

Cutaneous Immunopathology

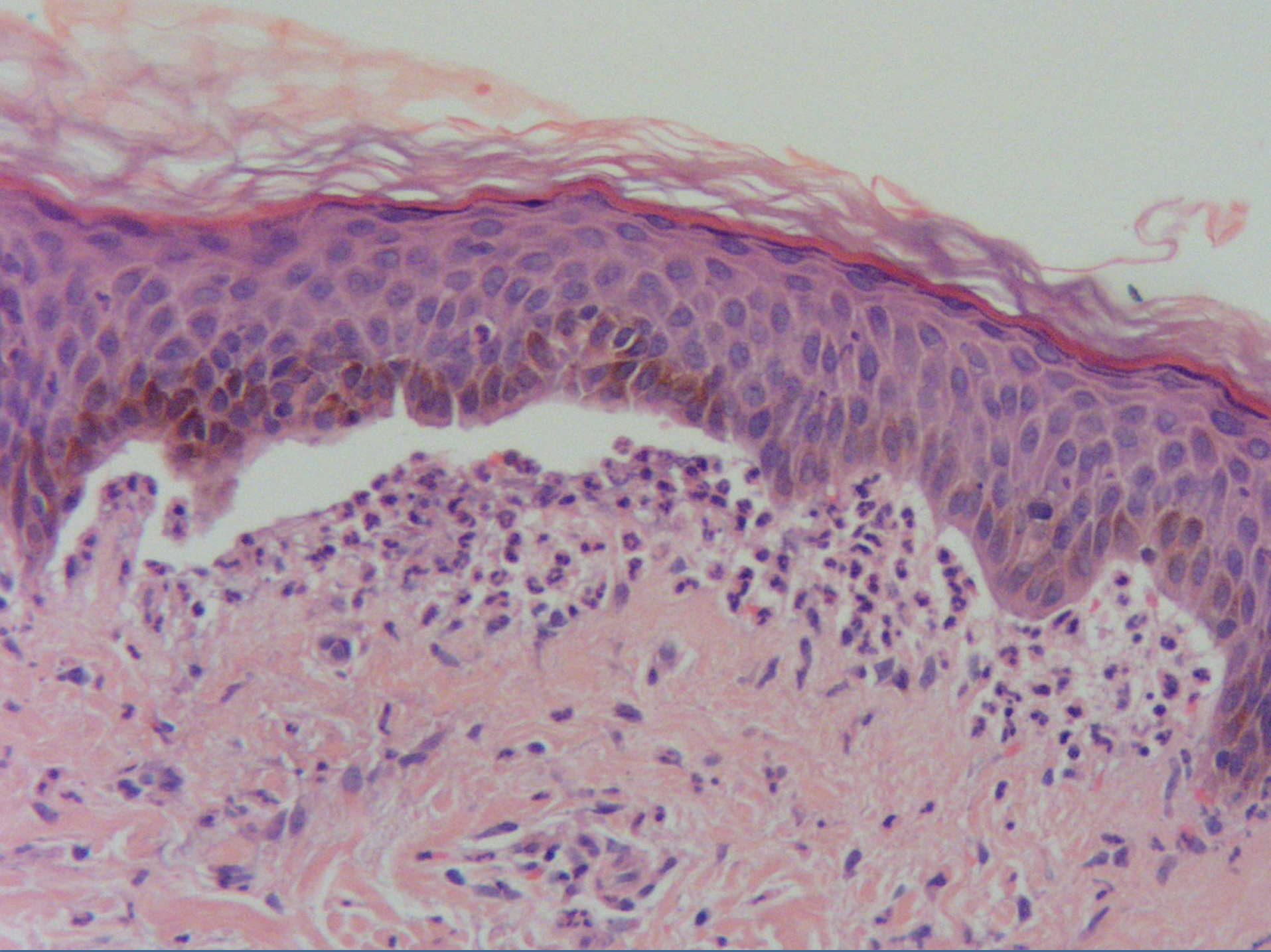
Paul K. Shitabata, M.D.

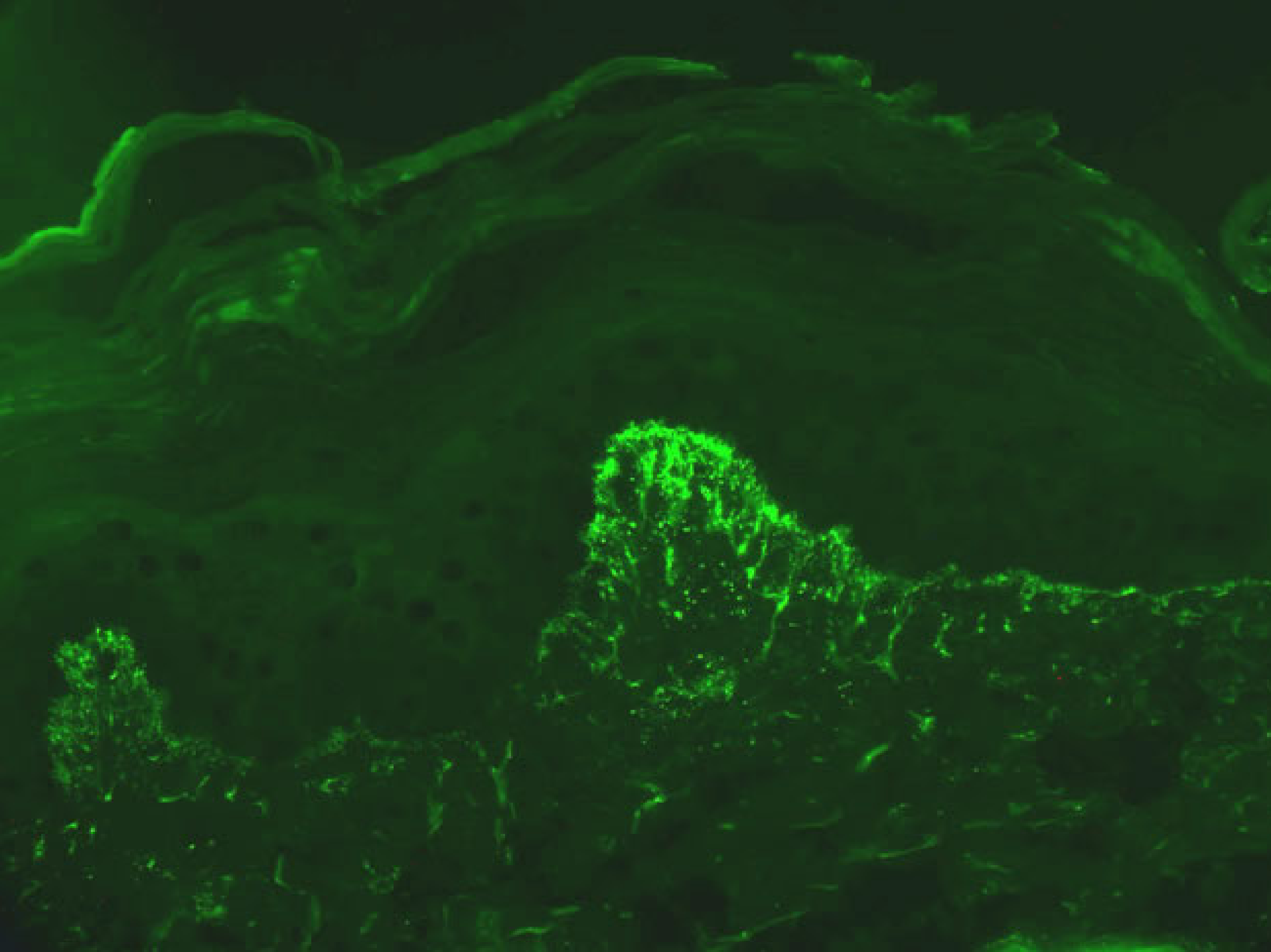
Dermatopathologist

APMG









Dermatitis Herpetiformis

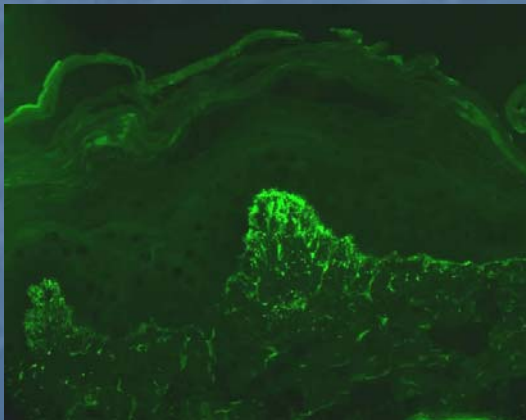
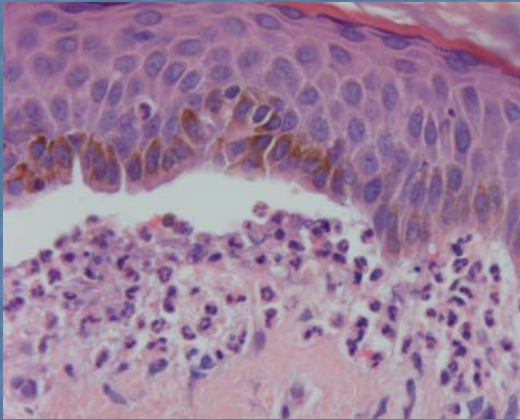
- Flesh-colored-to-erythematous vesicles appear in a herpetiform pattern
 - Symmetrically distributed over extensor surfaces including elbows, knees, buttocks, shoulders, and the posterior (nuchal) scalp
 - Erythematous papules and urticarialike plaques occur less frequently, bullae rare
 - Erosions 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	1 st biopsy edge of lesion 2 nd 3 mm from lesion
Pemphigus or pemphigoid, oral	1 st biopsy 3mm from lesion 2 nd 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

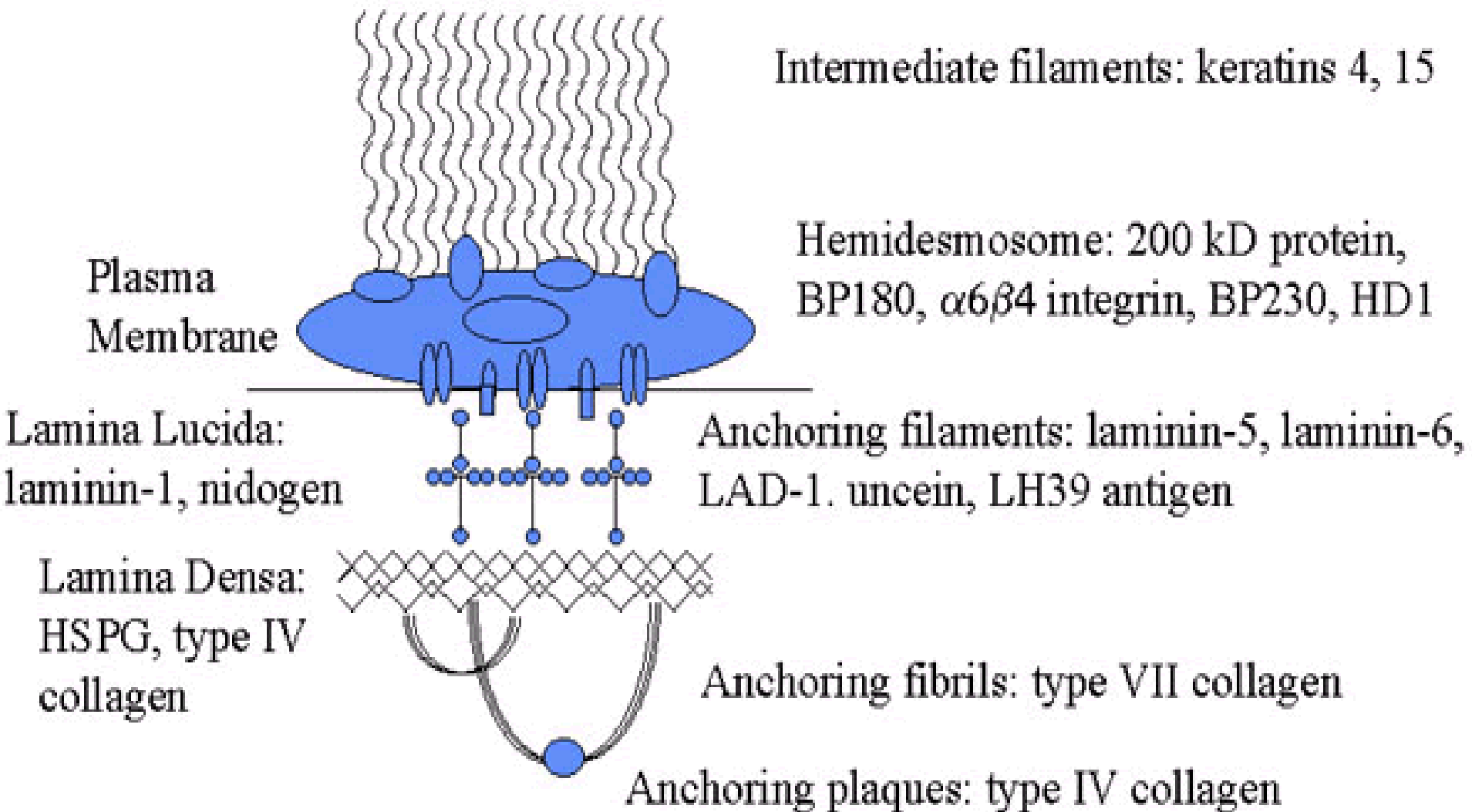
Disorders with Negative/Nonspecific IF

- 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



Location of Components

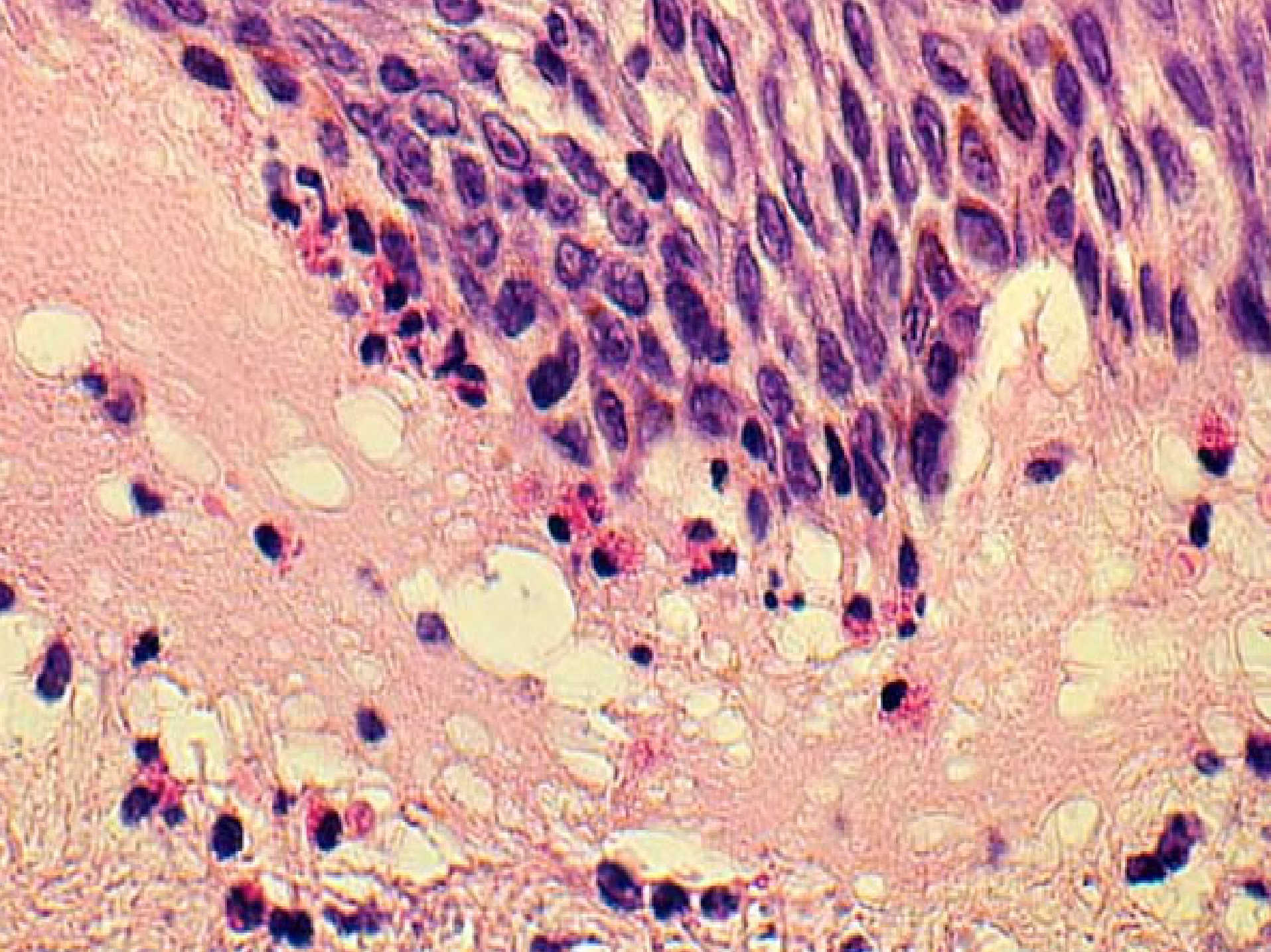
Plasma membrane	BP antigen
Lamina lucida	Laminin
Lamina densa	Type IV collagen EBA antigen Heparin sulfate

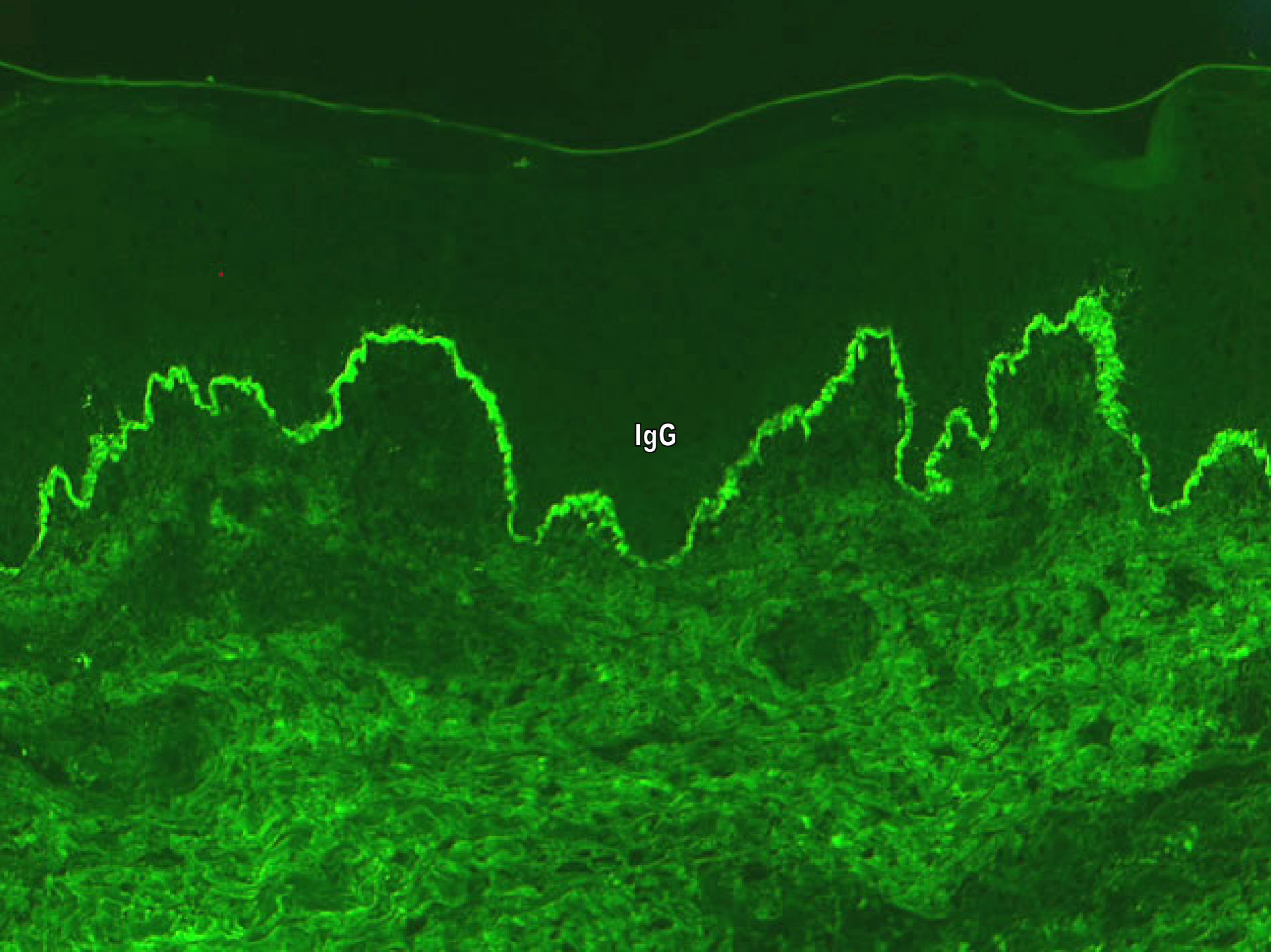
Component	Disease
Epiligrin	Anti-epiligrin cicatricial pemphigoid Some junctional EB
Uncein	Overlap syndrome with features of CP and EBA
Ladinin (LAD1)	Chronic bullous disease of childhood Linear IgA disease
EBA antigen	EBA

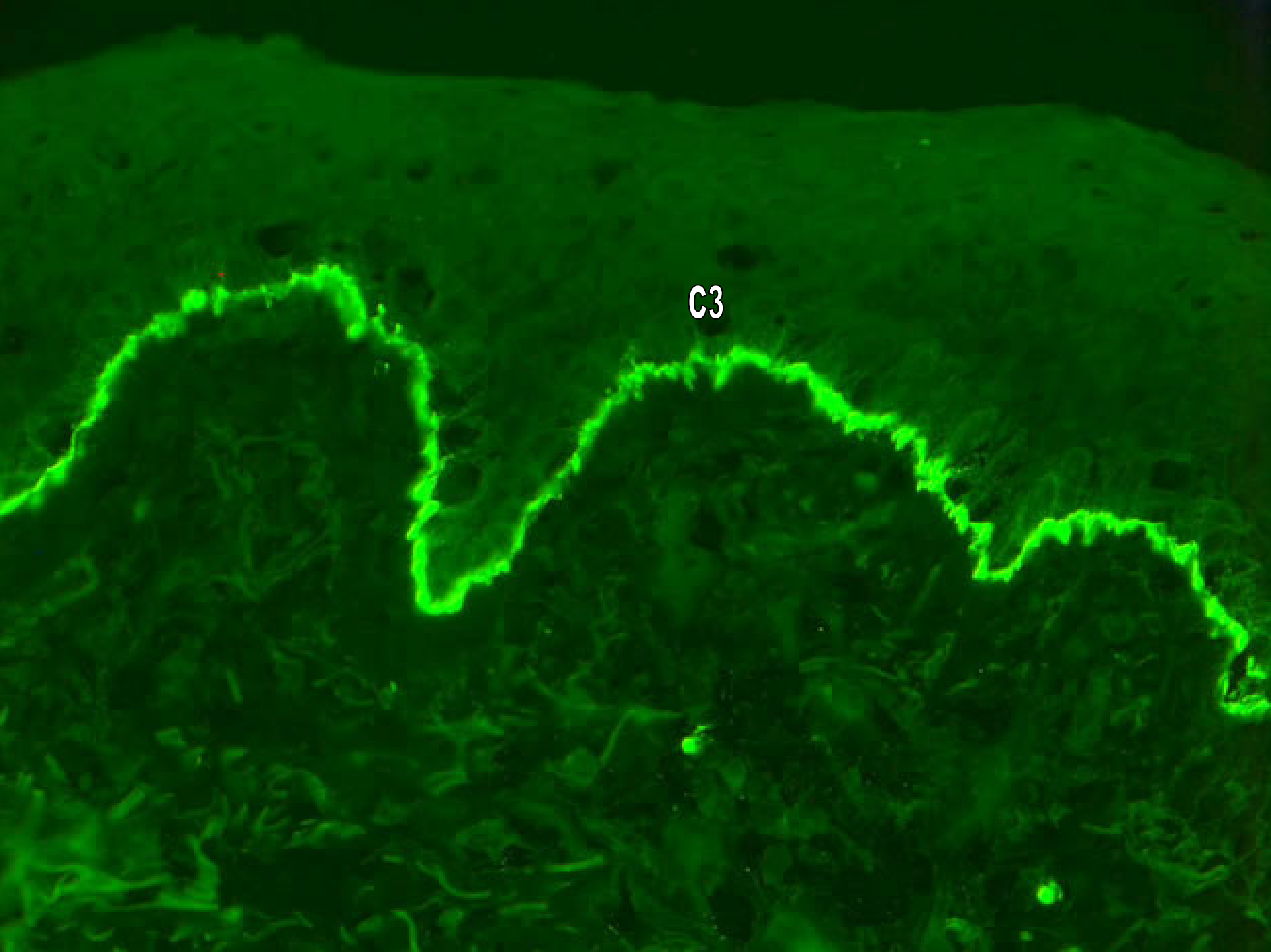
Technical Considerations

- 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



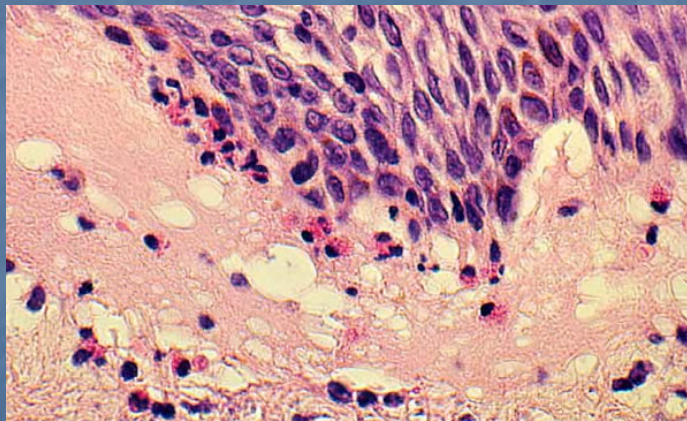






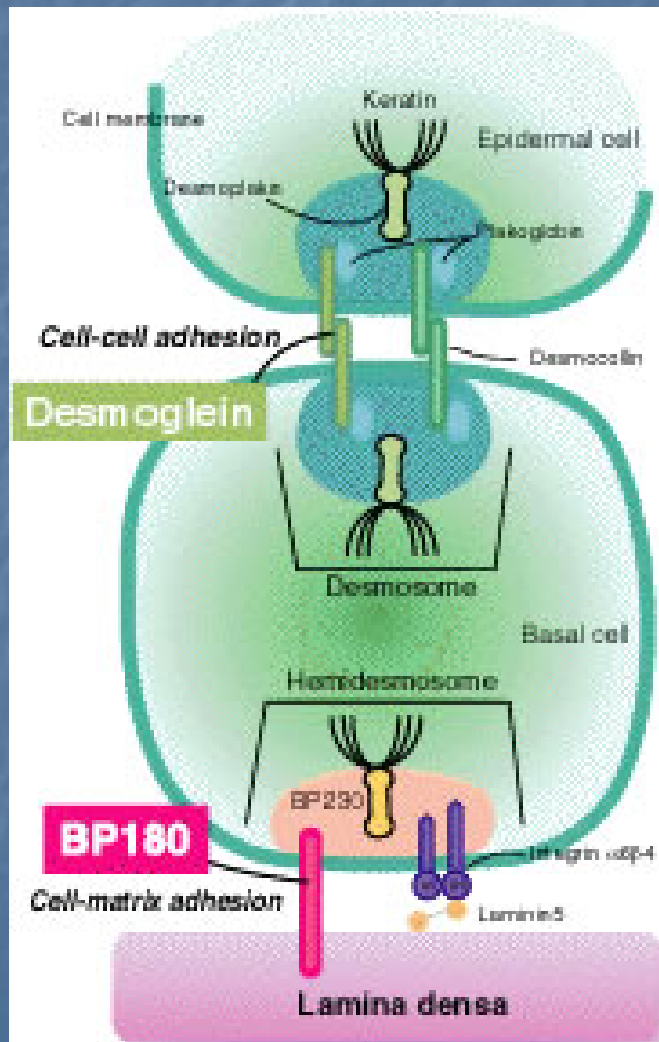
C3

Bullous Pemphigoid



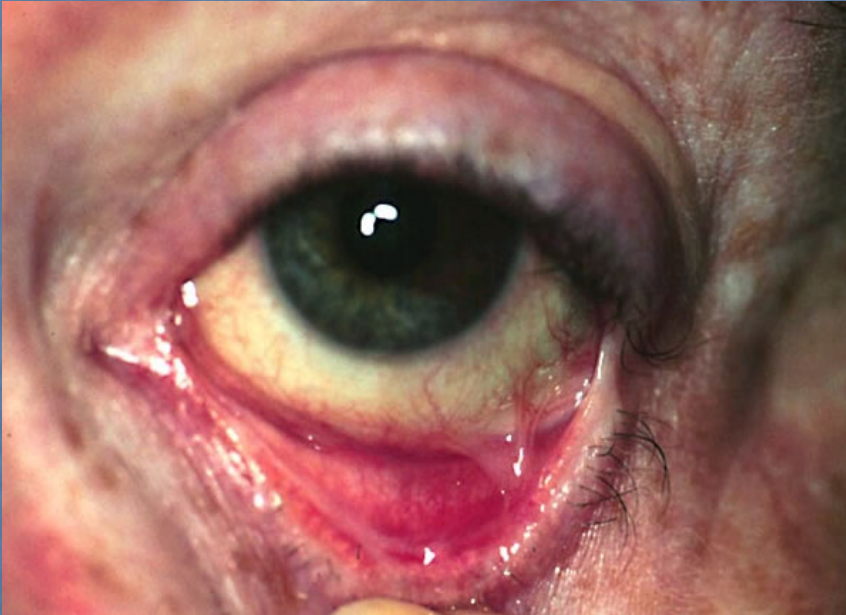
- Tense bullae on erythematous base
- Negative Nikolsky
- Subepidermal bullous dermatosis with eosinophils
- DDX: Herpes gestationis, Bullous LE, Cicatricial pemphigoid

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 portion is antigenic epitope site for BP and HG

Cicatricial Pemphigoid

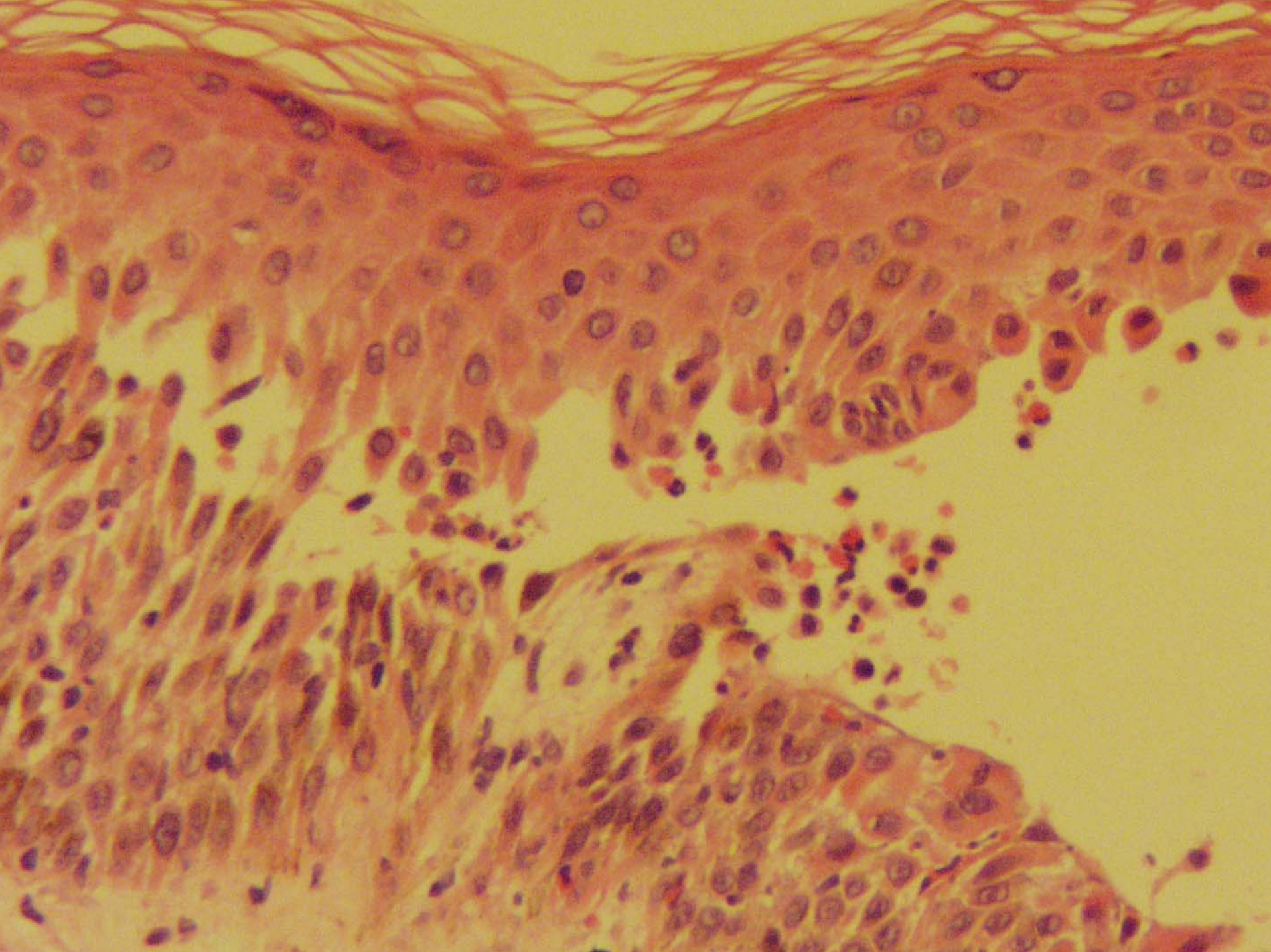


- Brunstig-Perry variant
 - Scarring blisters on head and neck
 - Mucosa rare
- Antiepiligrin variant
 - Associated with malignancy including endometrial, lung, and stomach
 - May be paraneoplastic blistering disease

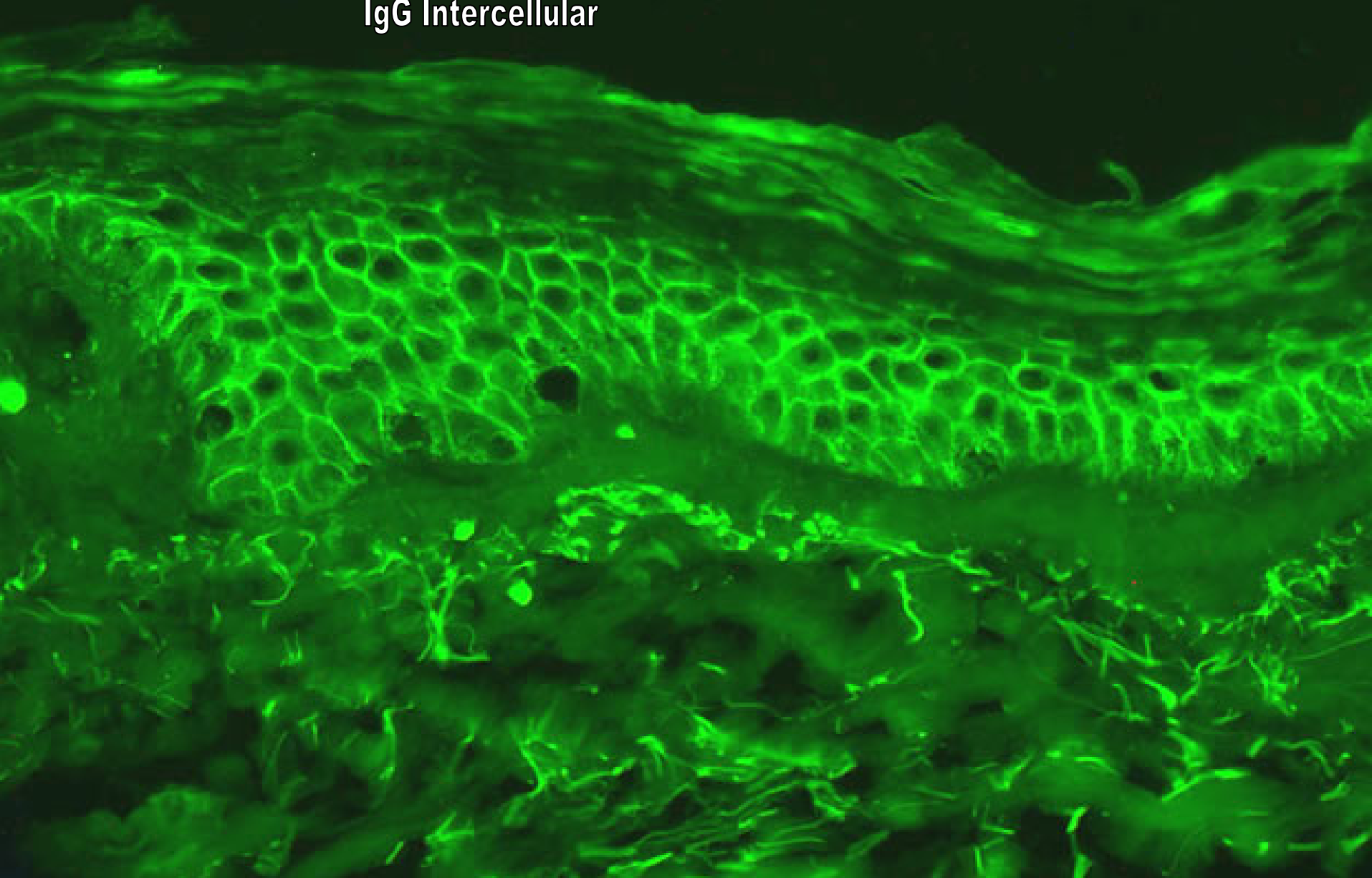
Cicatricial Pemphigoid- Histopath/IF

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





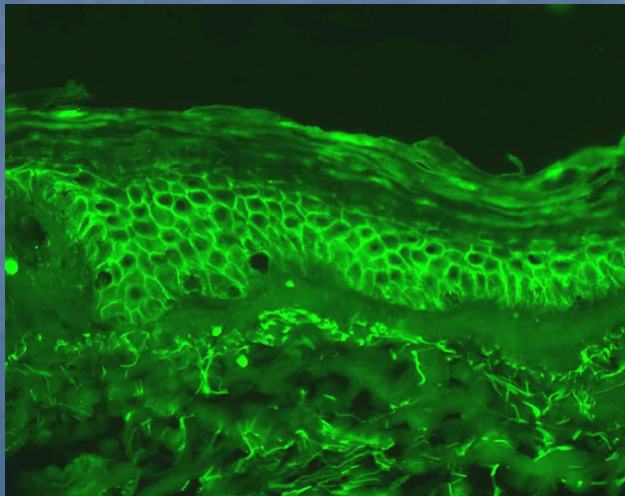
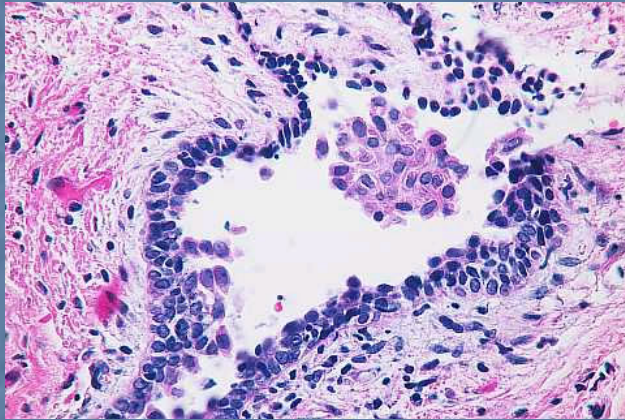
IgG Intercellular



Pemphigus Vulgaris

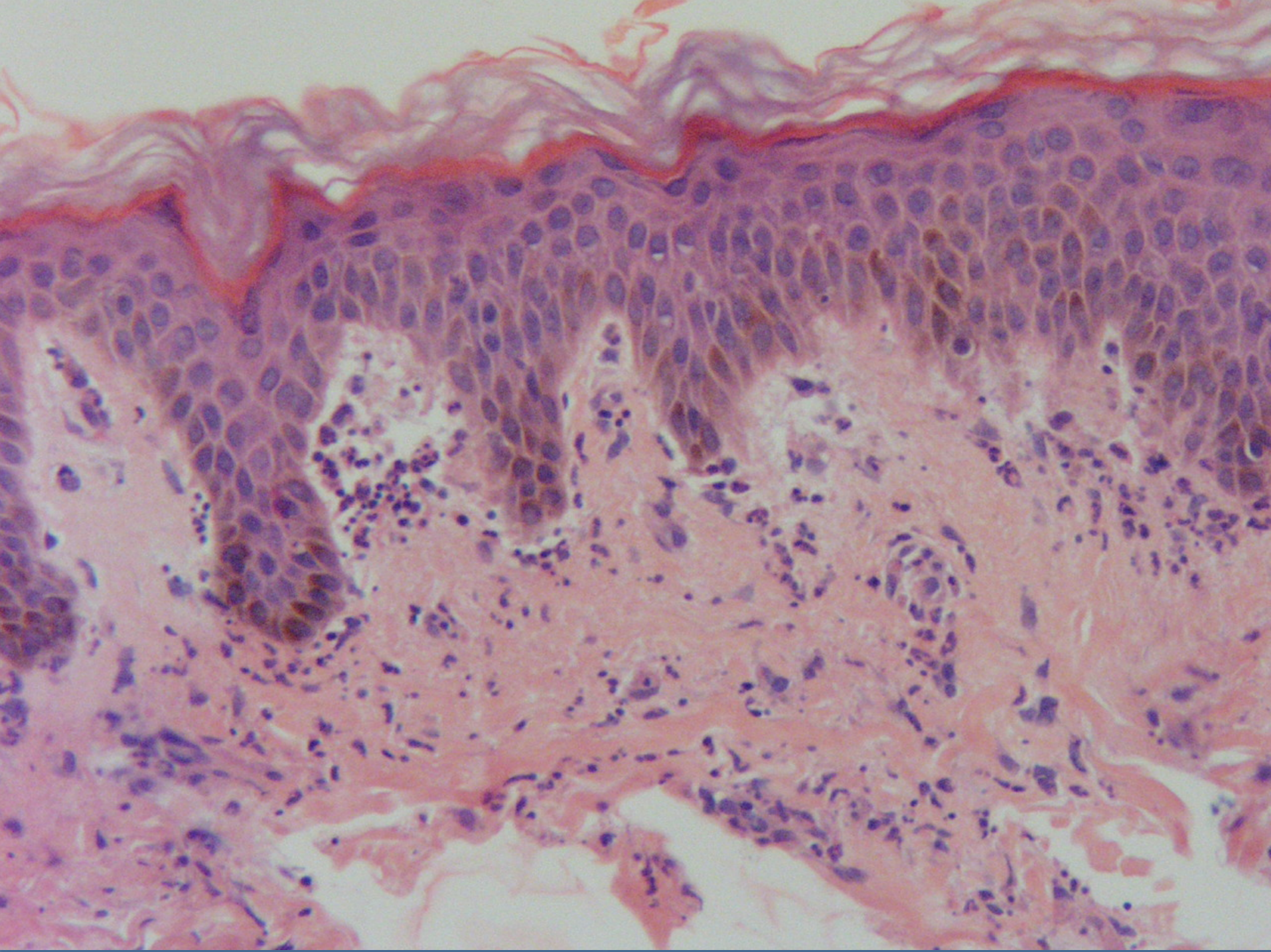
- Mucous membranes, usually oral cavity with erosions
- Flaccid and fragile skin blister filled with clear fluid that arises on normal skin or erythematous base
- Vegetating PV frequently in intertriginous areas and scalp or face
- Nikolsky sign
 - Firm sliding pressure with a finger separates normal-appearing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

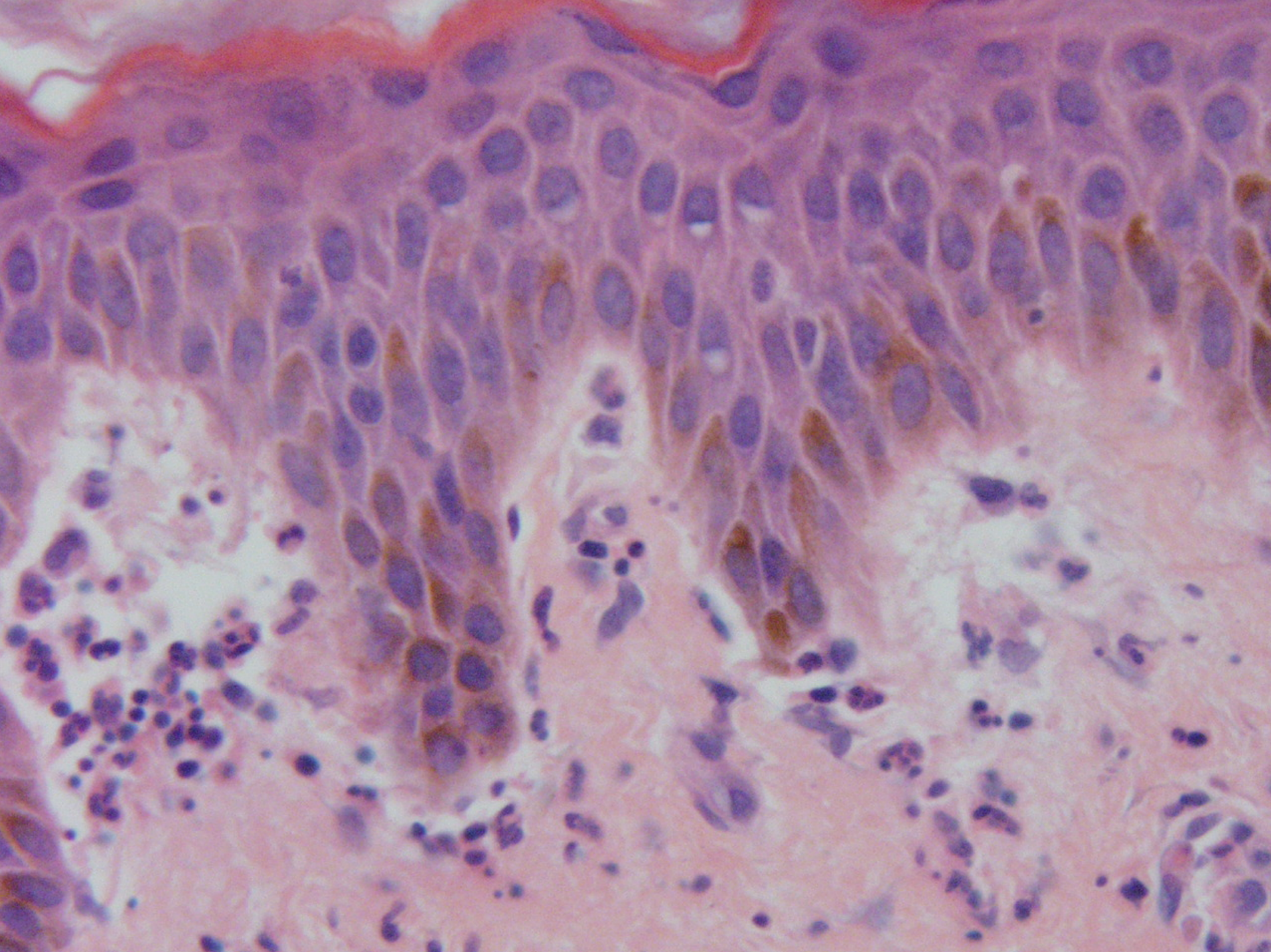
Pemphigus Vulgaris Histopathology



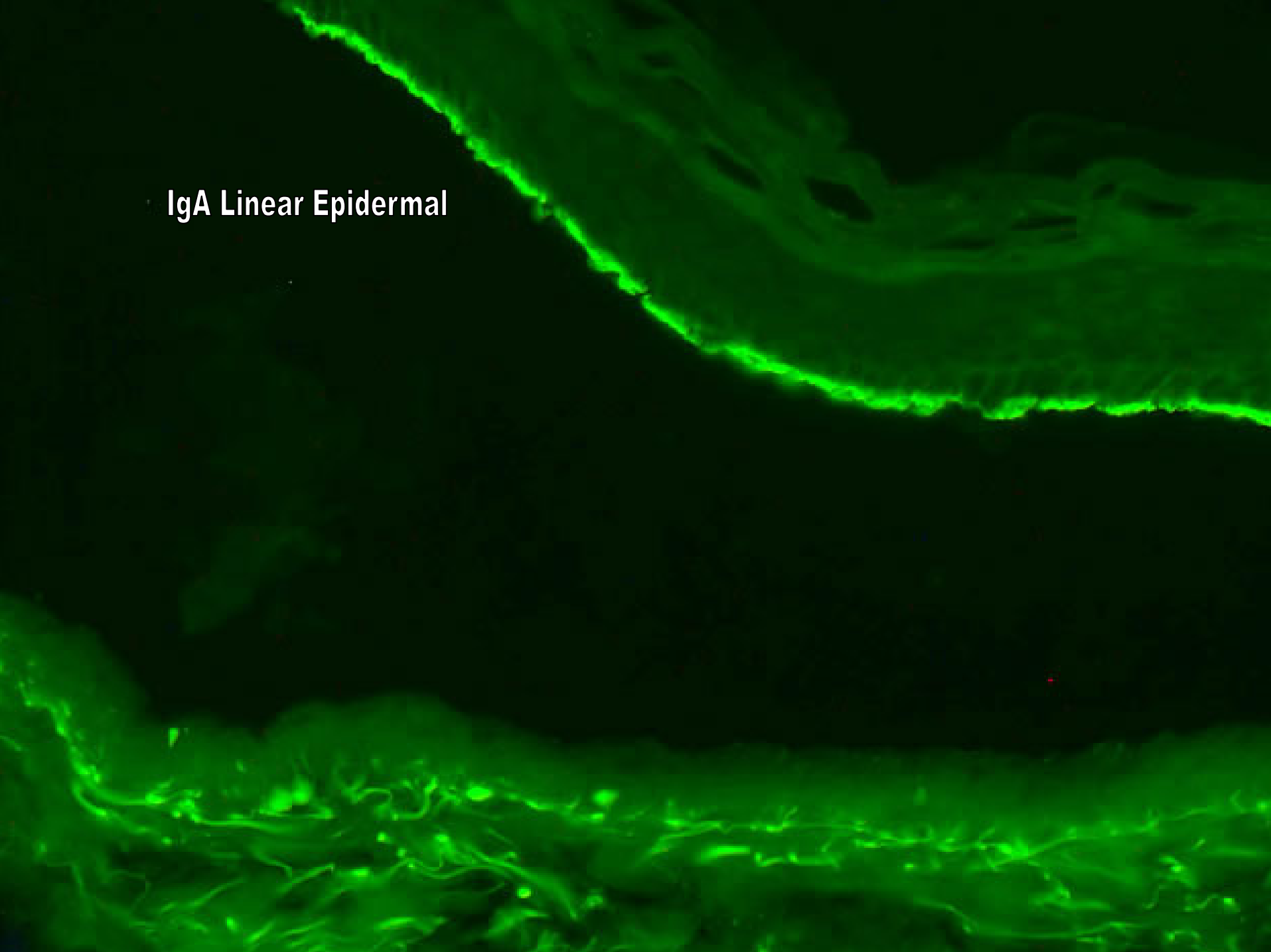
- Intraepidermal blister with suprabasal clefting and acantholysis
- May have preceding eosinophilic spongiosis
- DIF intercellular IgG
 - IgG1 and IgG4 subclasses
 - C3 and IgM less frequent
- IIF circulating IgG autoantibodies that bind to epidermis
 - 80-90% of patients
 - Titer of antibody correlates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

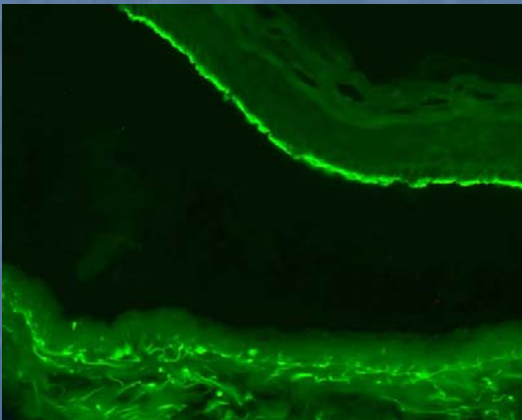
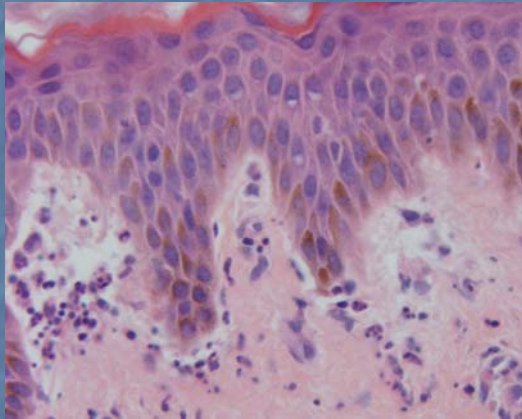
Linear IgA Disease

- 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

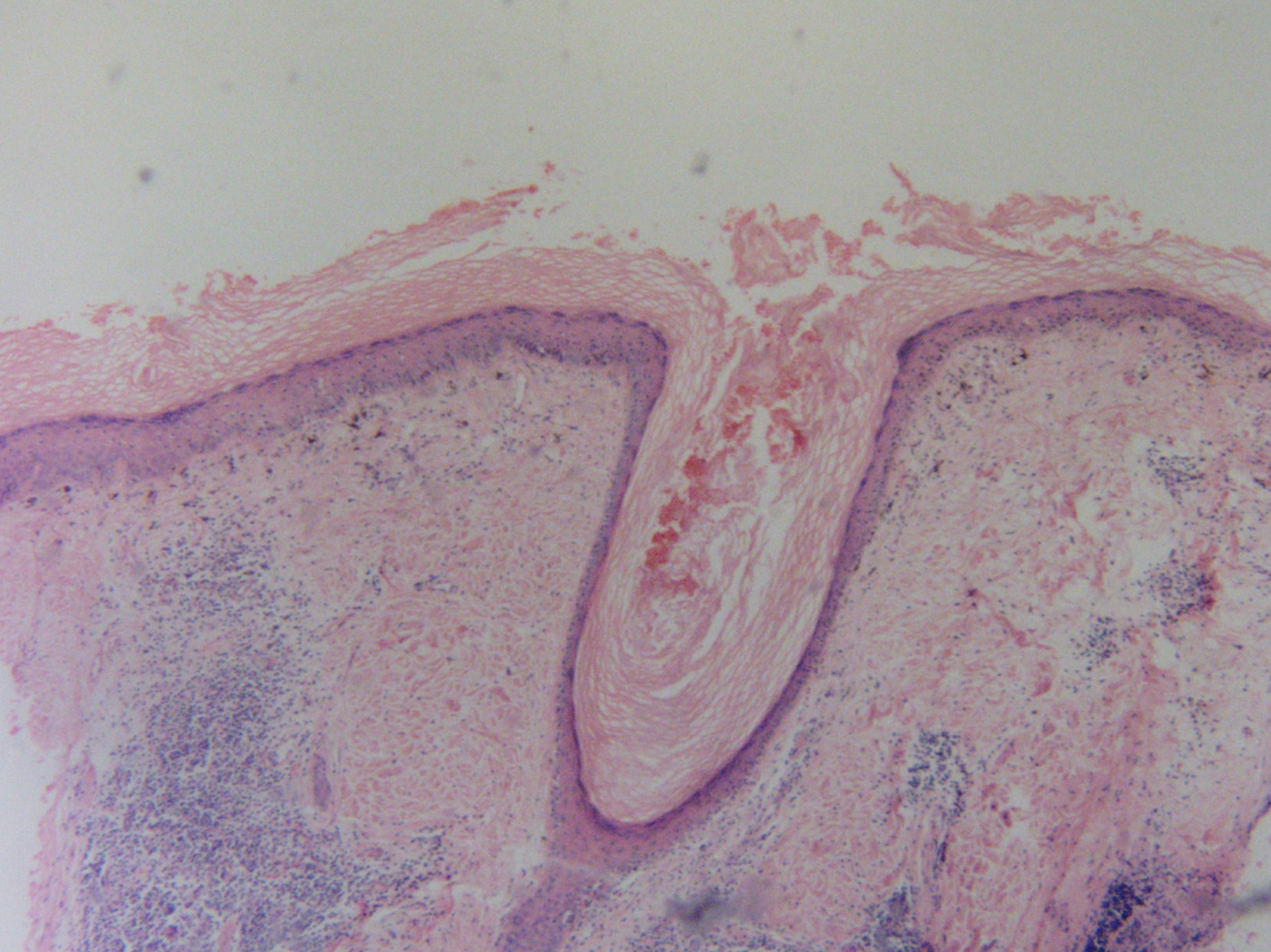
- Drug related
 - Vancomycin
 - Penicillin
 - Lithium
 - Dilantin
 - Diclophenac
- Lesions clear after cessation
- Rechallenge may have more severe changes

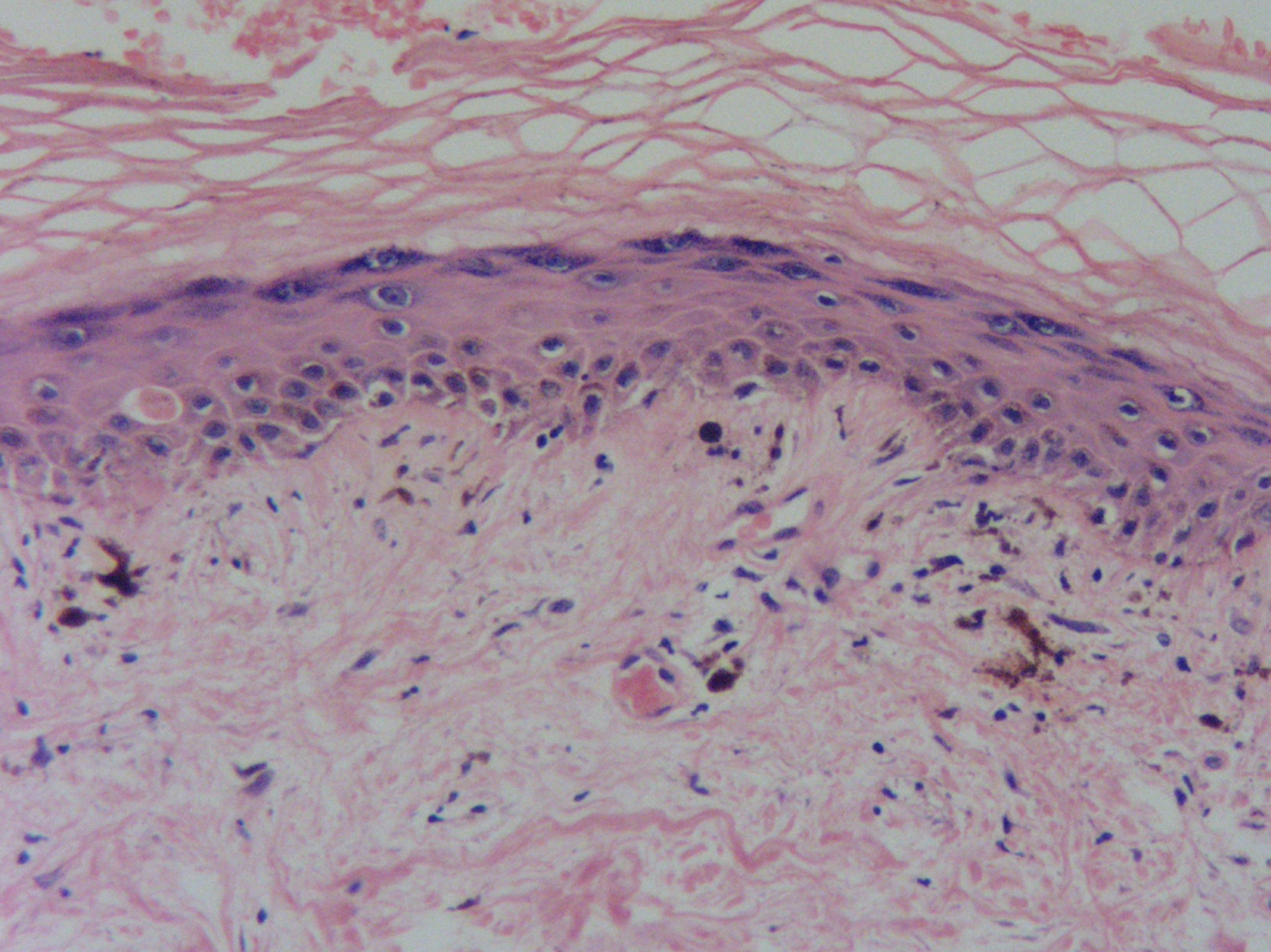
Linear IgA Disease-Histology and IF

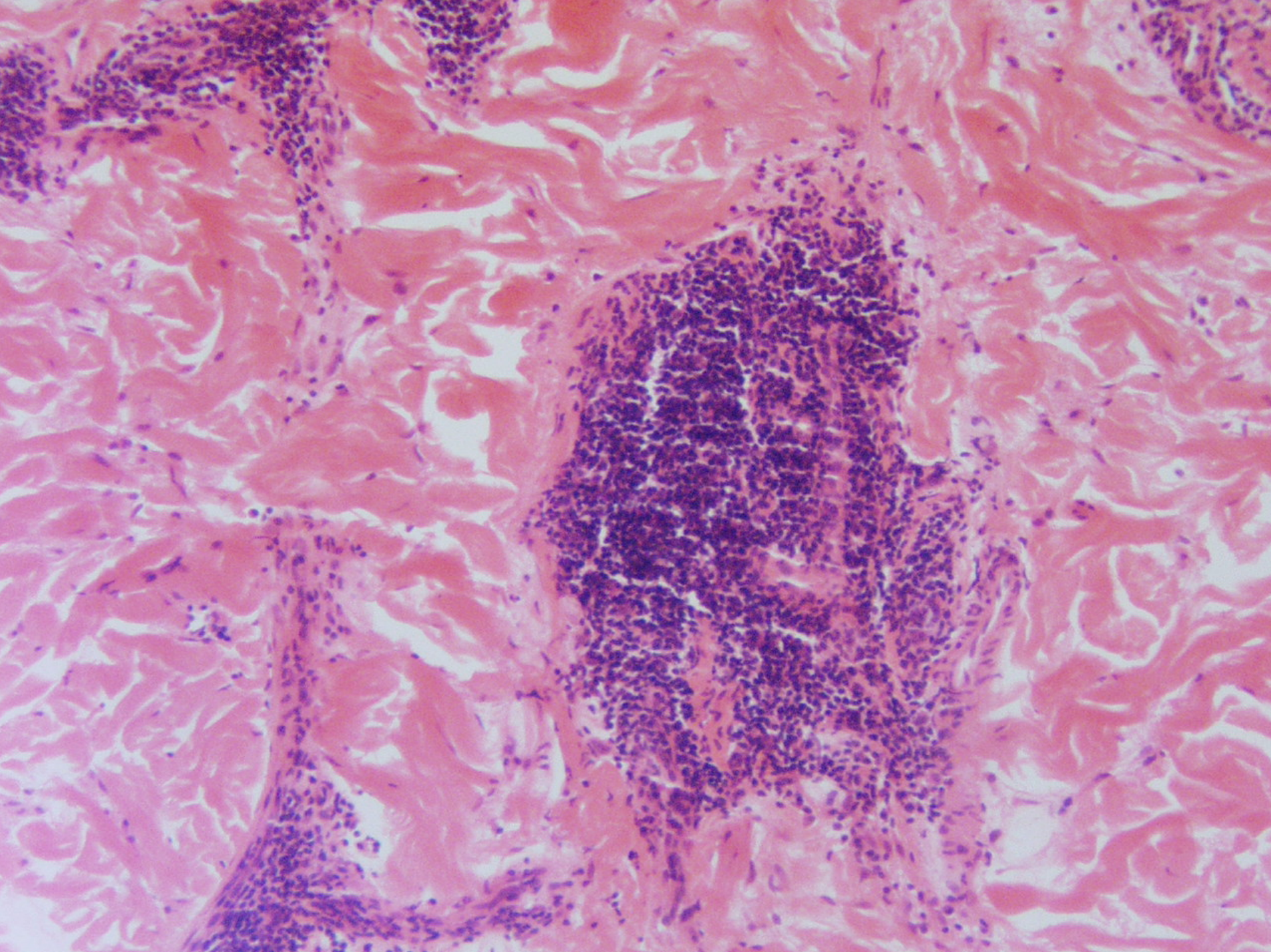


- Neutrophil rich interface dermatitis
- Homogenous sharp linear band for IgA
- Linear granular variant
 - No deposits within the dermal papillae, resembles DH
 - Low level of HLAB8 and gluten sensitivity unlike DH









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

Sensitivity and Specificity

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

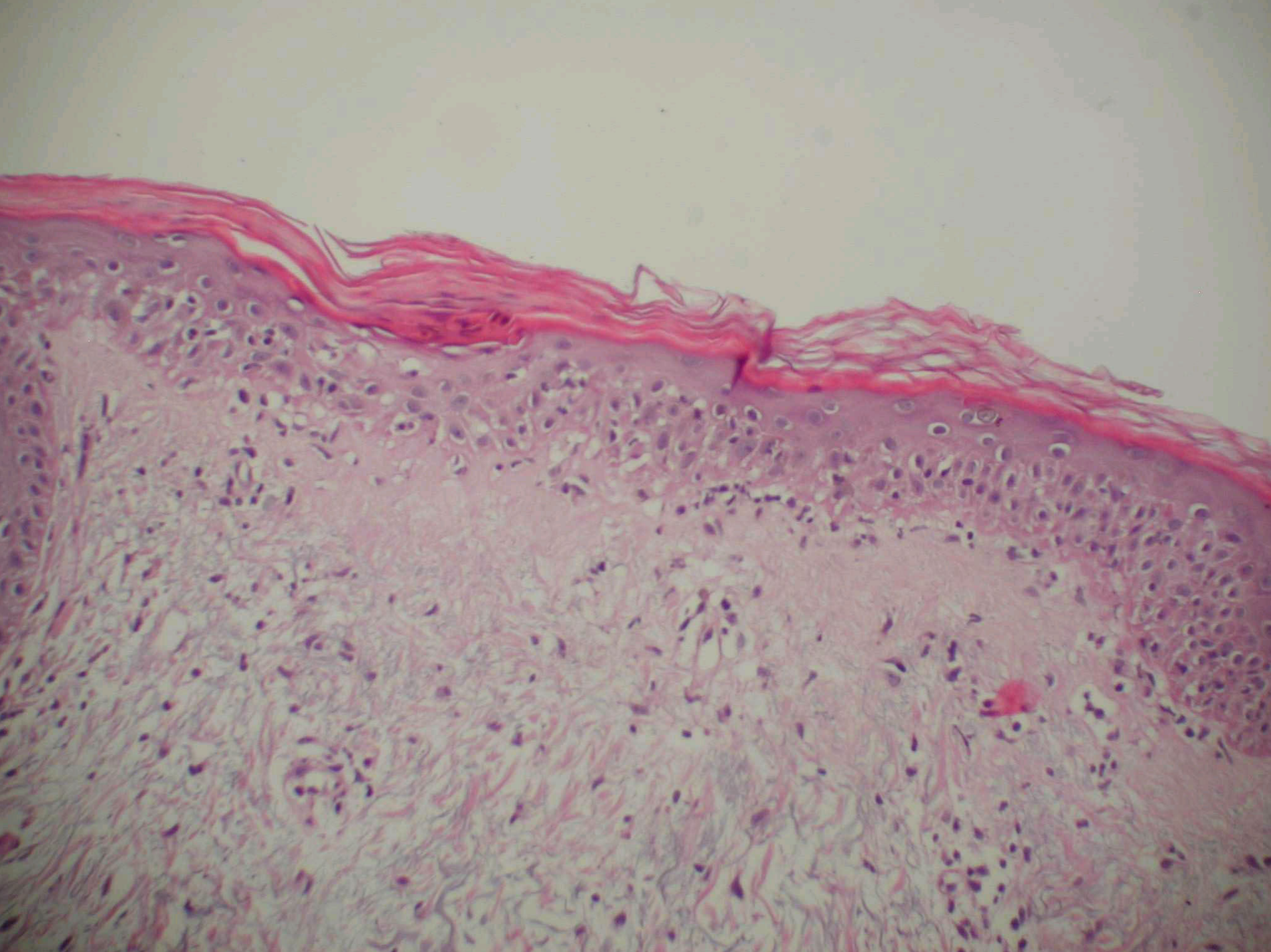
Lupus Band Test and Prognosis

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

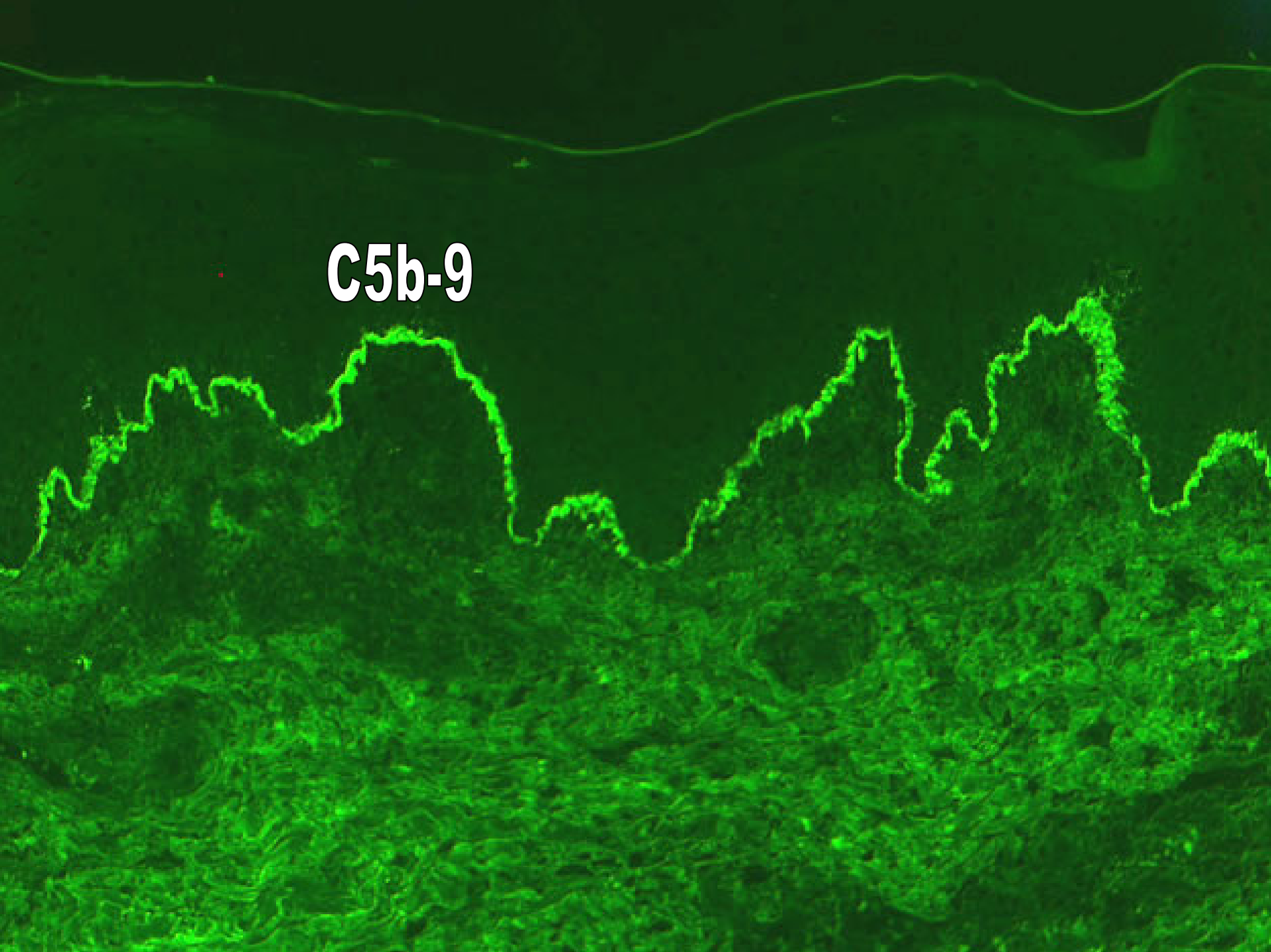




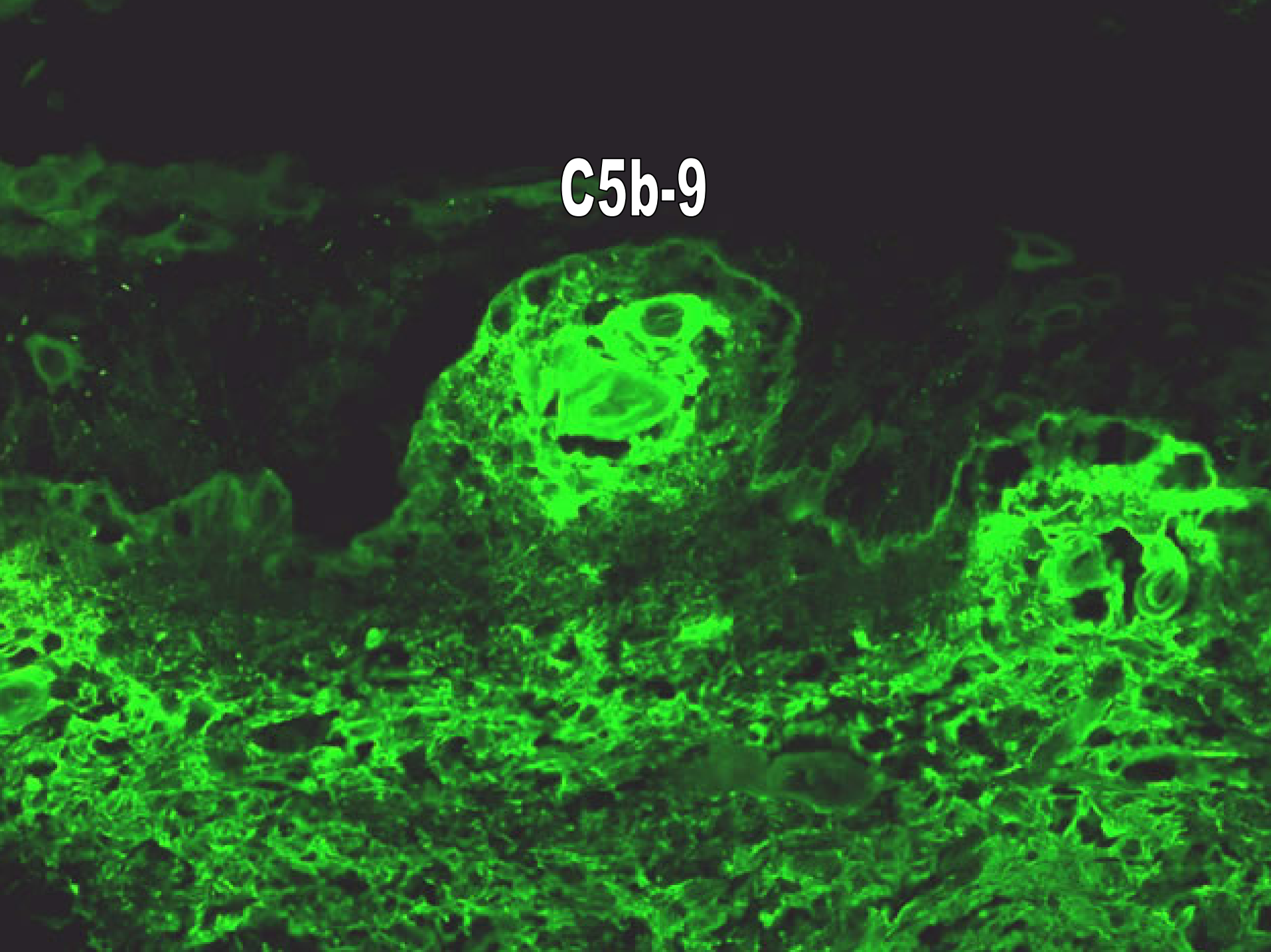
dermatomyositis



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

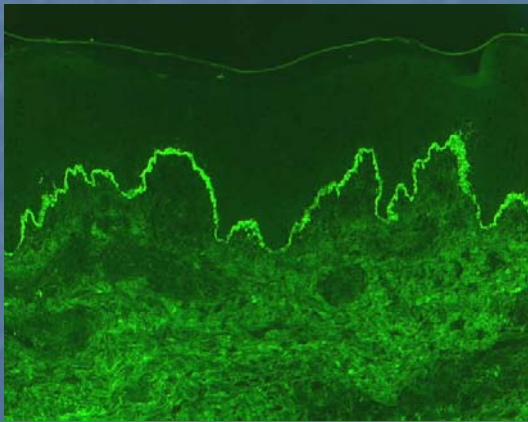
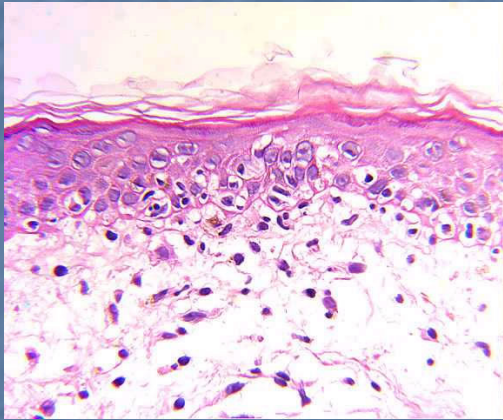
Dermatomyositis

- 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

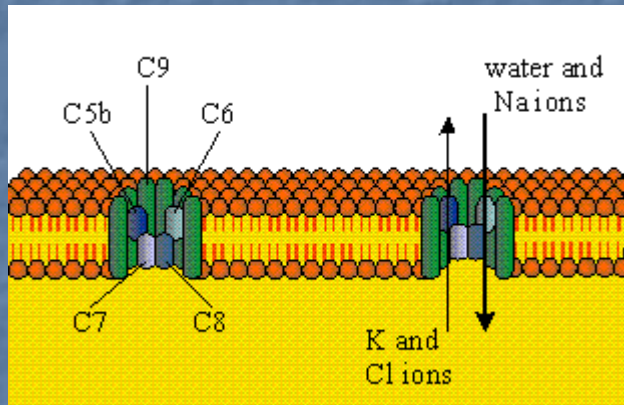
- Muscle enzyme levels abnormal
 - CK, AST, LDH
 - Myositis-specific antibodies (antisignal recognition protein and anti-Ku)
- ANA positive
 - Anti-Mi-1 is highly specific for DM, but it lacks sensitivity because only 25%
 - Anti-Jo-1 is associated with pulmonary involvement, more common in patients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

Dermatomyositis Histopathology

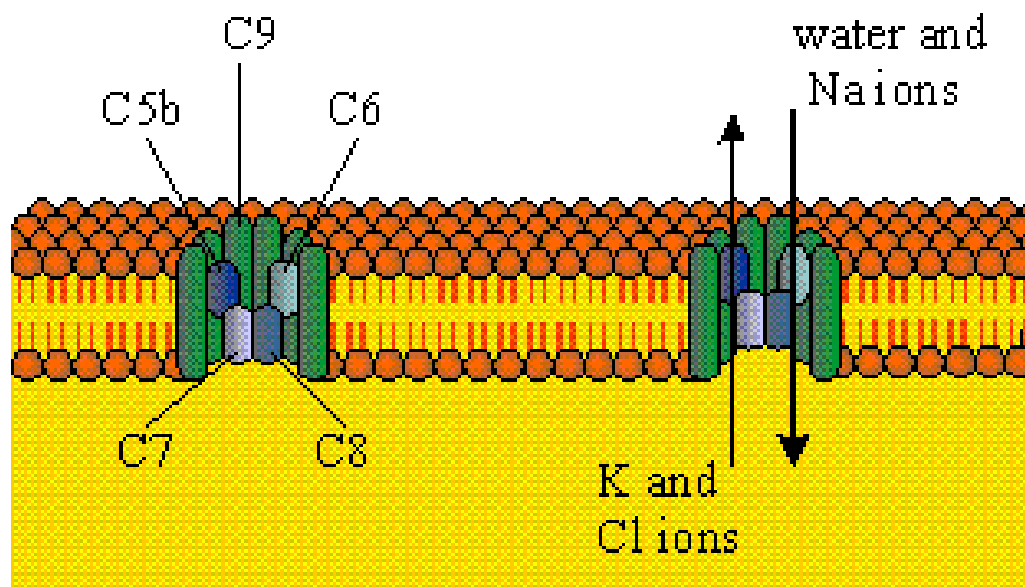
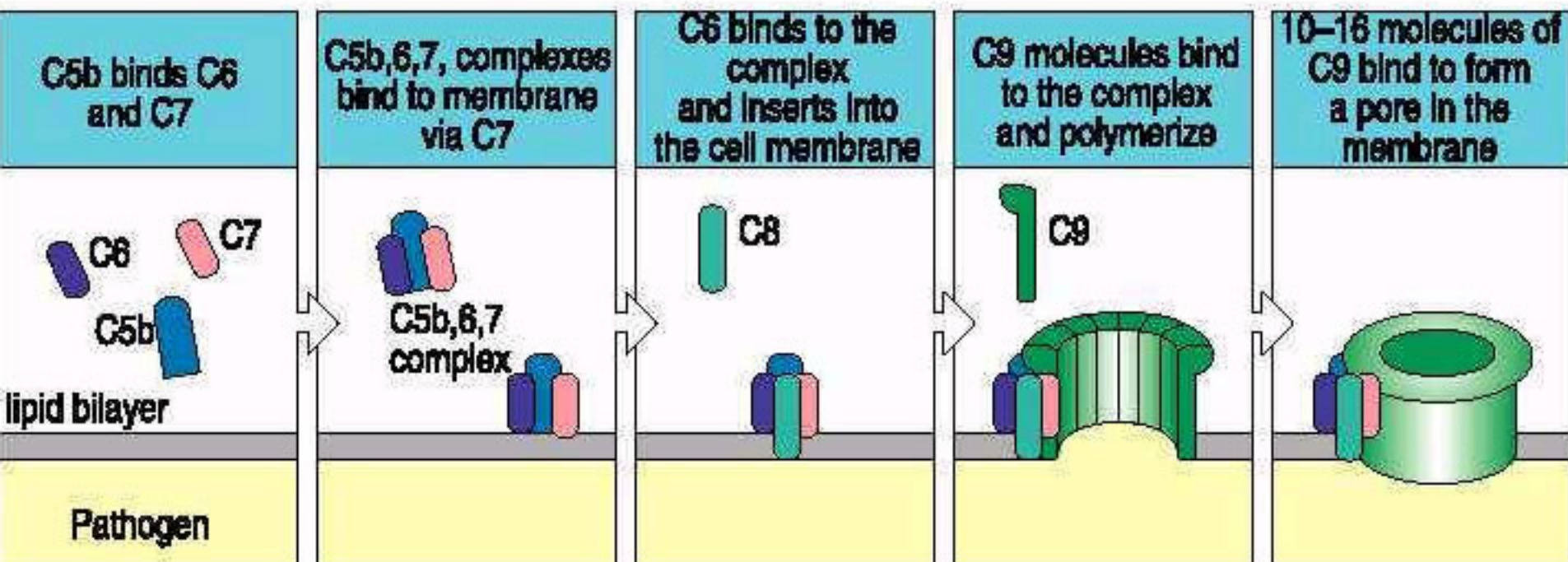


- Cell poor interface dermatitis with dermal mucinosis
- May be identical to DLE, SCLE, SLE
- DIF with Variable Lupus band
- Utilize C5b-9

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



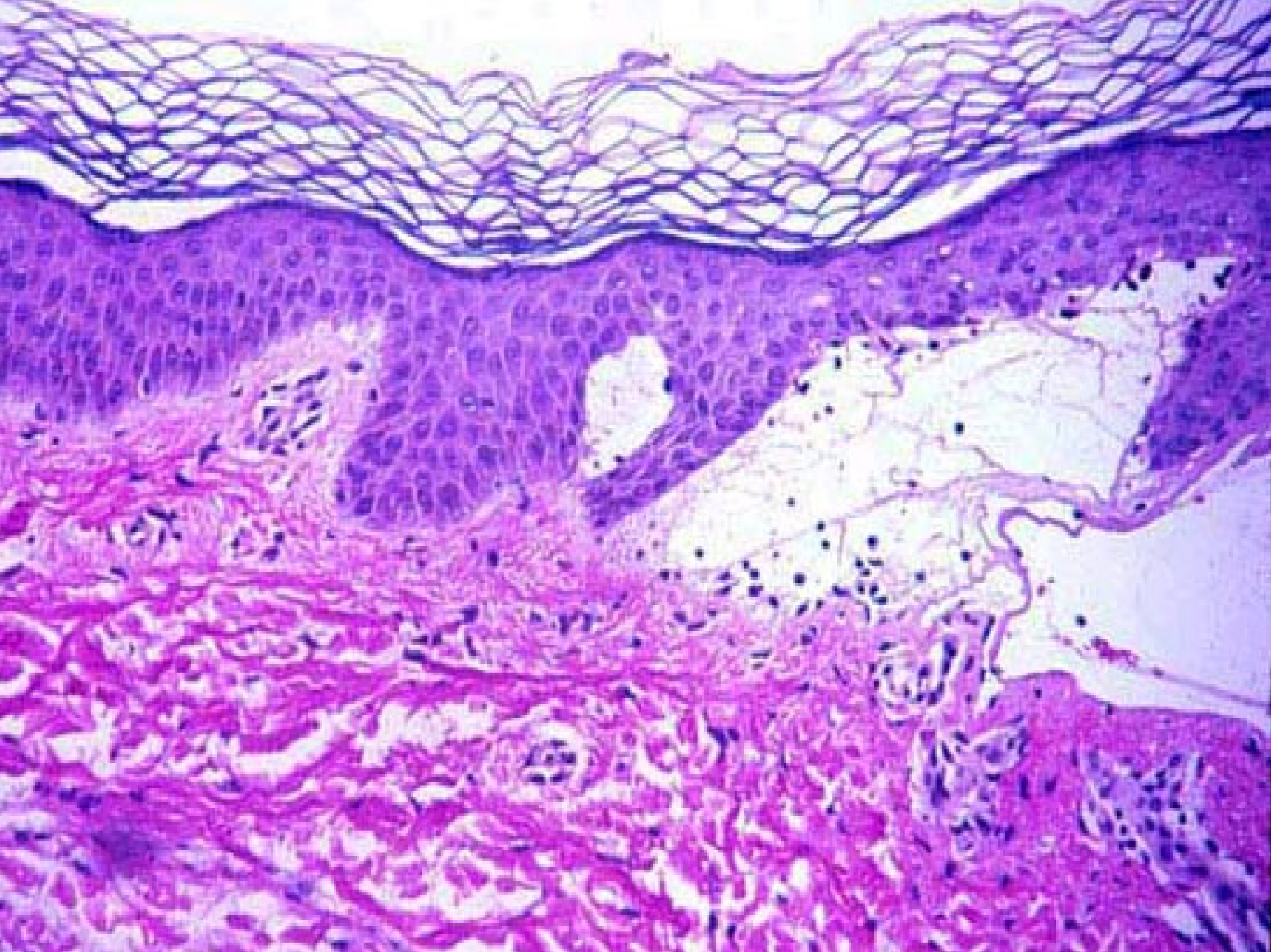
MAC Diseases and Patterns

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

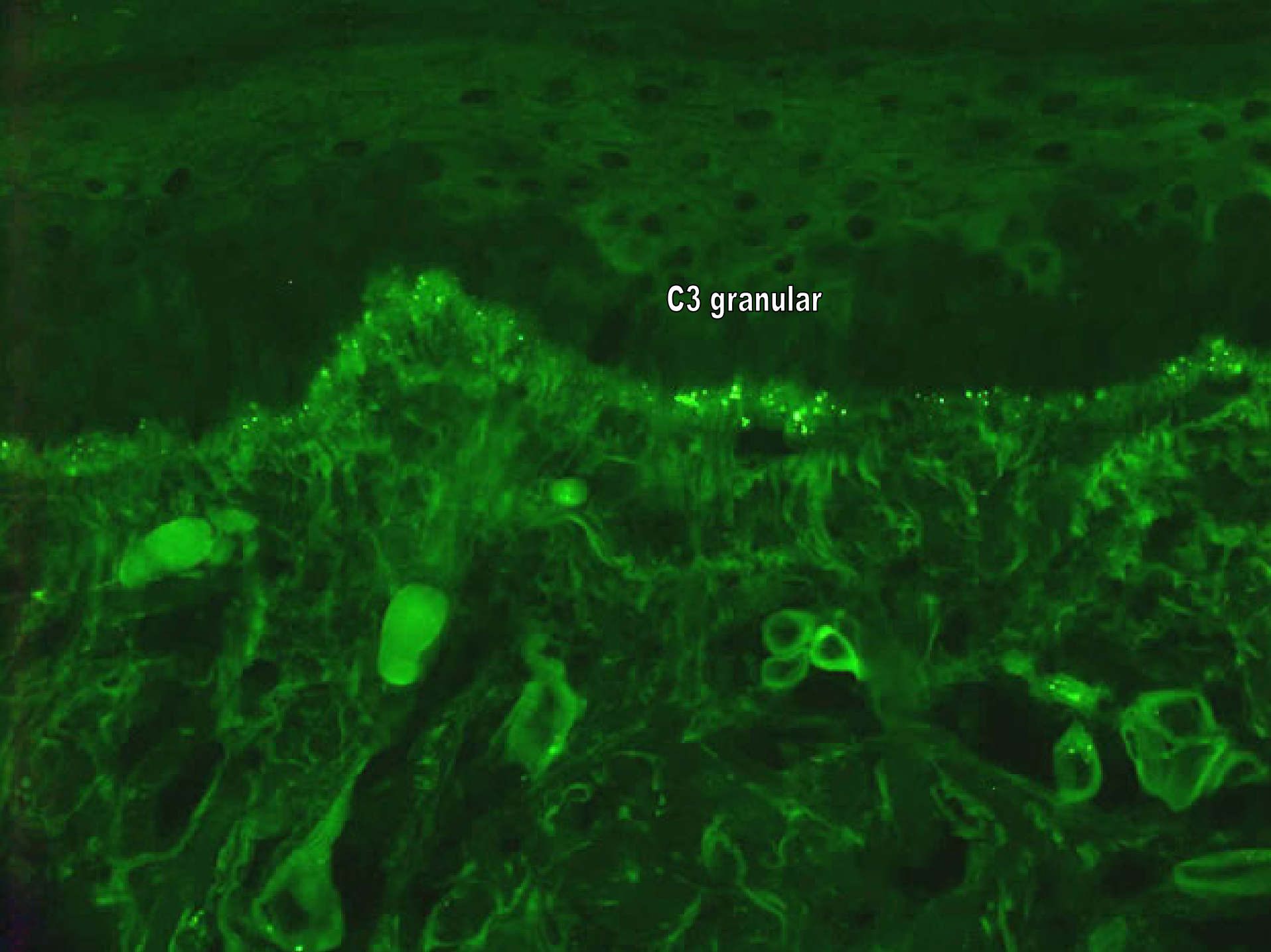
Overlap

- 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

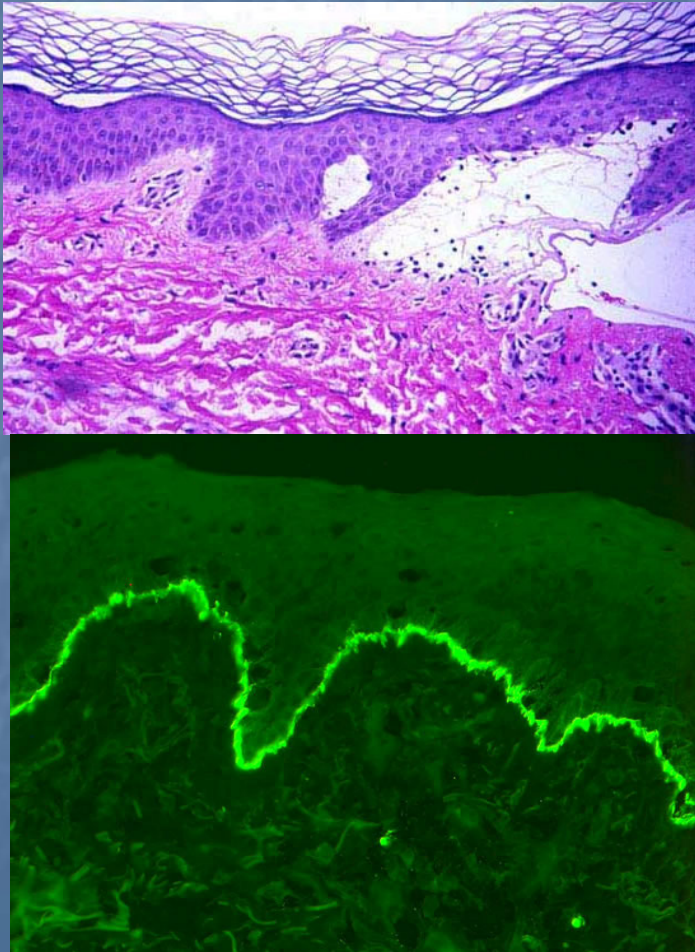
EBA

- Third variant of EBA predominantly involves mucous 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

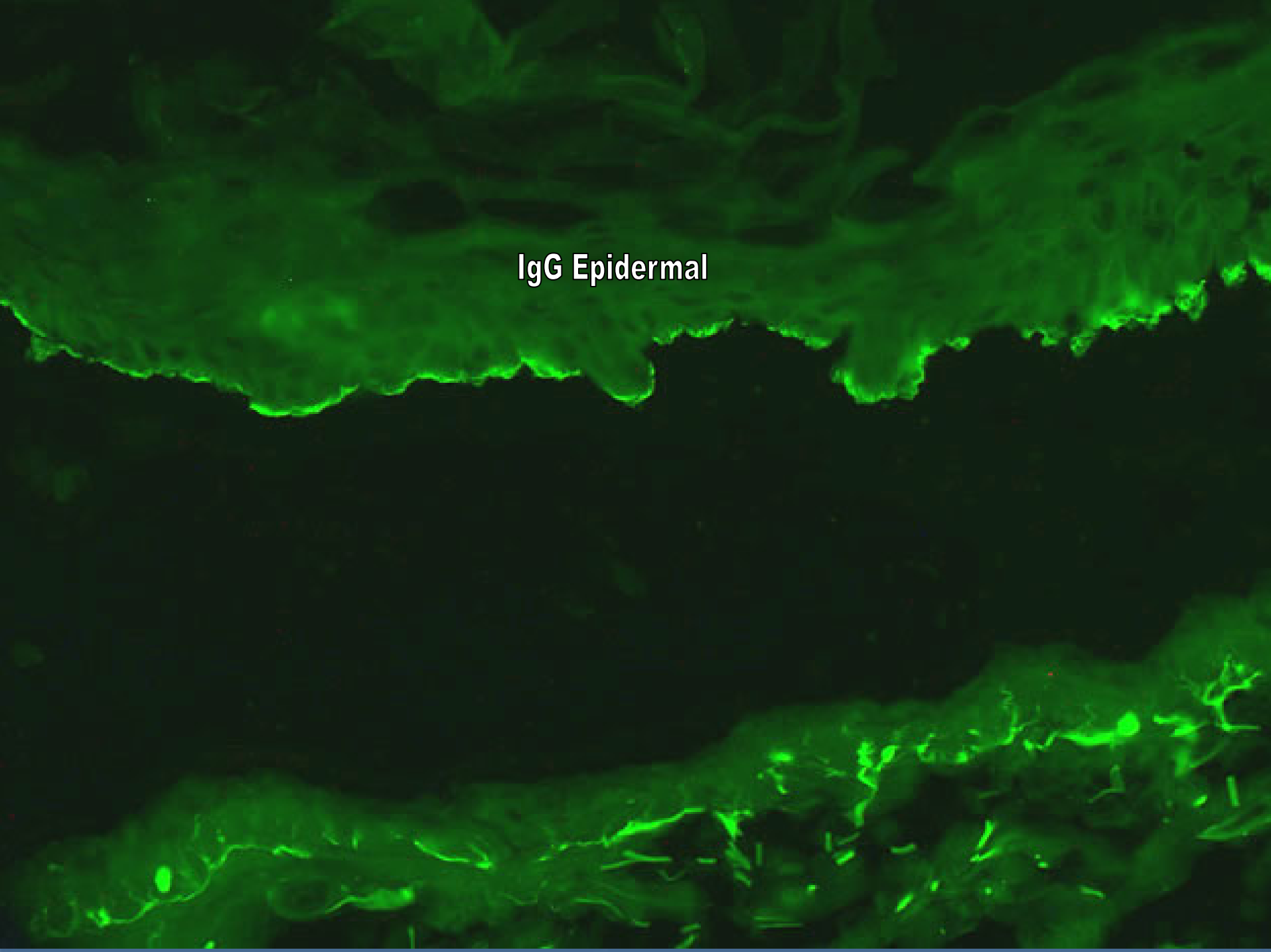
EBA Histopathology



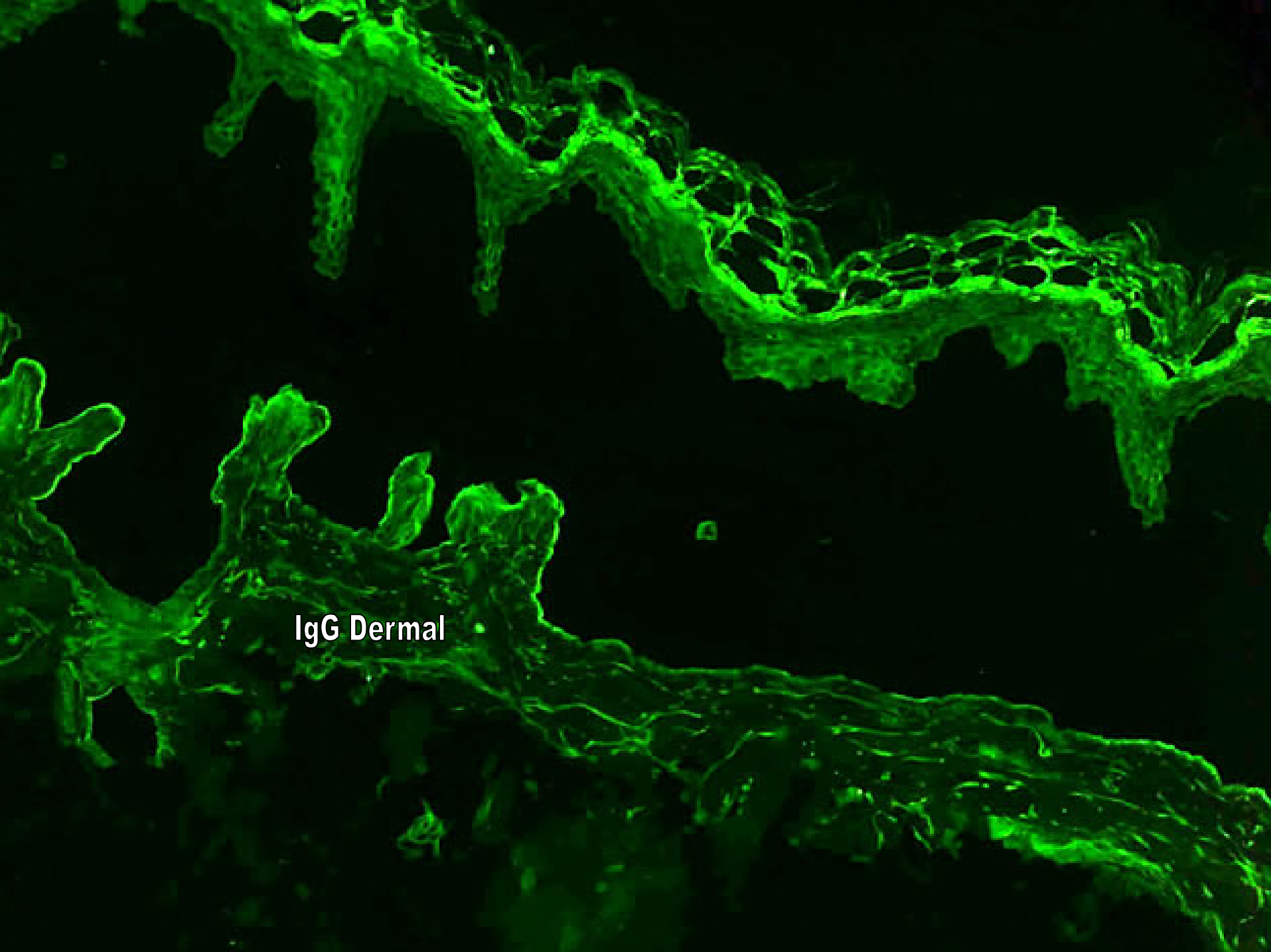
- Subepidermal blister with mixed inflammation
- DIF linear thick band of IgG, and to a lesser extent C3 at basement membrane zone
 - Occasionally IgM or IgA
- IIF IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component, type VII collagen.
 - Bind to the 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

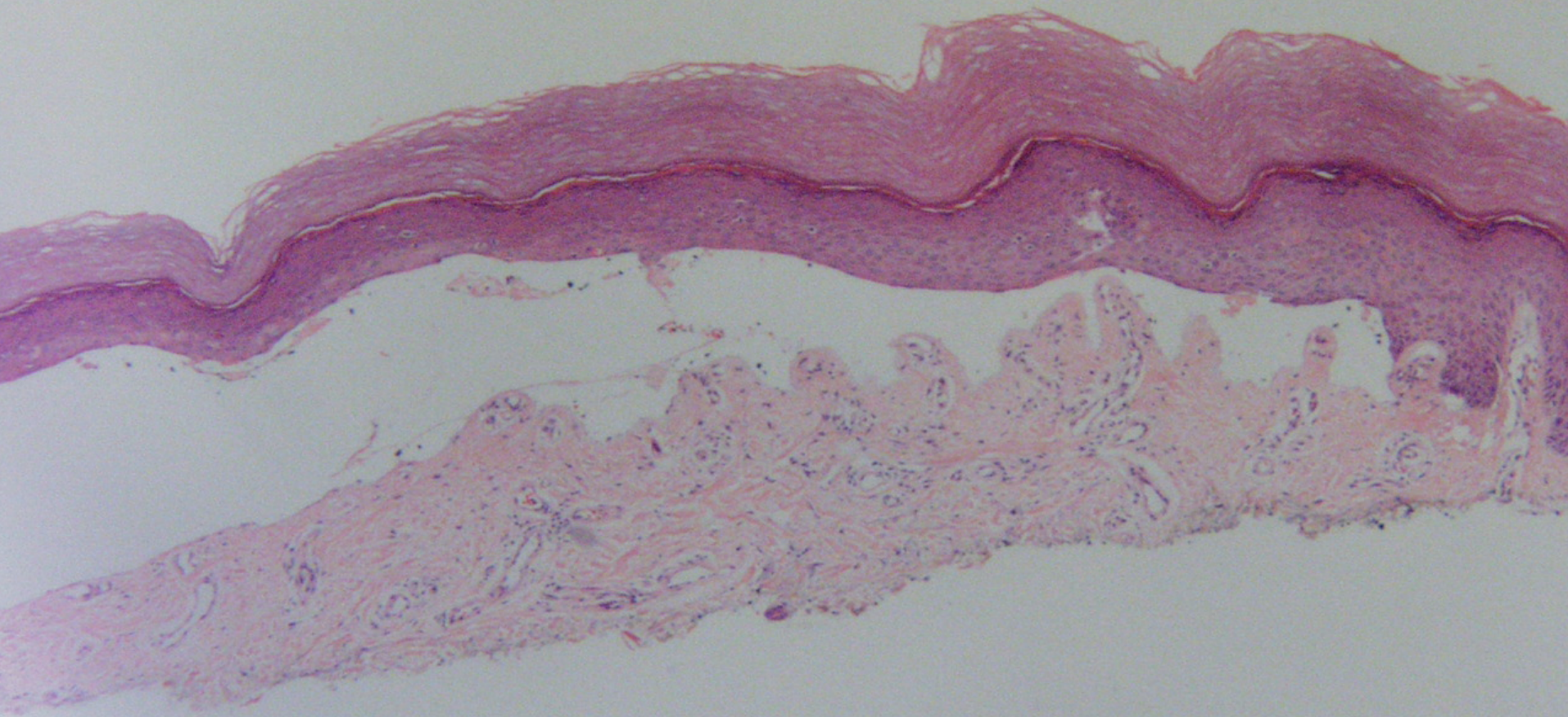


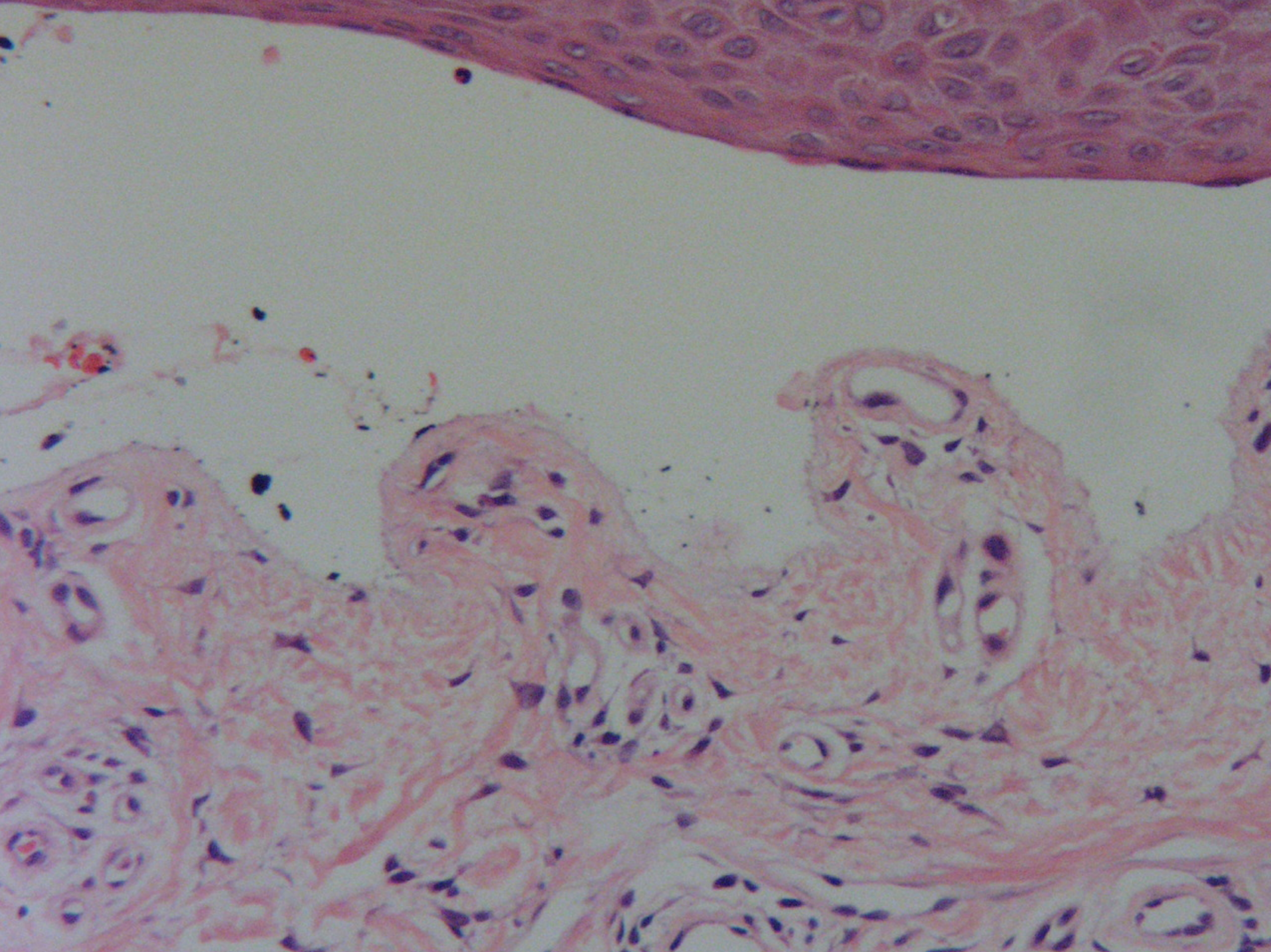
IgG Dermal

SSSS

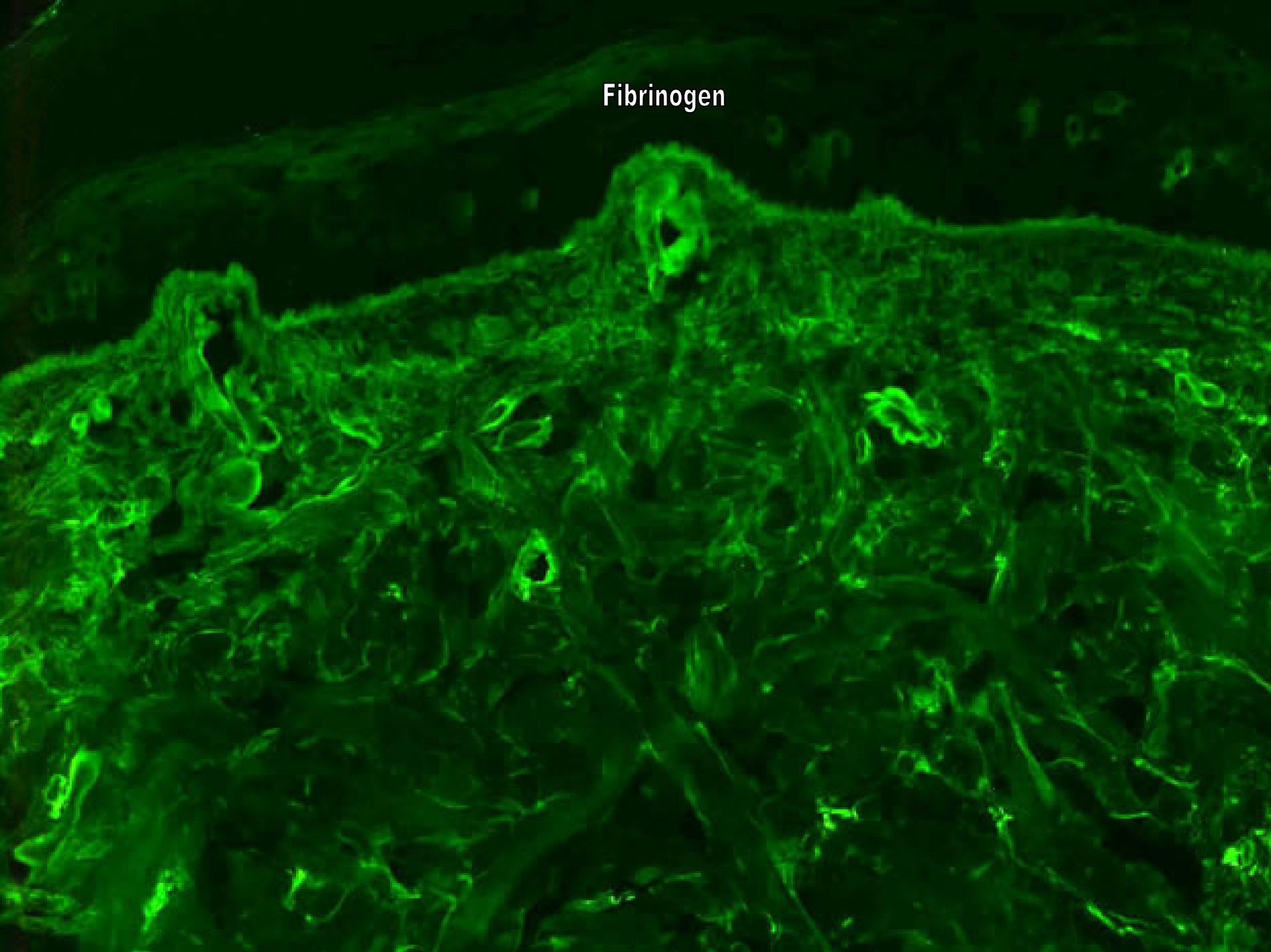
Split	Disease
Epidermal	Bullous pemphigoid
Dermal	EBA Bullous lupus erythematosus Anti-epiligrin cicatricial pemphigoid Anti-p105 bullous pemphigoid







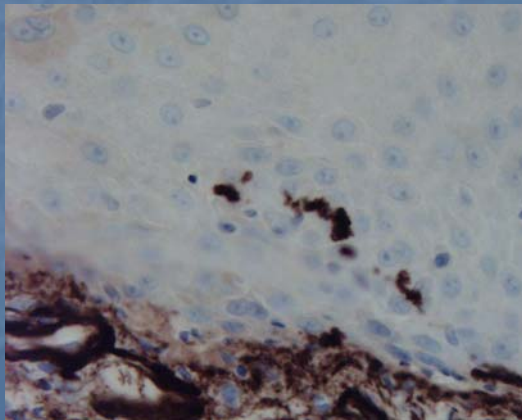
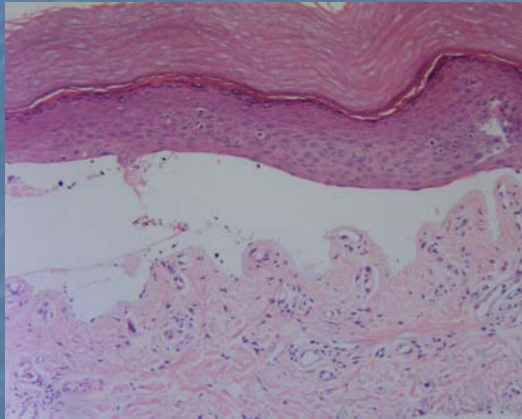
Fibrinogen



Porphyria

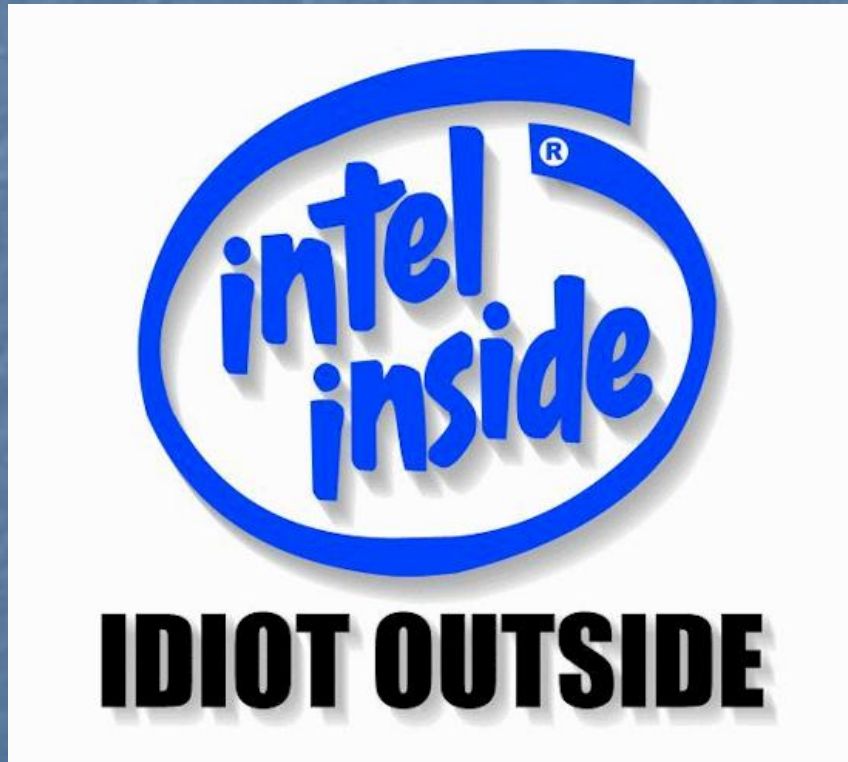
- Fragility of sun-exposed skin after trauma
 - Erosions and bullae on the dorsal aspects of the hands, the forearms, and the face
 - Healing of crusted erosions and blisters leaves scars, milia, and hyperpigmented and hypopigmented atrophic patches.
- Hypertrichosis
 - Temporal and malar facial areas
 - 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 onycholysis 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