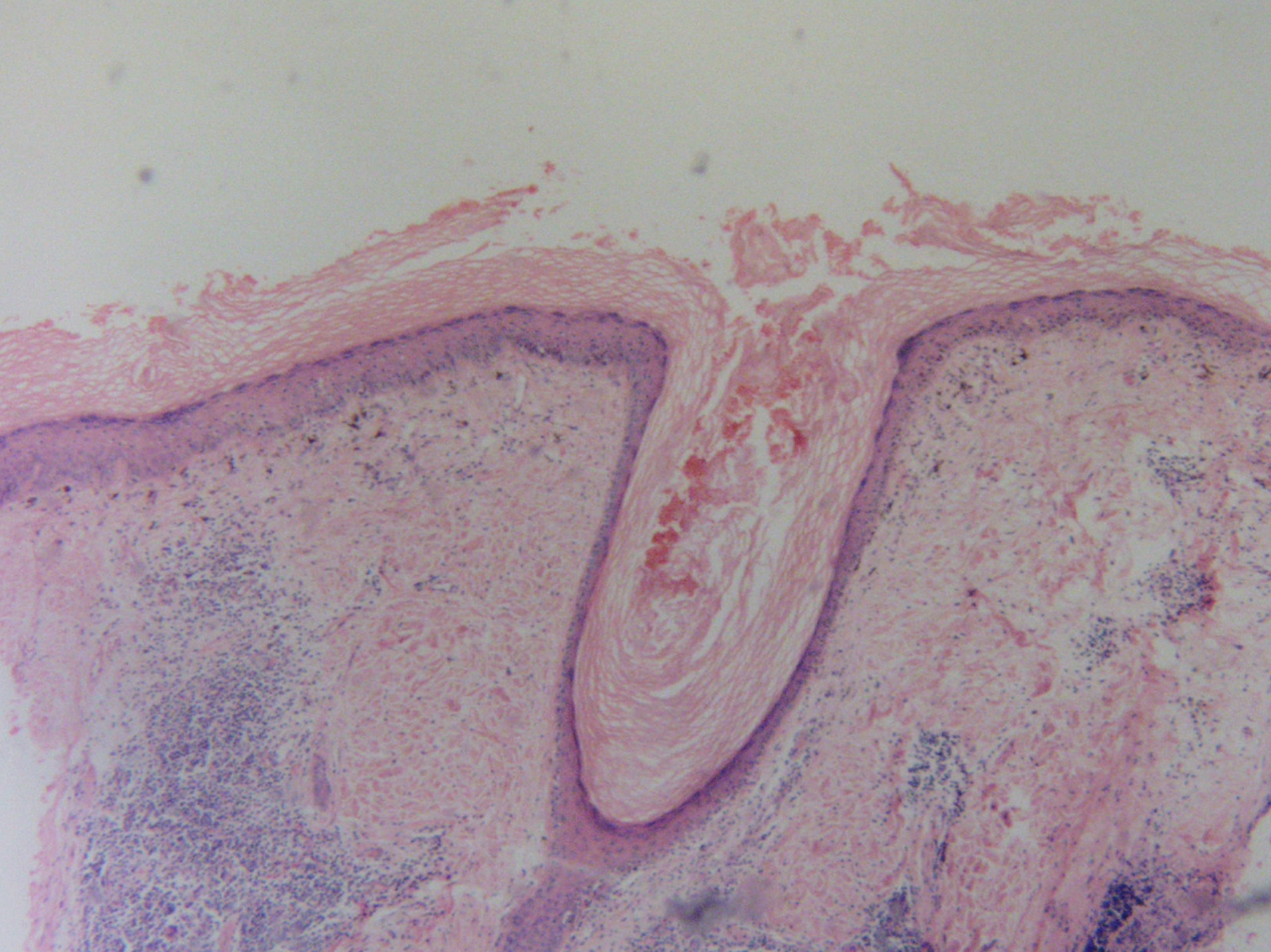
Linear IgA Disease-Histology and IF

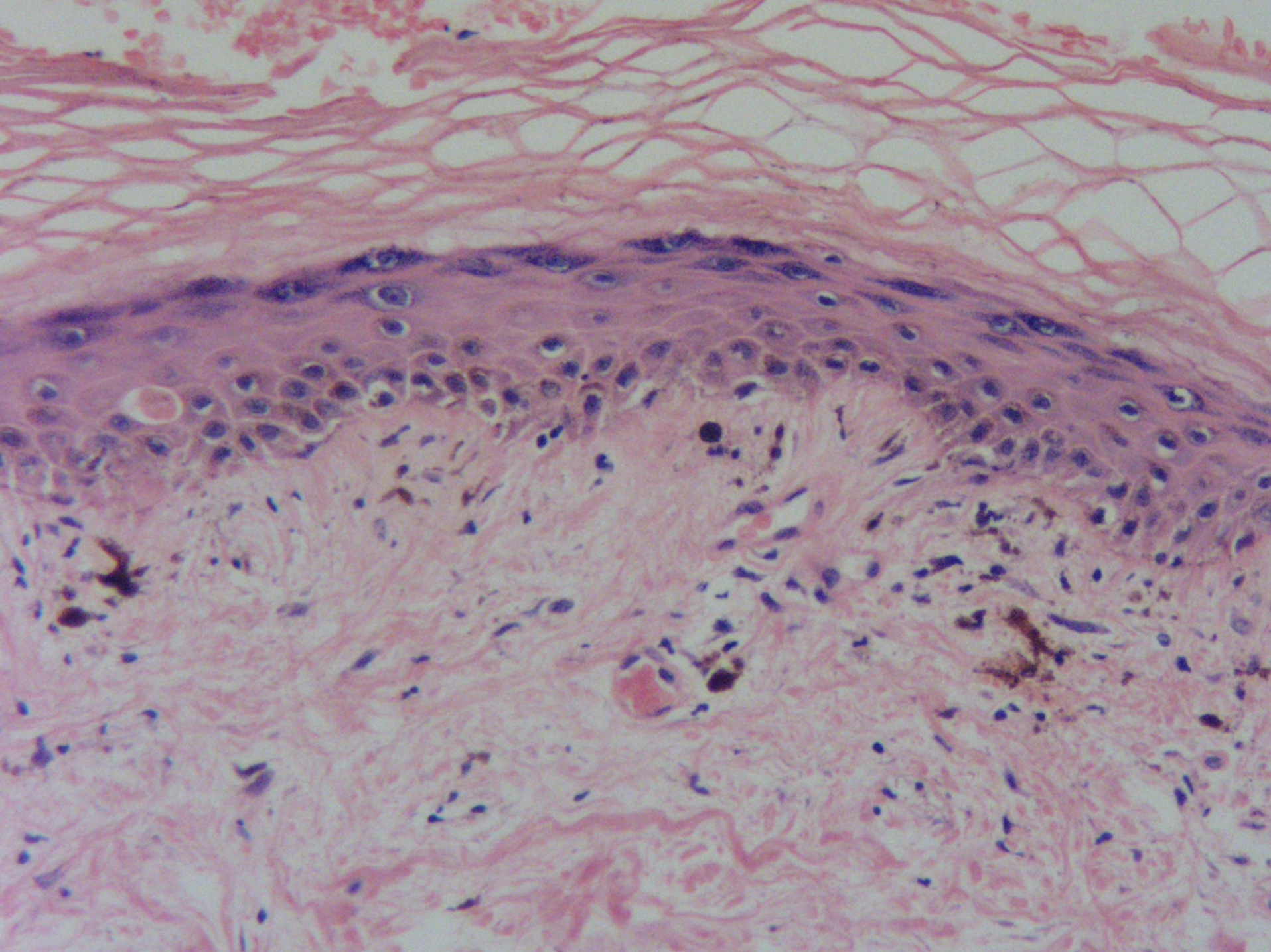


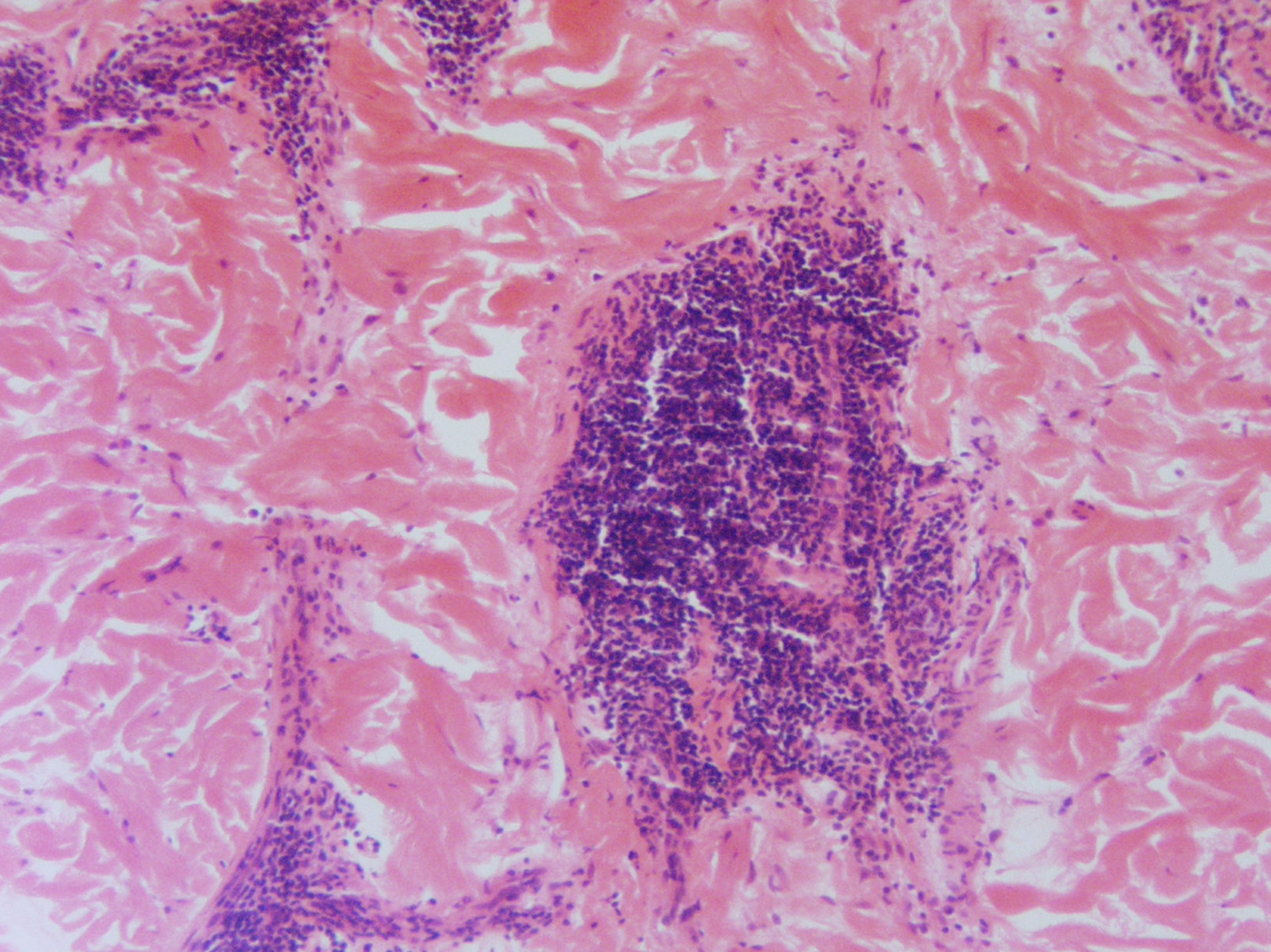


- Neutrophil rich interface dermatitis
- Homogenous sharp linear band for IgA
- Linear granular variant
  - No deposits within the dermal papillae, resembles DH
  - Low level of HLAB8 and gluten sensitivity unlike DH










IgM Granular

Lupus Band Test

- SLE
  - Best specificity is to take biopsy of normal skin of sun-exposed forearm (Positive in 67%)
  - Normal unexposed skin will be positive only in severe cases (35-40%)
- DLE
  - Biopsy of untreated skin lesion in exposed area that has been present for at least 3 months

Lupus Band Test-Baseline

- Deposition of Ig at the DEJ in lesional and nonlesional skin
  - IgM most frequent deposit
  - IgA least frequent
- Granular pattern most frequent
  - Sharp linear band not accepted

Baseline

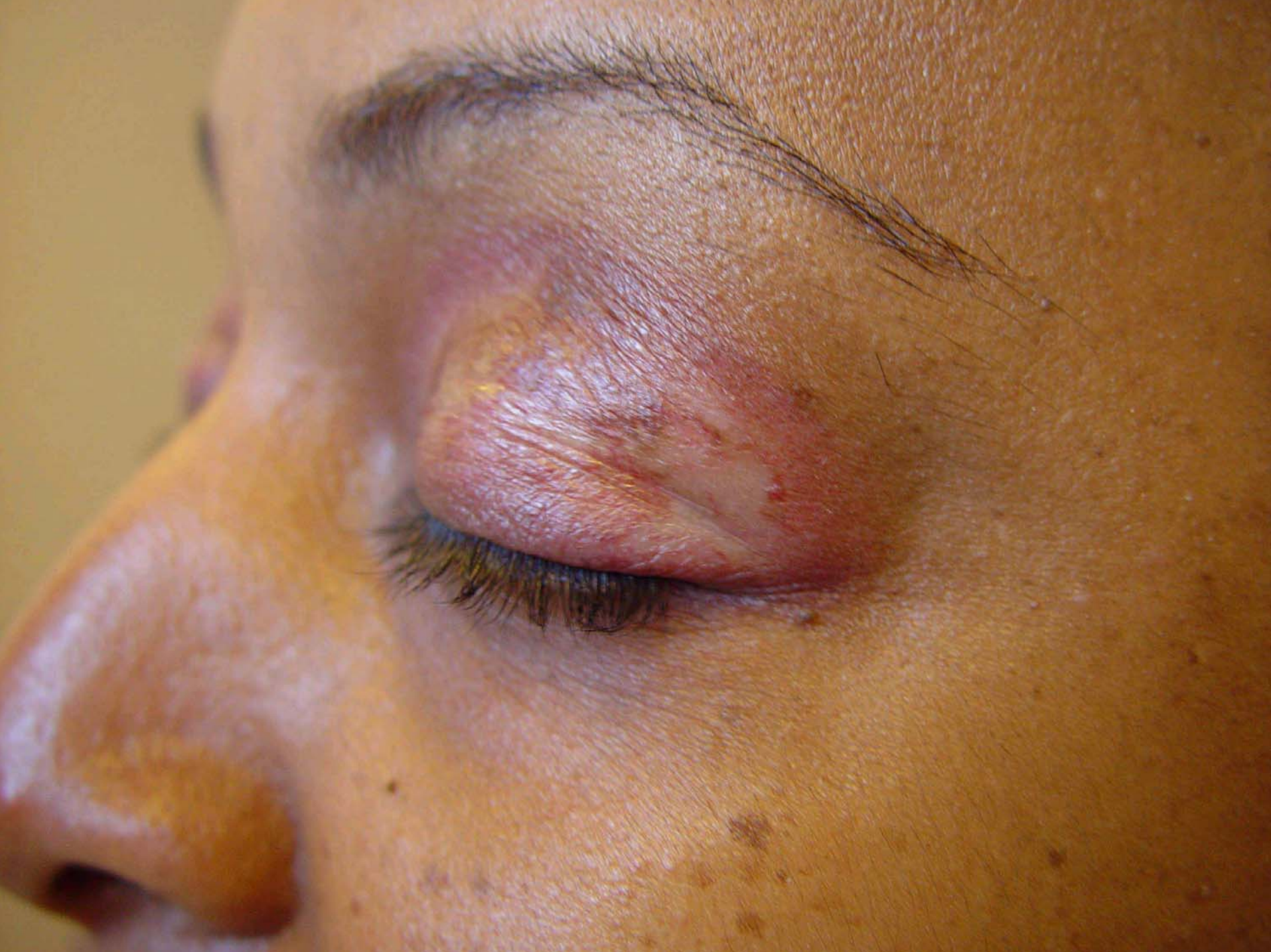
Sun exposed skin	IgM continuous distribution over at least 50% width of biopsy with moderate intensity 25% of normal skin show weak interrupted linear granular IgM/C1q
Non-sun exposed	Interrupted IgM of moderate intensity If IgA present, high specificity

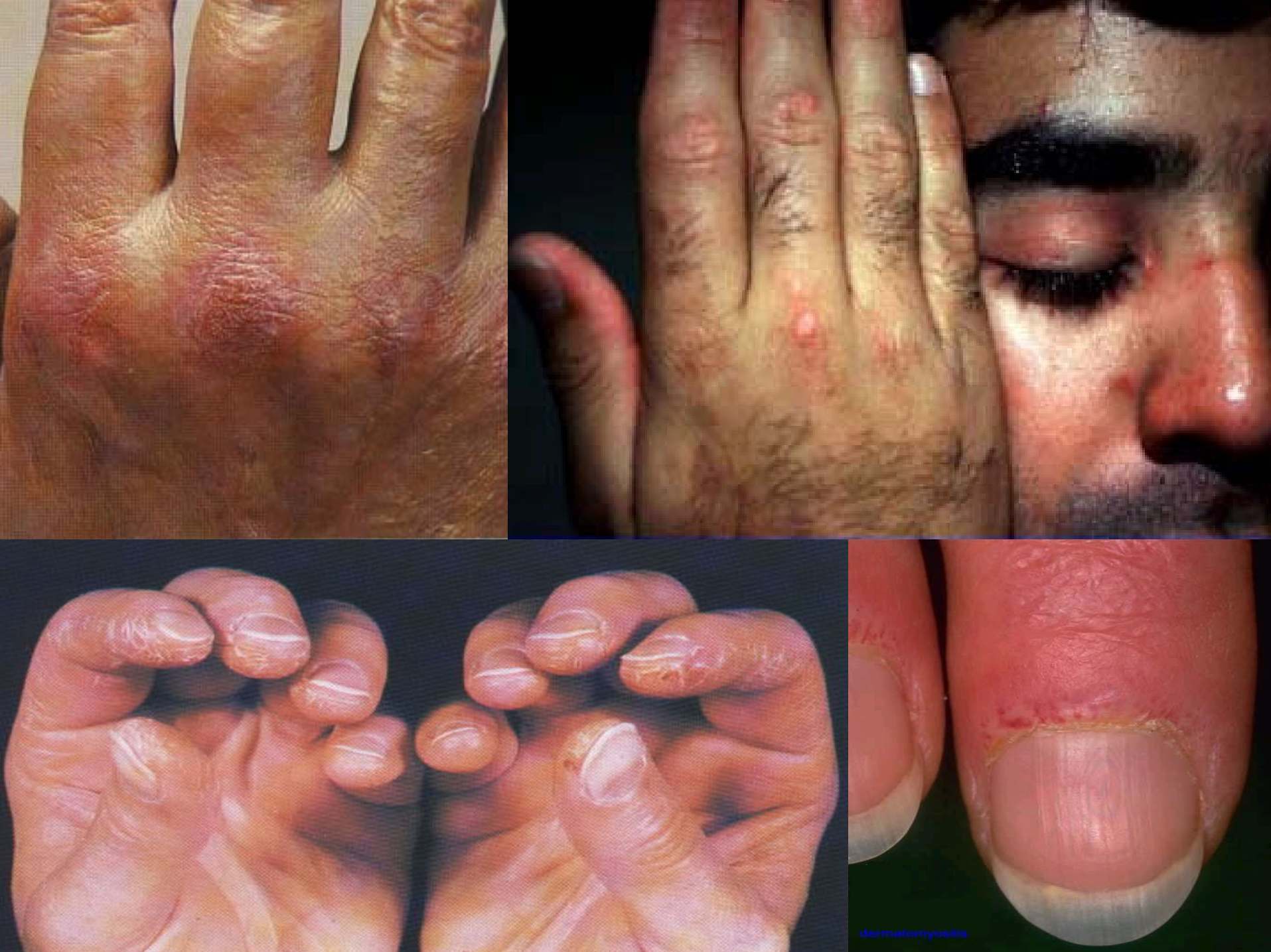
Sensitivity and Specificity

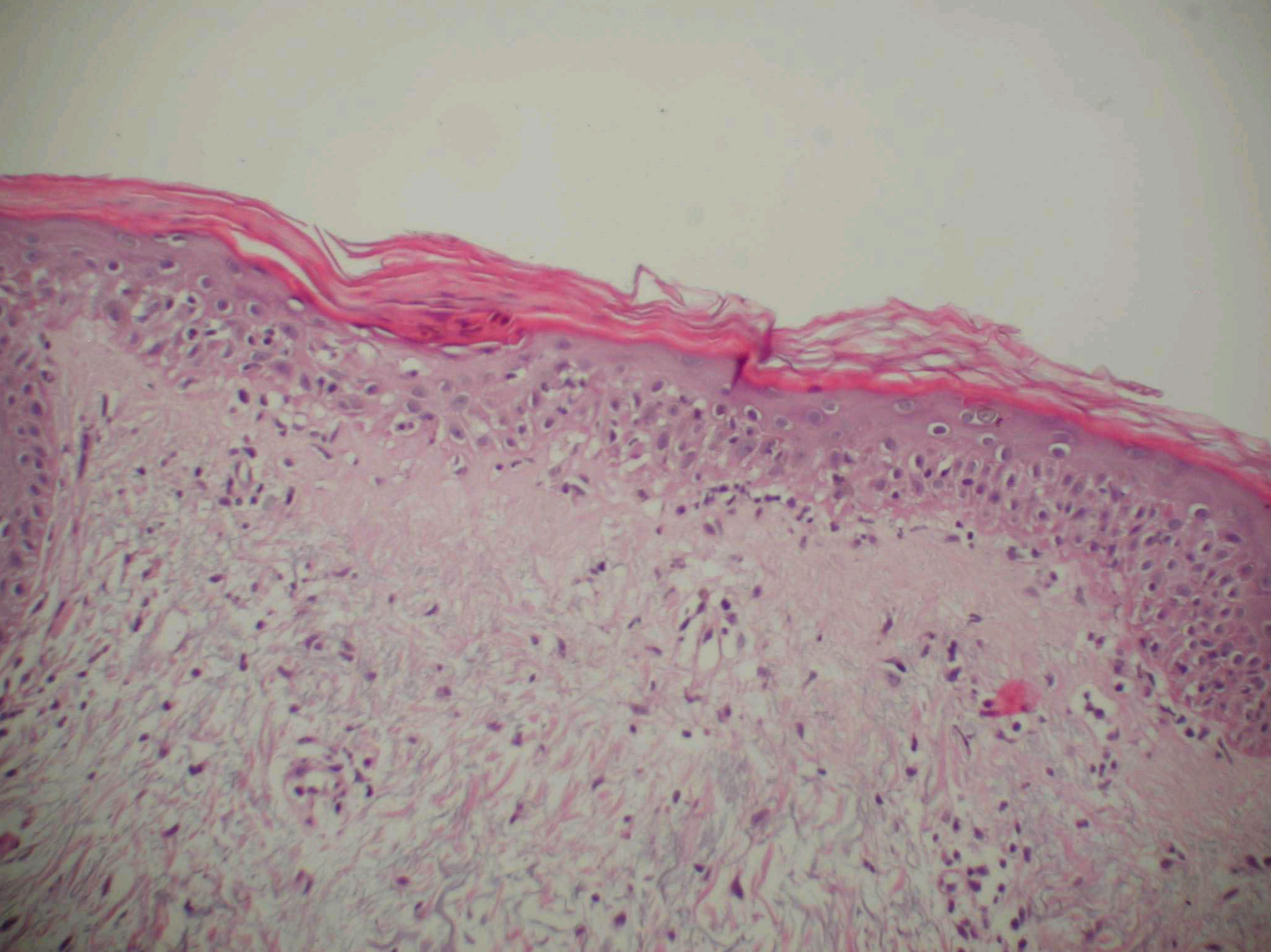
SLE	70-80% of patients with SLE in sun-exposed skin Non sun-exposed non lesional skin, only positive in SLE pts with severe extracutaneous disease and positive for DS DNA Positive in 90% interface dermatitis
DLE	Negative in non-scarring cases Positive in 90% interface dermatitis

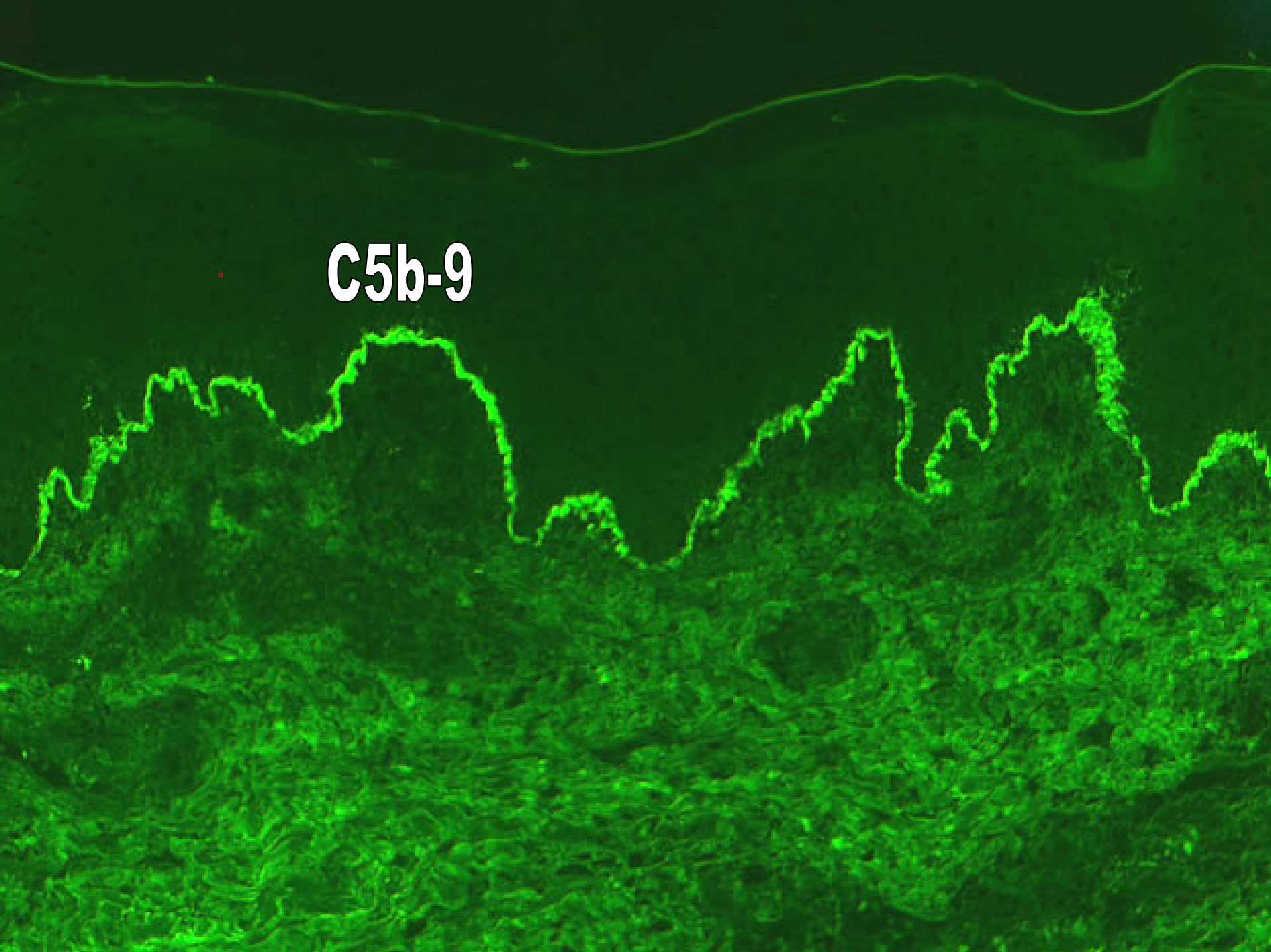
Lupus Band Test and Prognosis

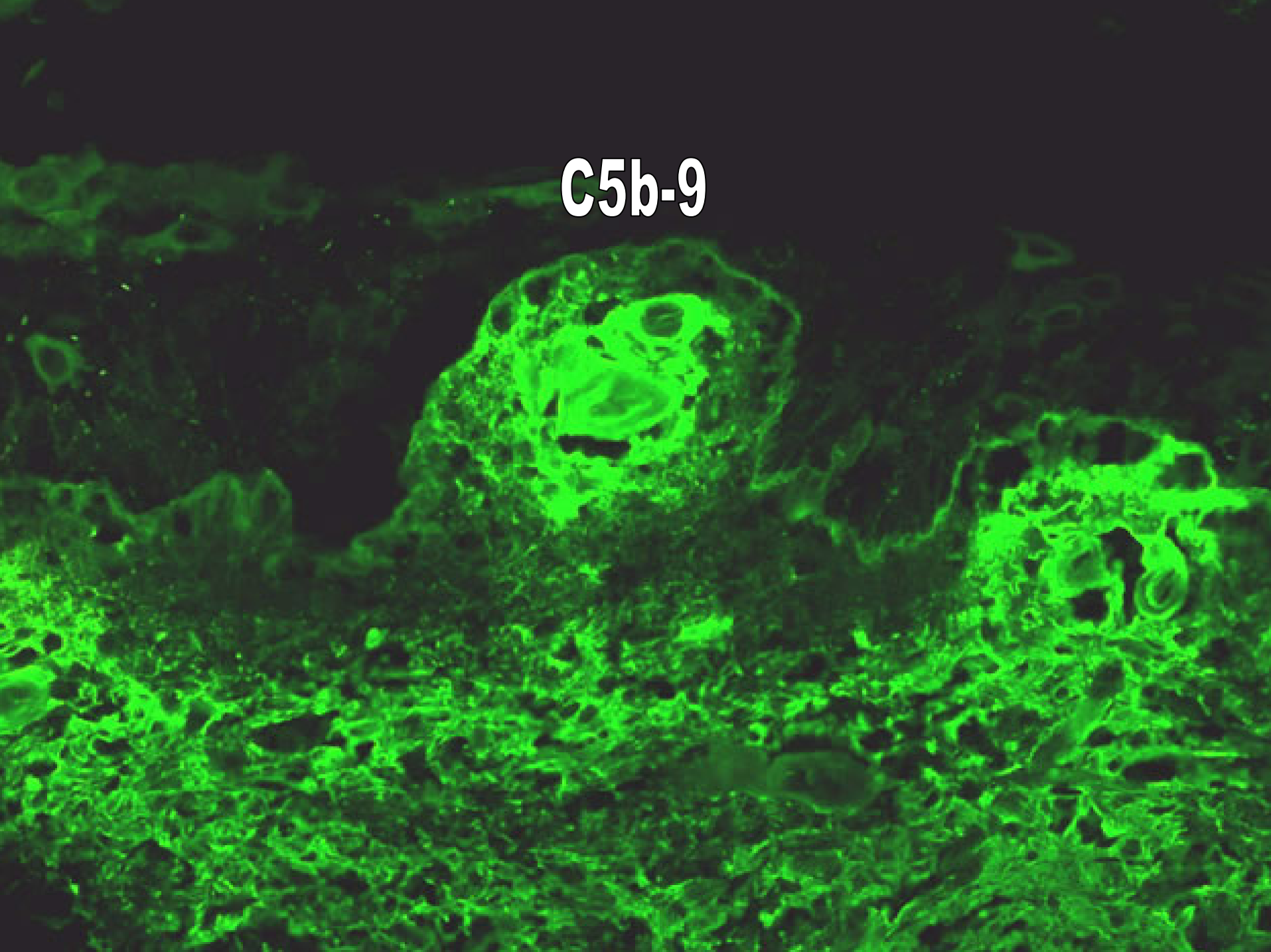
- 70% of patients with active nephritis with LBT on normal skin
- C1q deposits-higher incidence of renal disease




dermatomyositis




C5b-9


C5b-9

Dermatomyositis

- Heliotrope rash and Gottron papules
- Malar erythema, poikiloderma in a photosensitive distribution, violaceous erythema on the extensor surfaces, and periungual and cuticular changes
- Nail fold changes-periungual telangiectases
- Poikiloderma may occur on exposed skin or the upper part of the back (Shawl sign)
- Photodistributed and photoexacerbated, except for heliotrope rash
- Facial erythema rarely

Dermatomyositis

- Scalp involvement in DM is relatively common (coup d'sabre)
- Calcinosis of the skin or the muscle
  - Unusual in adults
  - 40% of children or adolescents
  - Calcinosis cutis manifests as firm yellow nodules

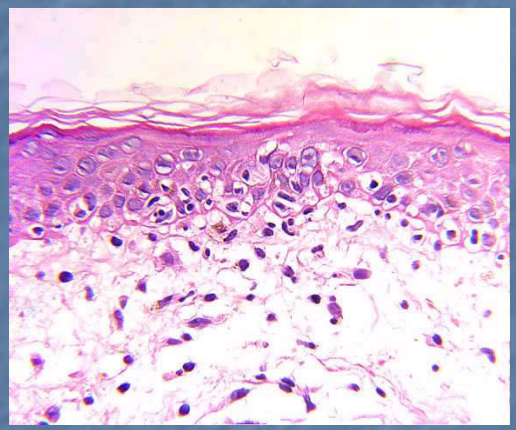
Dermatomyositis

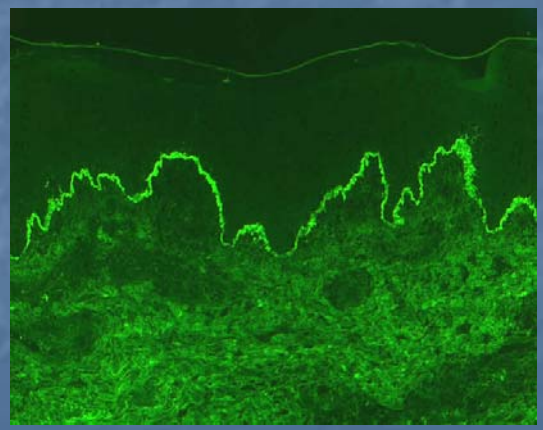
- Muscle findings include weakness and, sometimes, tenderness.
  - Muscle disease manifests as a proximal symmetrical muscle weakness.
  - Distal strength is almost always maintained
  - Muscle tenderness variable finding
- Other systemic features
  - Joint swelling occurs
  - Small joints of the hands are the most frequently involved
  - Non-deforming arthritis
  - Pulmonary disease with abnormal breath sounds.
  - Patients with an associated malignancy may have physical findings relevant to the affected organs

Dermatomyositis

- Muscle enzyme levels abnormal
  - CK, AST, LDH
  - Myositis-specific antibodies (antisignal recognition protein and anti-Ku)
- ANA positive
  - Anti-Mi-1 is highly specific for DM, but it lacks sensitivity because only 25%
  - Anti-Jo-1 is associated with pulmonary involvement, more common in patients with PM than DM

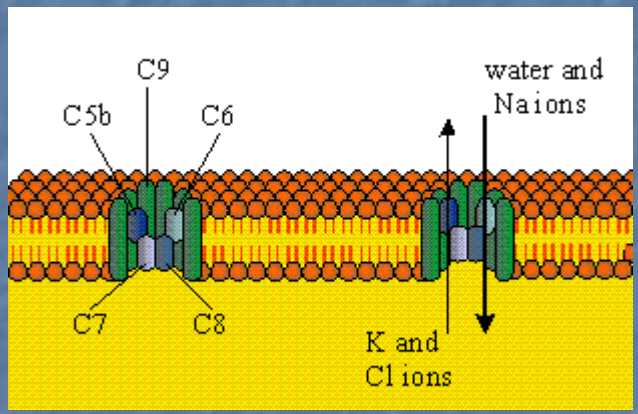
Dermatomyositis Histopathology



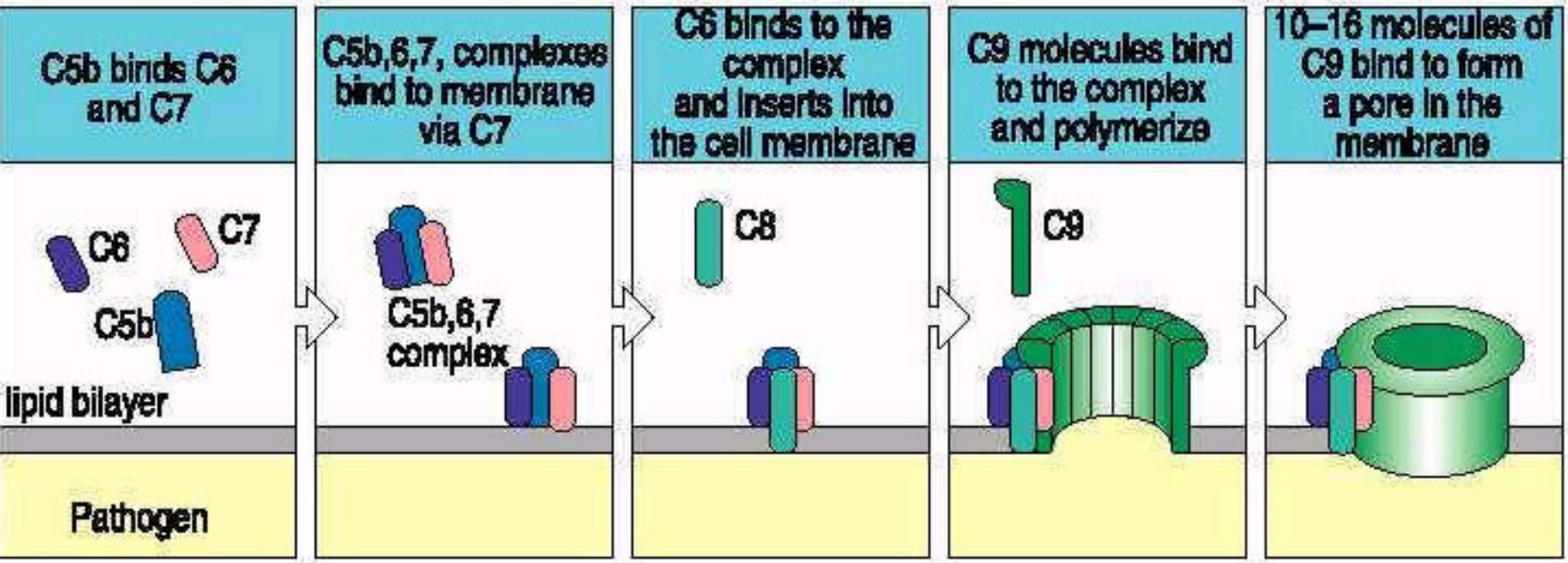


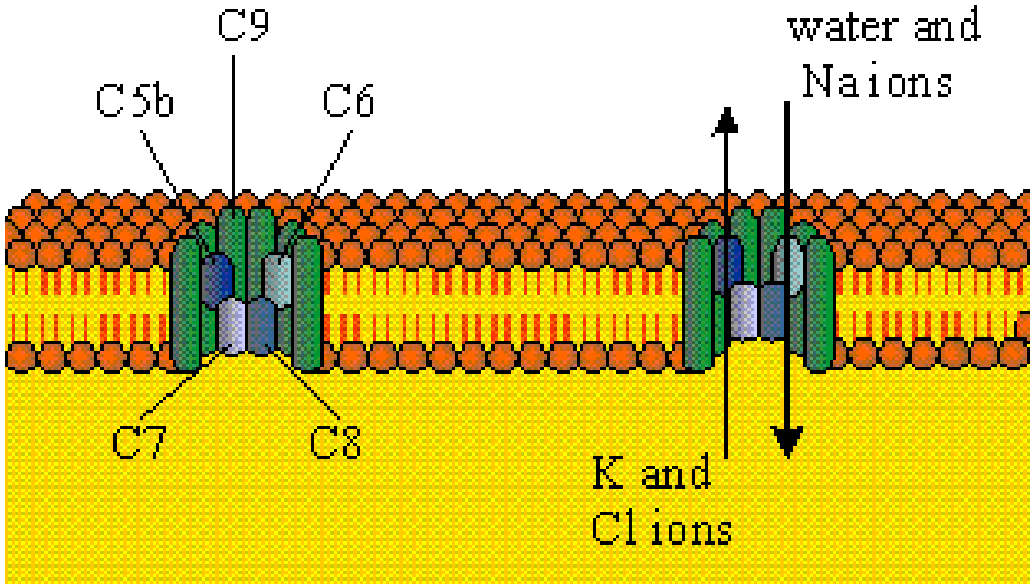
- Cell poor interface dermatitis with dermal mucinosis
- May be identical to DLE, SCLE, SLE
- DIF with Variable Lupus band
- Utilize C5b-9

C5b-9 and Disease



- Terminal complement, membrane attack complex (MAC)
- Formation of membrane pores allow circulating Ab access to nucleus and cytoplasm
- Represent activation of complement pathway within the BMZ


C5b binds C6 and C7
C5b,6,7, complexes bind to membrane via C7
C6 binds to the complex and inserts into the cell membrane
C9 molecules bind to the complex and polymerize
10–16 molecules of C9 bind to form a pore in the membrane
C6
C7
C5b
lipid bilayer
C5b,6,7 complex
C8
C9
Pathogen

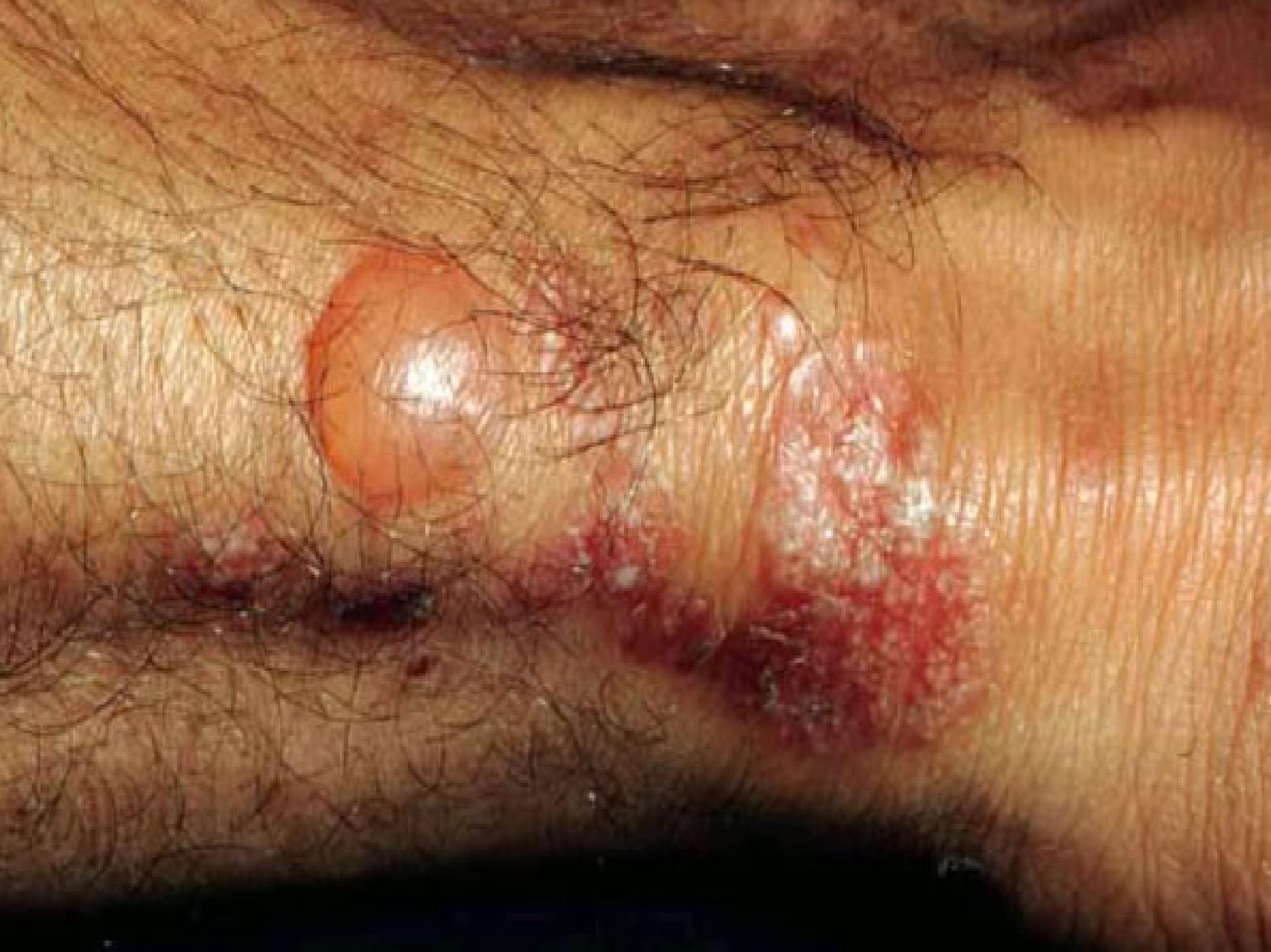

C9
water and Na ions
C5b
C6
C7
C8
K and Cl ions

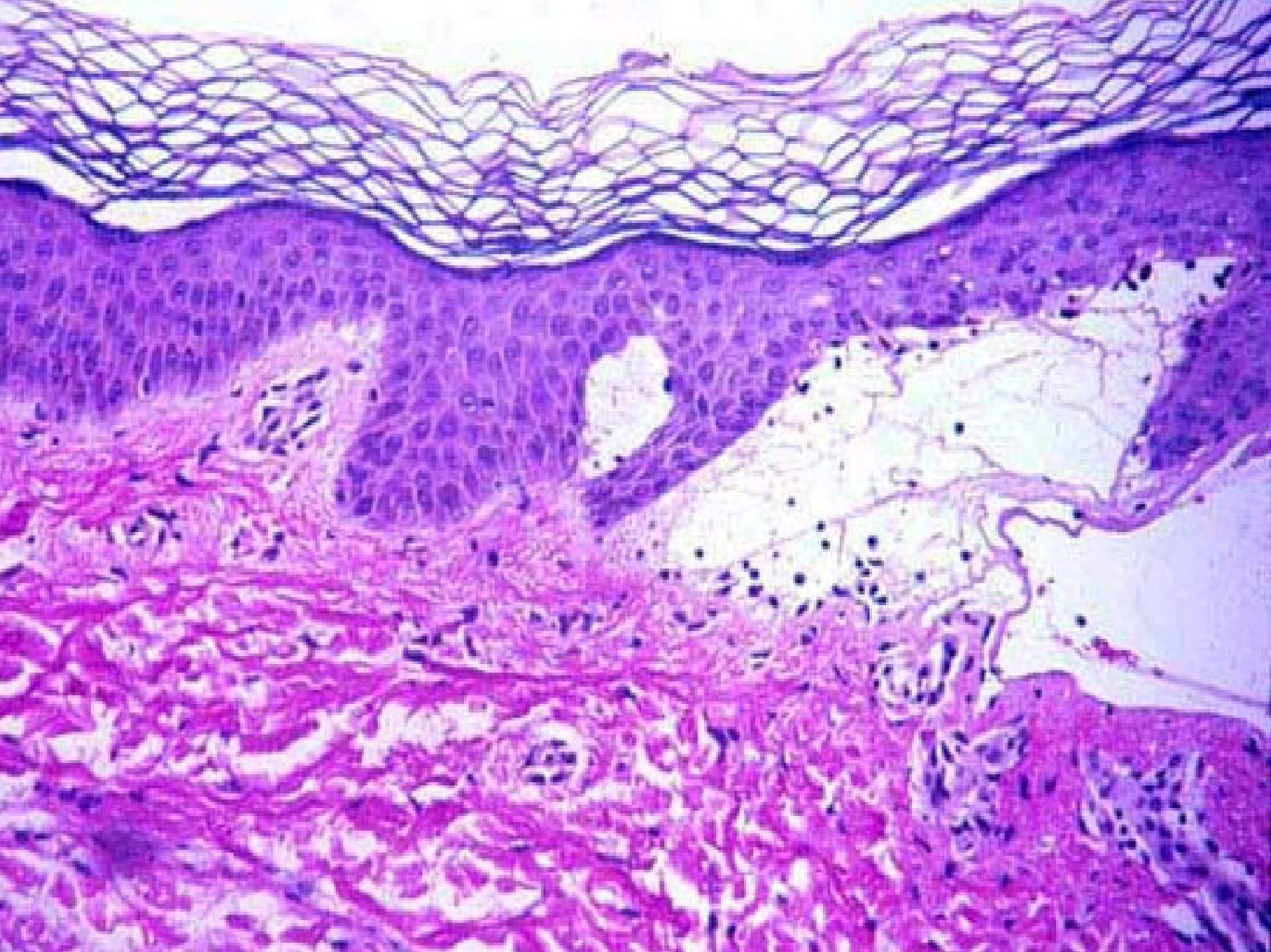
MAC Diseases and Patterns

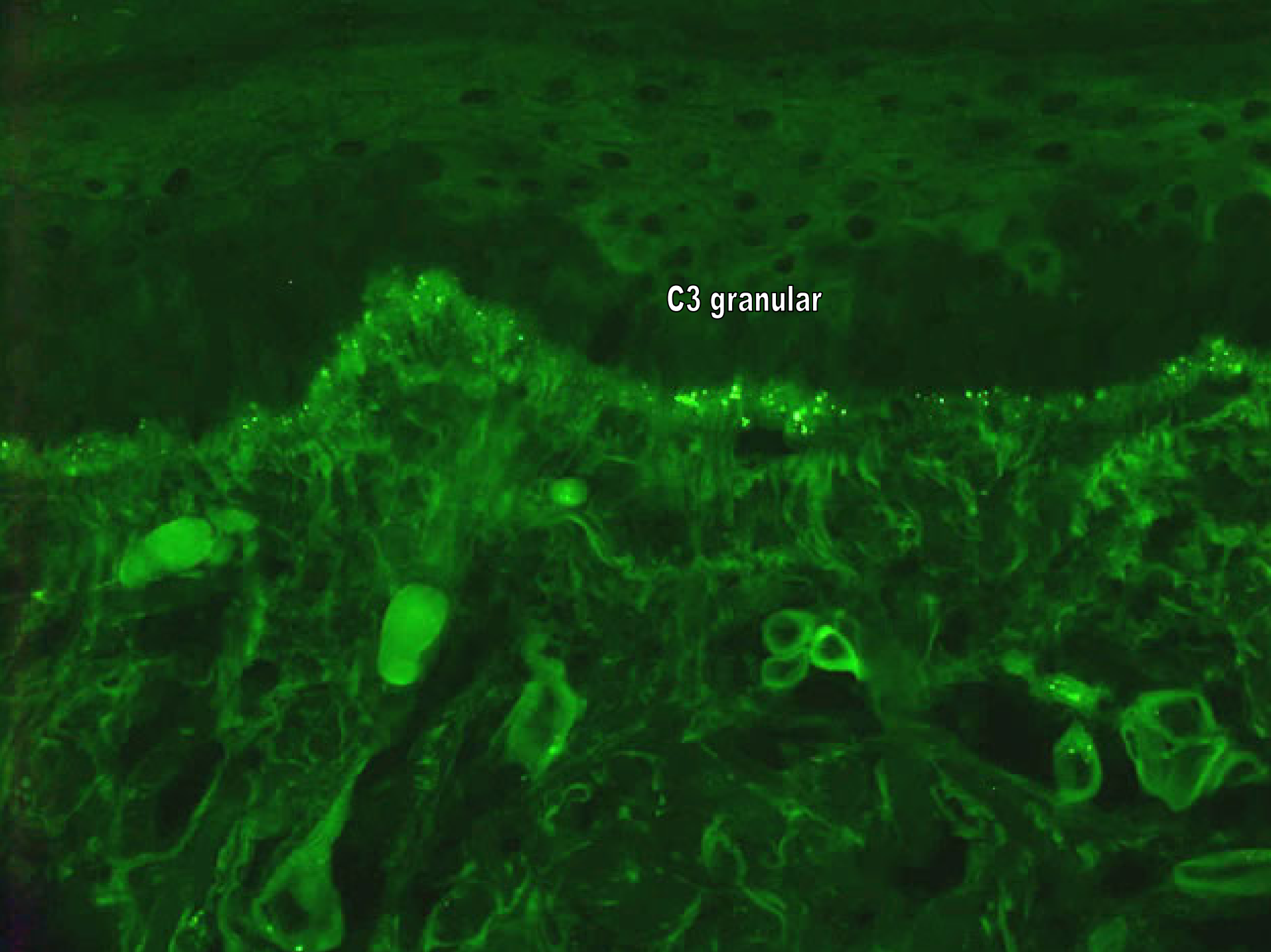
SLE	Intense granular DEJ 80%
SCLE	Granular DEJ 60% Granular nuclear/cytoplasmic epidermal
DLE	DEJ 60%
MCTD	Granular nuclear/cytoplasmic epidermal 100% DEJ 100%
Dermatomyositis	DEJ 90% Endothelial cells Dermal papillary capillaries

Overlap

- Anti-Ro associated SLE, Dermatomyositis, and MCTD
  - Endothelial decoration for C5b-9
  - Endothelial cell necrosis and denudement
  - Reduction in vascular plexus
  - Granular and cytoplasmic decoration within keratinocytes for C5b-9
  - Differentiate by LBT and clinical
- Non-lesional skin
  - Usually negative or very weak






C3 granular

Epidermolysis Bullosa Acquisita

- Noninflammatory or mildly inflammatory form
  - Most common
  - Tense vesicles and bullae, and erosions primarily on the extensor surfaces of hands, knuckles, elbows, knees, and ankles
  - Blisters may be hemorrhagic
  - Blisters on mucus membranes rupture easily
  - Usually heals with significant scar and milia formation
  - Nail dystrophy and scarring alopecia rarely
  - Resembles porphyria cutanea tarda in elderly patients,
  - Resembles the dominantly inherited form of epidermolysis bullosa dystrophica in children

EBA

- Generalized inflammatory form
  - Widespread, tense vesicles and bullae (some hemorrhagic)
  - Not localized to trauma-prone sites
  - Generalized erythema, urticarial plaques, and generalized pruritus may occur
  - Usually heals with minimal scarring and milia formation
  - Usually heals with minimal scarring and milia formation
  - Clinically resembles bullous pemphigoid or linear IgA bullous dermatosis

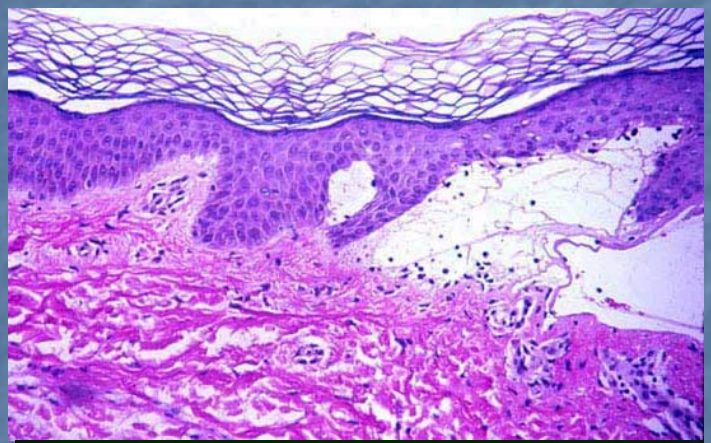
EBA

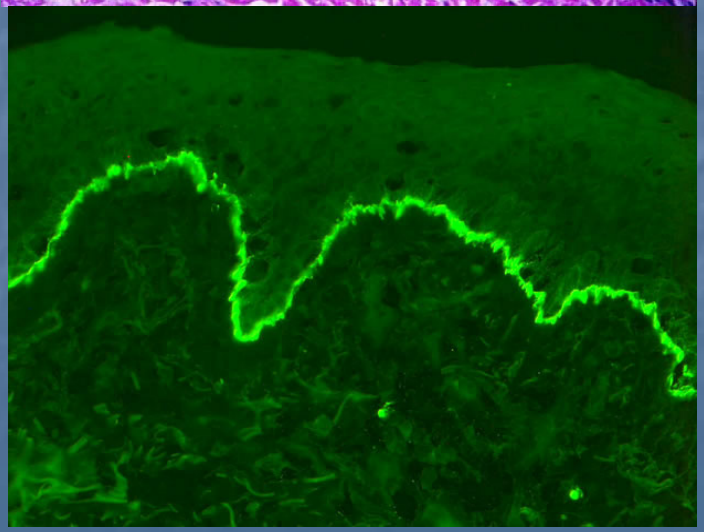
- Third variant of EBA predominantly involves mucus membranes
  - Affects mucous membranes of buccal, conjunctival, gingival, palatal, nasopharyngeal, rectal, genital, and esophageal mucosa
  - Resembles mucous membrane pemphigoid and can result in significant mucosal scarring and dysfunction
  - Recent international consensus statement (2002) reassigned this group of patients to the category of mucous membrane pemphigoid

EBA-Pathogenesis

- Autoimmune disease with IgG autoantibodies targeting non-collagenous domain of collagen VII in basement membrane
  - Initiating event unknown
- Subset of clinically milder EBA
  - IgA autoantibodies
  - IgG autoantibodies to the collagenous domain, rather than the NC1 domain of collagen VII

EBA Histopathology

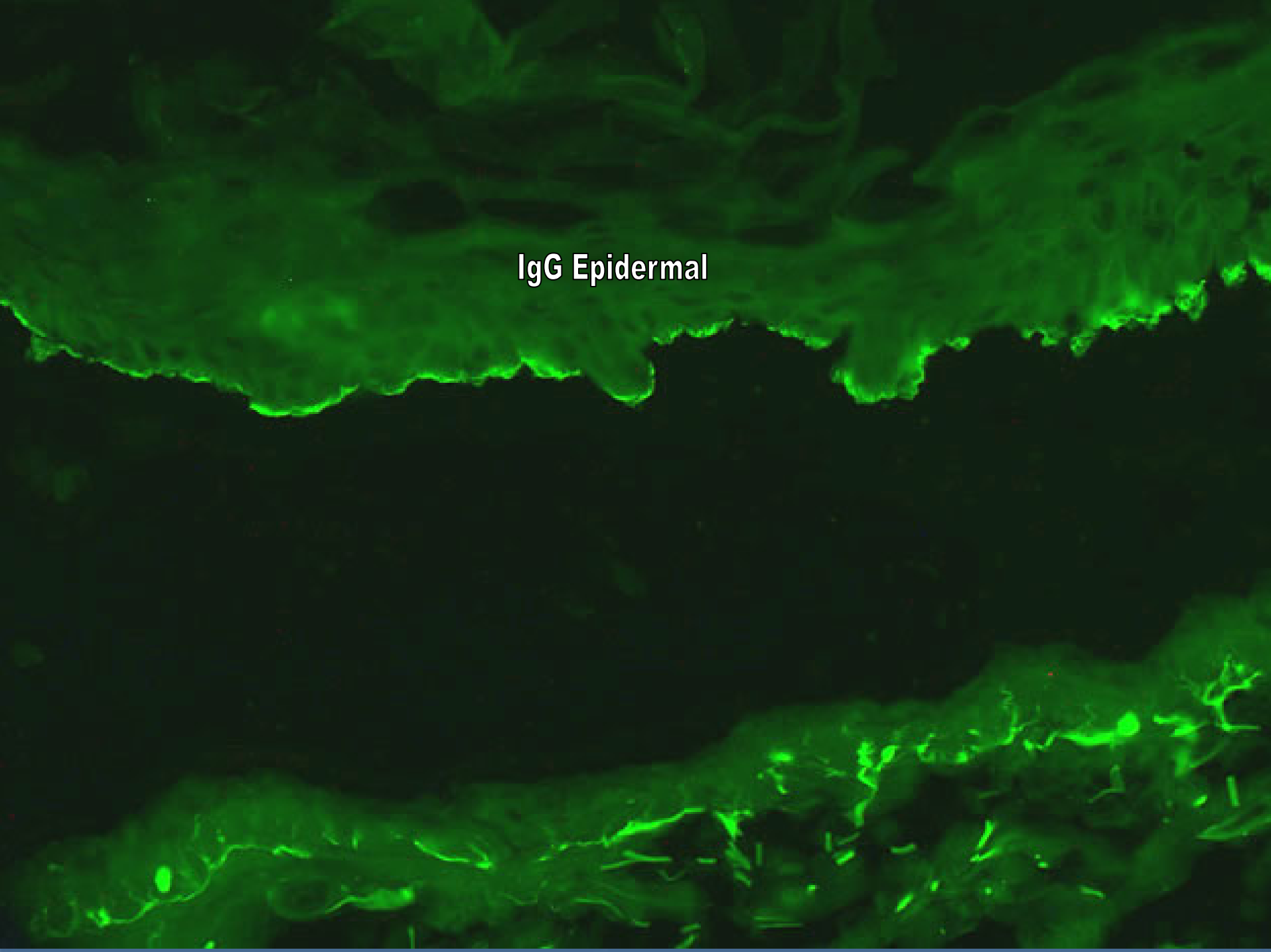


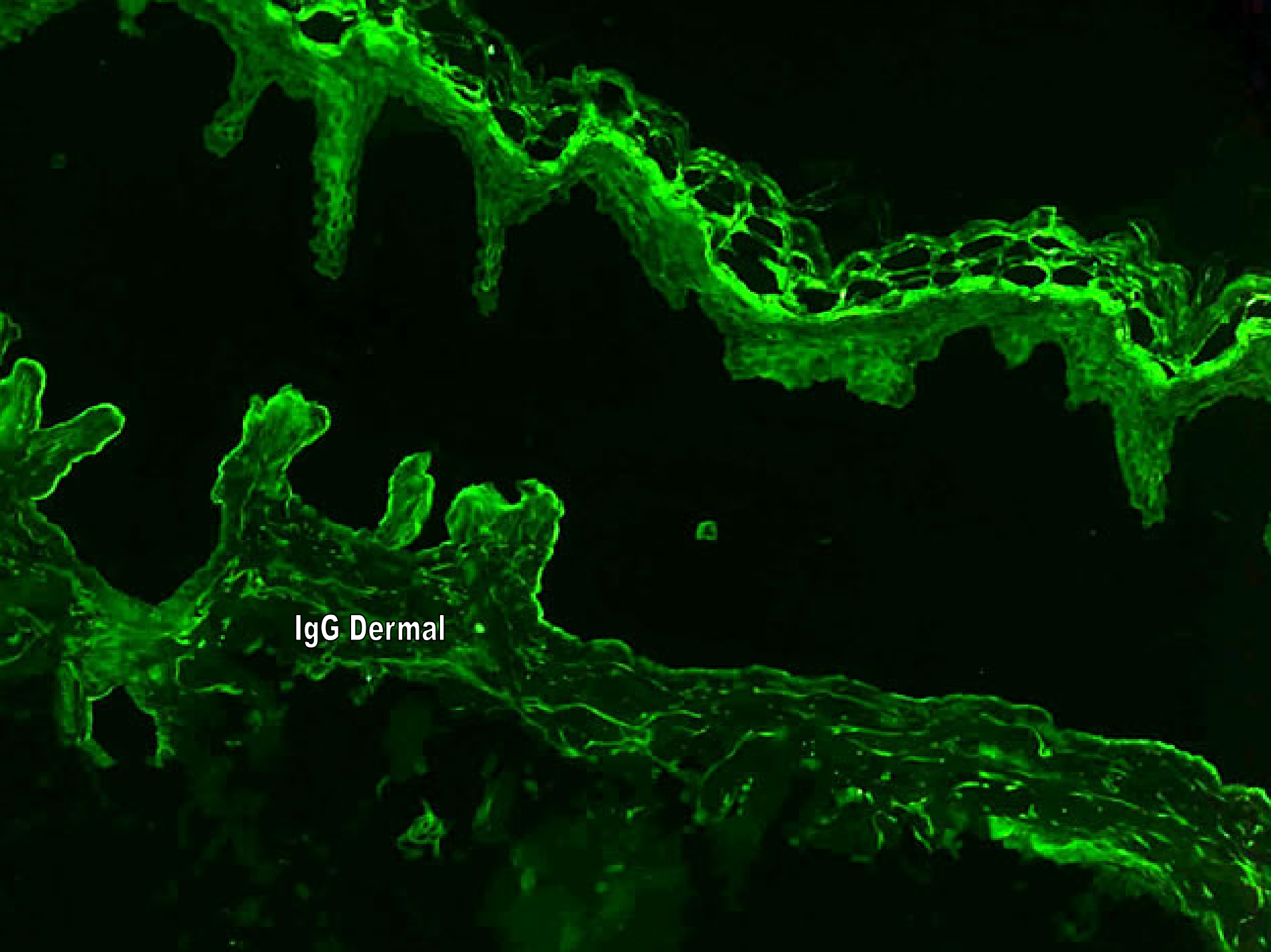


- Subepidermal blister with mixed inflammation
- DIF linear thick band of IgG, and to a lesser extent C3 at basement membrane zone
  - Occasionally IgM or IgA
- IIF IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component, type VII collagen.
  - Bind to the dermal floor (lower part) on salt-split normal human skin substrate

Salt-Split Skin Assay

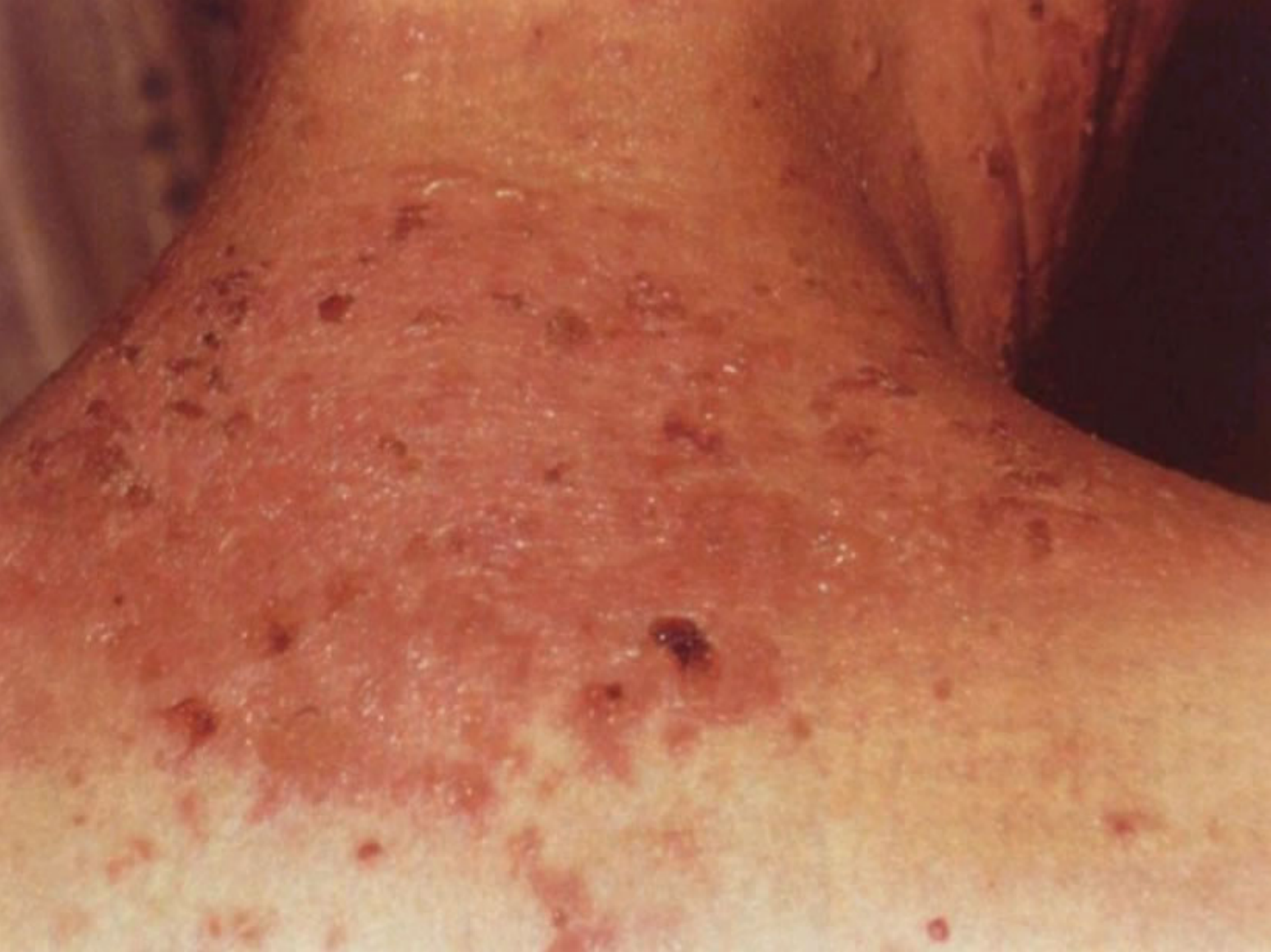
- IIF-utilize patient's serum
- Incubate normal skin with 1M NaCl
- Separates the epidermis from dermis
- Epidermal half
  - Upper lamina lucida and hemidesmosomes
  - BP antigen
- Dermal half
  - Laminin 5
  - Lamina densa, anchoring fibrils

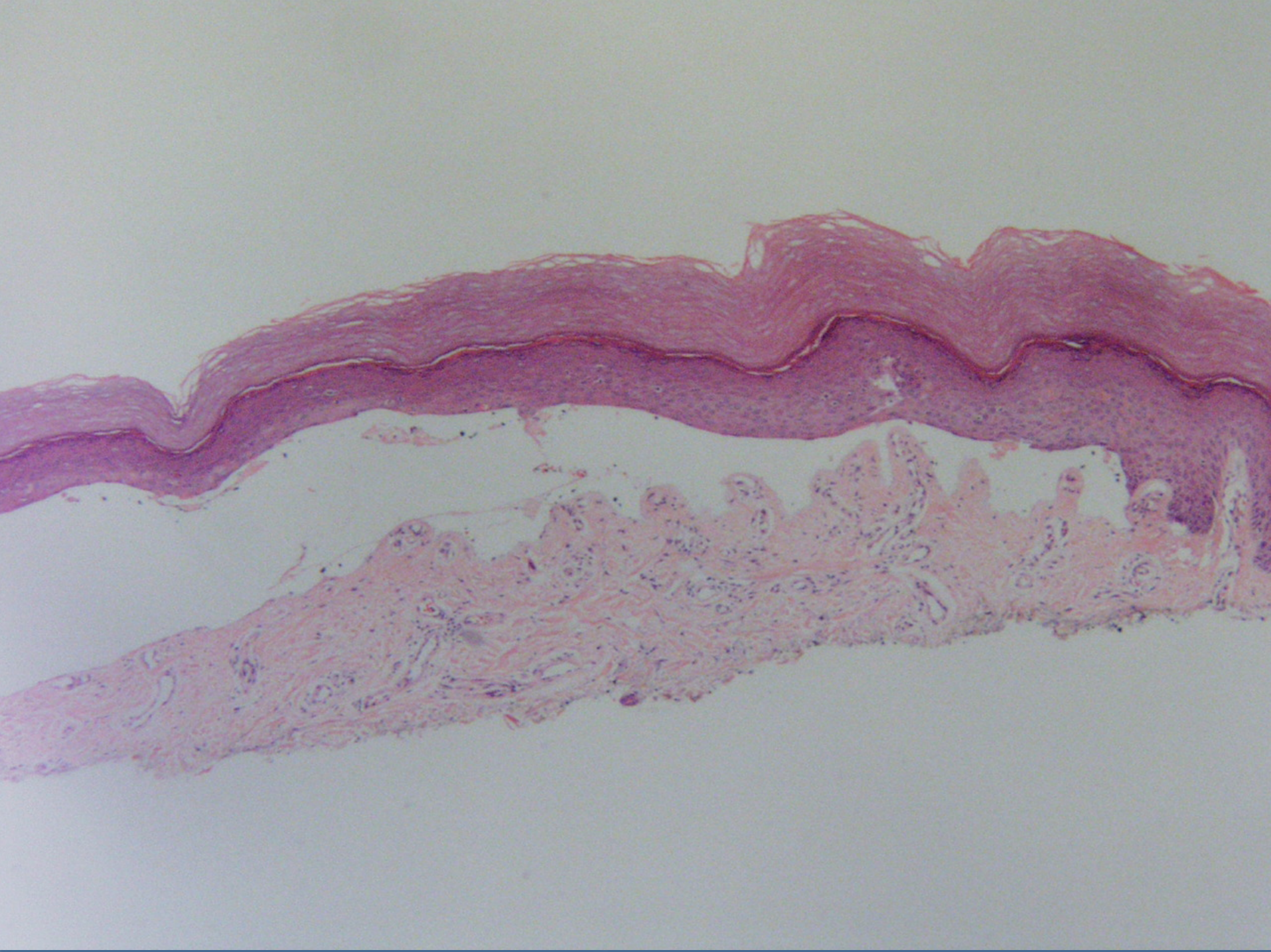

IgG Epidermal

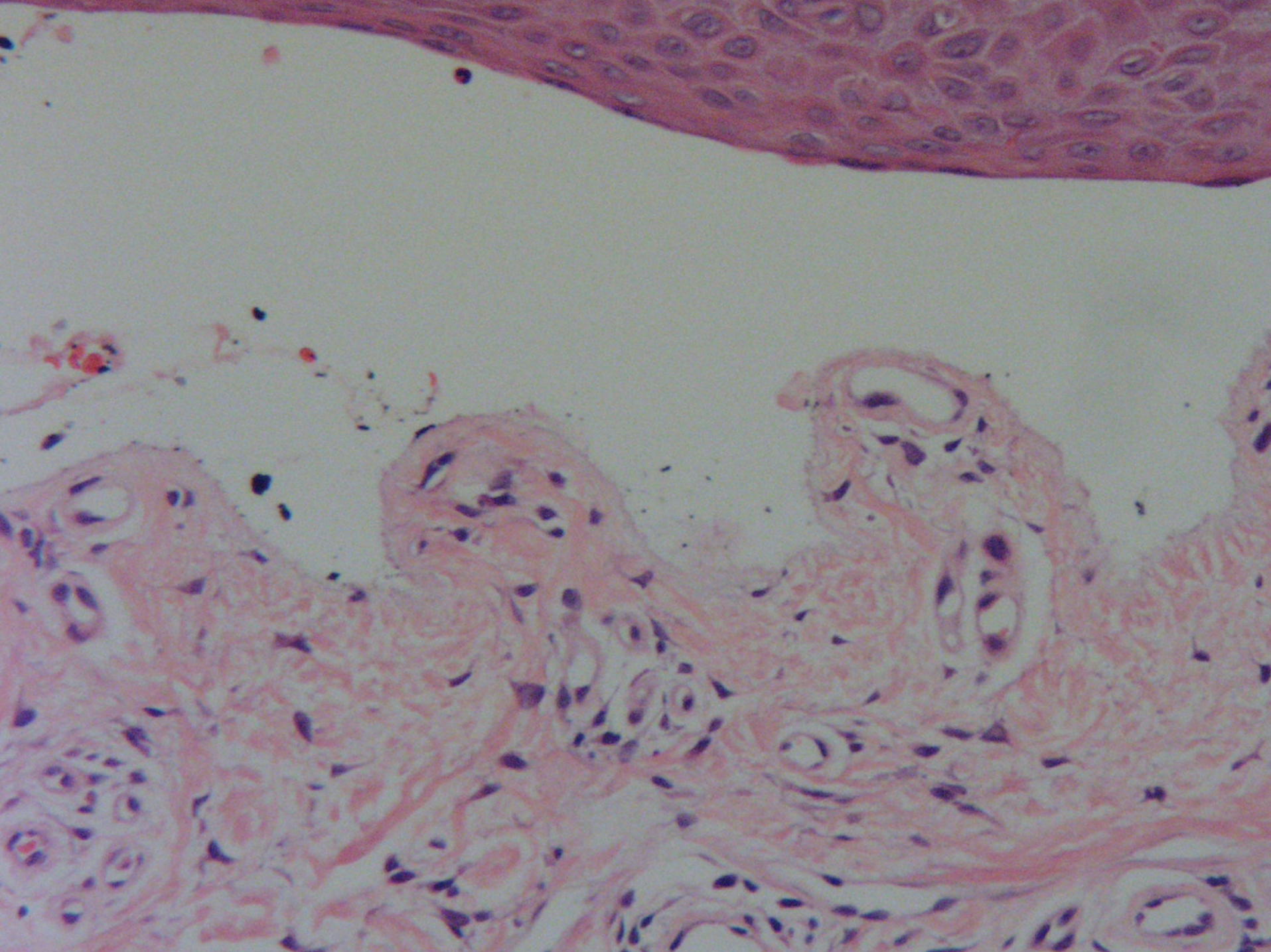

IgG Dermal

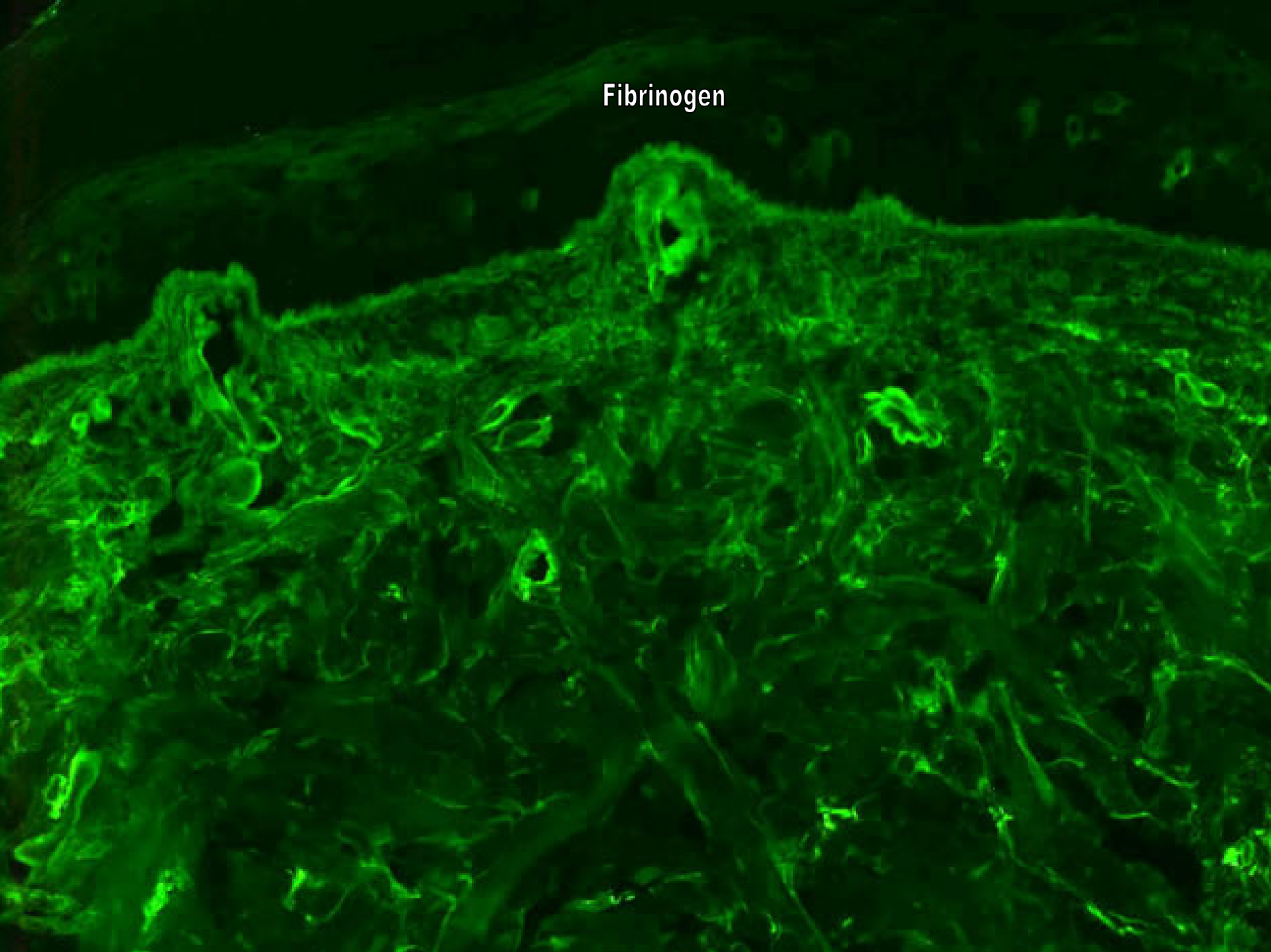
SSSS

Split	Disease
Epidermal	Bullous pemphigoid
Dermal	EBA Bullous lupus erythematosus Anti-epiligrin cicatricial pemphigoid Anti-p105 bullous pemphigoid





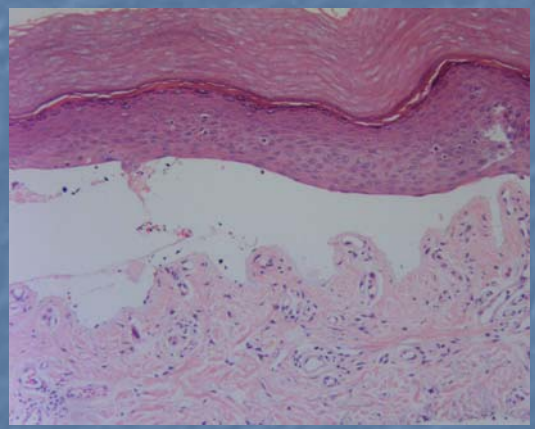


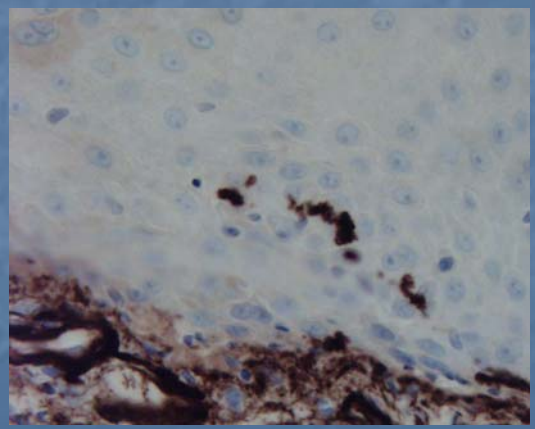

Fibrinogen

Porphyria

- Fragility of sun-exposed skin after trauma
  - Erosions and bullae on the dorsal aspects of the hands, the forearms, and the face
  - Healing of crusted erosions and blisters leaves scars, milia, and hyperpigmented and hypopigmented atrophic patches.
- Hypertrichosis
  - Temporal and malar facial areas
  - Arms, legs
- Indurated, waxy, yellowish sclerodermal-like plaques-upper trunk
- Melasmalike hyperpigmentation of the face
- Erythematous suffusion or plethora of face and upper trunk
- Severe cases with scarring alopecia and onocholysis and contractures
  - Urine sample may have a tea- or wine-colored tint

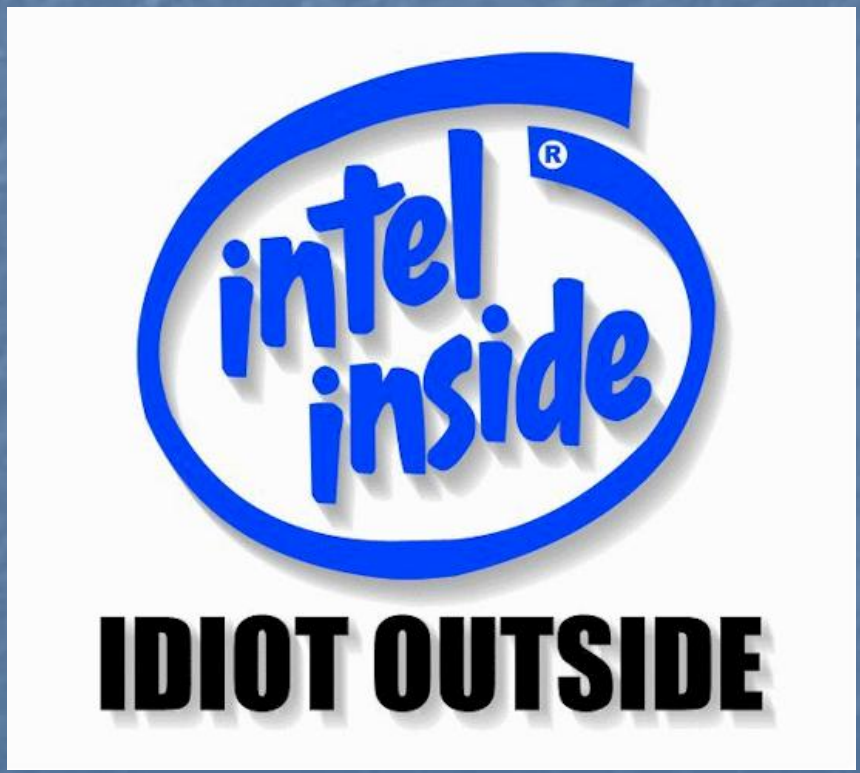
Porphyria





- Subepidermal bullae with minimal dermal inflammatory infiltrate festooning of dermal papillae
- Thickened upper dermal capillary walls and dermoepidermal basement membrane zones
- Elastosis and sclerosis
- Trapped basement membrane zone (caterpillar bodies) in epidermal roof (Ab to Collagen IV/laminin)
- DIF with immunoglobulins and complement in and around the dermal capillaries and at the basement membrane zone

Questions



- The trouble with facts is that there are so many of them.

Samuel McChord Crothers
The Gentle Reader