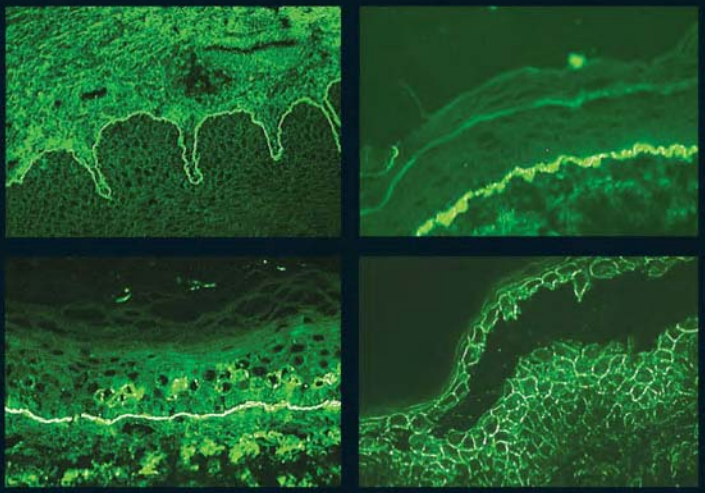
Mayo Clinic Atlas of Immunofluorescence in Dermatology

Patterns and Target Antigens



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Preface

This atlas reviews the different immunofluorescence patterns for various dermatologic conditions through the use of photographs, brief descriptions, tables, and flowcharts. Some important aspects of immunofluorescence are described in the following paragraph.

Immunofluorescence testing is important for diagnosing immunobullous diseases, connective tissue diseases, and vasculitis. Direct immunofluorescence involves the overlay of fluorescein-conjugated antibodies (IgG, IgM, IgA), complement (C3), and fibrinogen onto frozen sections of tissue obtained from patients. Biopsy specimens for direct immunofluorescence in immunobullous disease should be taken from perilesional normal-appearing skin within a few millimeters of the edge of the blister. Obtaining a biopsy specimen from the blister or too close to the blister can result in a false-negative finding. This result is especially possible when dealing with mucosal surfaces because they are already prone to epithelial detachment. However, when a biopsy specimen is needed for diagnosis of connective tissue disease or vasculitis, a lesional biopsy is optimal.

Indirect immunofluorescence studies involve the detection of circulating autoantibodies in the patient's serum which target specific antigens in the patient's skin or mucosa. The technique for indirect immunofluorescence is helpful in immunobullous diseases. It involves incubating the patient's serum, which contains the autoantibodies, with frozen sections of epithelial substrate. The substrate is usually monkey esophagus, but pig esophagus also has been used. Rat bladder is used to rule out paraneoplastic pemphigus. After washing, fluoroscein-labeled animal anti-IgG conjugate against human immunoglobulin, such as IgG, is added. This fluoroscein-labeled animal conjugate binds to the patient's circulating IgG, which is already bound to the target antigen on the epithelial surface. Indirect immunofluorescence allows titration of the patient's serum to determine the highest titration yielding visible fluorescence. In cases of pemphigus, the titer of these autoantibodies correlates with disease activity.

This atlas systematically reviews the different immunofluorescence patterns found in immunodermatology for various immunobullous diseases, connective tissue diseases, vasculitis, and some miscellaneous conditions such as porphyria and lichenoid reactions. In addition, the direct and indirect immunofluorescence findings and the target antigens the autoantibodies bind to in various diseases are summarized in an easy-to-follow table.

I hope that this atlas will aid in understanding the different immunofluorescence patterns in many dermatology conditions. This atlas should be used by dermatologists, pathologists, residents, fellows, and medical students who obtain immunofluorescence results from patients. This atlas also will be a valuable resource for dermatology and pathology residents preparing for board examinations and is dedicated to all persons who have an interest in immunodermatology.

Immunodermatology has a long and rich tradition at Mayo Clinic, and I thank all my mentors in immunodermatology. You have inspired and taught, and I hope this atlas will help inspire the next generation of immunodermatologists. It has been a pleasure and a privilege to work with all my distinguished colleagues in dermatology at Mayo Clinic. Thank you for your teaching, mentoring, and friendship. I am grateful to my co-author and friend, Marie Nicolas, for her significant contributions to this atlas.

I especially thank my family for their love and support, which I cherish above all else. To my late father, I miss you and I thank you for your wisdom and continued inspiration.

Amer N. Kalaaji, MD

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Abbreviations

The following abbreviations are used throughout the book:

ANA	antinuclear antibodies
BMZ	basement membrane zone
BP	bullous pemphigoid
ICS	intercellular space
SSS	salt-split skin

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Linear Basement Membrane Zone Staining Pattern

A. Bullous Pemphigoid

B. Pemphigoid Gestationis (Herpes Gestationis)

C. Lichen Planus Pemphigoides

D. Mucous Membrane Pemphigoid

E. Bullous Lupus Erythematosus

F. Epidermolysis Bullosa Acquisita

G. Linear IgA Bullous Dermatosis

Bullous Pemphigoid (BP)

Clinical

- Tense bullae on erythematous, urticarial, or normal skin
- Flexural predominance
- Elderly patients (typically older than 60 years)
- Generalized pruritus commonly associated
- Mucous membrane involvement (10%-40%)
- Absence of scarring (differs from cicatricial pemphigoid and epidermolysis bullosa acquisita)
- Variants
  - Localized BP to lower extremities (elderly)
  - Pemphigoid nodularis (prurigo nodularis with or without bullae)
  - Generalized pruritus and dermatitis
  - Urticarial pemphigoid
  - Tense acral bullae in infants and vulvar involvement in pre-pubertal girls

Direct Immunofluorescence

- Linear basement membrane zone (BMZ): IgG (90%)
- Linear BMZ: C3 (>90%, nearly all) (Fig. 1.1)

Indirect Immunofluorescence

- Linear BMZ: IgG on monkey esophagus substrate (circulating IgG antibody in 75% of cases; Fig. 1.2)
- Salt-split skin (SSS): epidermal pattern (Fig. 1.3)
- Occasionally combined epidermal-dermal pattern

Target Antigens

- BP230 (BPAG1)
- BP180 (BPAG2)
  - NC16A (immunodominant region of BP180)

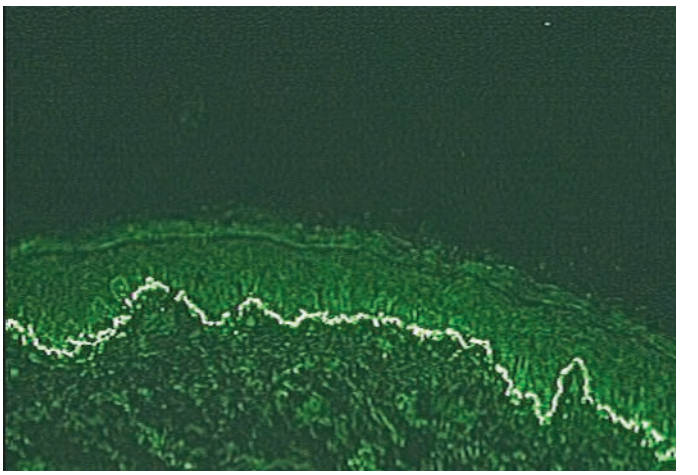

Fig. 1.1 Linear BMZ: C3

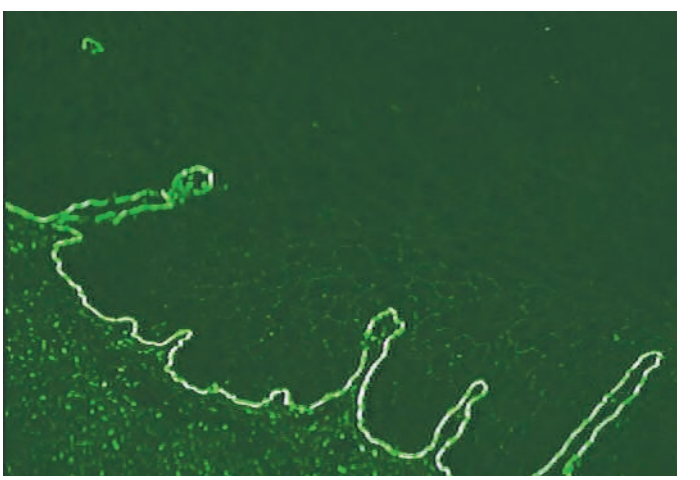

Fig. 1.2 Linear BMZ: IgG

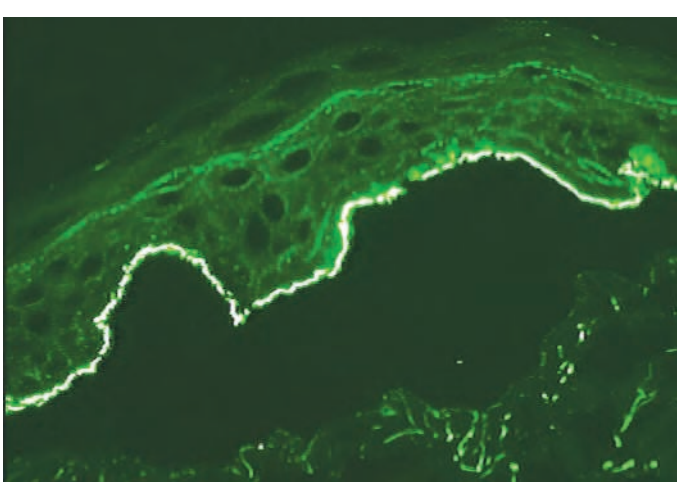

Fig. 1.3 SSS: epidermal pattern

Pemphigoid Gestationis (Herpes Gestationis)

Clinical

- Onset is usually during the second and third trimesters of pregnancy
- Can occur post partum (typically first 2-3 days post partum)
- Polymorphous skin eruption
  - Skin lesions range from urticarial papules and plaques to vesicles and bullae
- Typically spares mucous membranes
- Recurrences can develop with use of oral contraceptives
- Neonatal pemphigoid gestationis can occur from passive transfer of maternal IgG across the placenta

Direct Immunofluorescence

- Linear BMZ: IgG (approximately 25% of cases)
- Linear BMZ: C3 (100% of cases, diagnostic) (Fig. 1.4)

Indirect Immunofluorescence

- Linear BMZ: IgG (<25% of cases, does not correlate with disease activity)
- HG factor: 50% of cases
- SSS: epidermal pattern

Target Antigens

- BP230 (BPAG1)
- BP180 (BPAG2) (most important)
  - NC16A (immunodominant region of BP180)

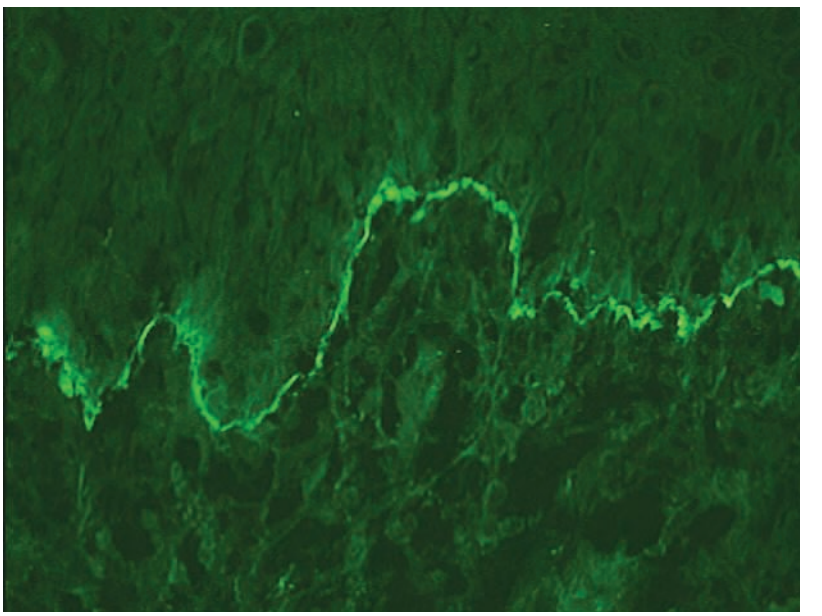

Fig. 1.4 Linear BMZ: C3

Lichen Planus Pemphigoides

Clinical

- Coexistence of lichen planus and bullous pemphigoid in the same patient
- Bullae develop on normal-appearing skin away from lichen planus lesions and are due to circulating autoantibodies
- In contrast, bullous lichen planus generally refers to bullae developing in lichen planus lesions as a result of the inflammatory infiltrate, epitope spreading, and no circulating antibodies

Direct Immunofluorescence

- Linear BMZ: IgG and C3 with changes of lichen planus (i.e., cytoid bodies with IgM, IgA, C3, and shaggy BMZ with fibrinogen) (Fig. 1.5)

Indirect Immunofluorescence

- Linear BMZ: IgG antibodies in 50% of patients
- SSS: epidermal pattern

Target Antigens

- BP230 (BPAG1)
- BP180 (BPAG2) (most important)
  - NC16A (immunodominant region of BP180)

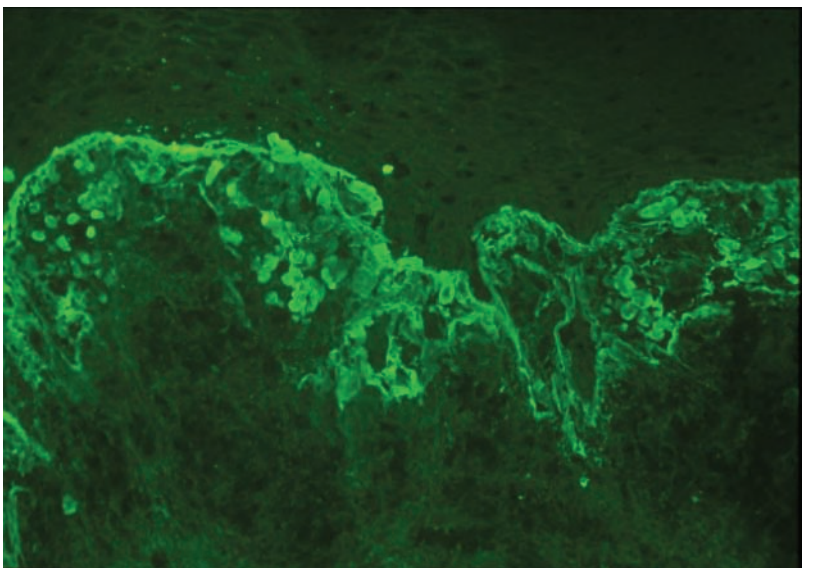

Fig. 1.5 Shaggy BMZ: fibrinogen

Mucous Membrane Pemphigoid

Clinical

- Autoimmune subepithelial blistering disorder
- Predominantly involves mucosal surfaces with less skin involvement
- Chronic and recurring course
- Scarring tends to occur
- A "disease phenotype" shared by a heterogeneous group of diseases
- Severe mucosal involvement can result in blindness and laryngeal and esophageal stenosis

Direct Immunofluorescence

- Linear BMZ: IgG, C3, IgA

Indirect Immunofluorescence

- Linear BMZ: IgG in 15% to 20% of cases
- SSS: epidermal, dermal, or combined (Fig. 1.6)

Target Antigens

- BP230 (BPAG1)
- BP180 (BPAG2) (C-terminus and some NC16A)
- β_4 integrin subunit
- Laminin-5 (also called epiligrin, nicein, kalinin, BM600)
- Laminin-6
- Type VII collagen (290 kd)

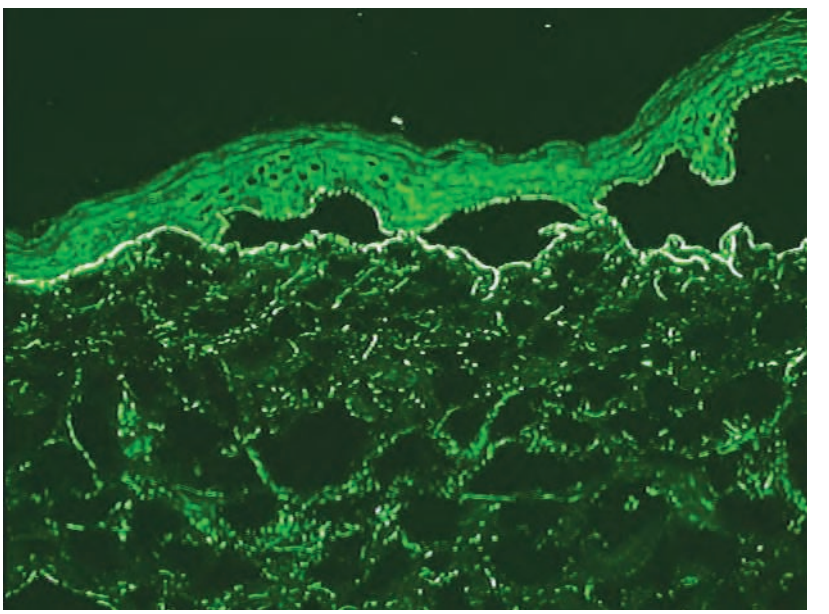

Fig. 1.6 SSS: combined epidermal-dermal pattern

Bullous Lupus Erythematosus

Clinical

- Occurs typically in patients with systemic lupus erythematosus
- Photosensitivity is common
- Skin findings can include tense bullae, vesicles, urticarial vasculitis-like lesions, and cutaneous manifestations of systemic lupus erythematosus
- Skin findings typically have a photodistribution
- Scarring can occur
- Mucous membrane involvement (especially oral) can occur

Direct Immunofluorescence

- Linear BMZ: IgG and C3; IgM and IgA also (if perilesional biopsy of bullae) (Fig. 1.7)
- Granular BMZ: IgG, IgM, C3 (if lesional biopsy of malar rash or other cutaneous involvement of lupus) (Fig. 1.8)

Indirect Immunofluorescence

- Antinuclear antibodies (ANA)
- BMZ antibodies not detected on monkey esophagus but may be detected on SSS
- SSS: dermal pattern (IgG)

Target Antigens

- Type VII collagen (290 kd)
  - NC1 domain

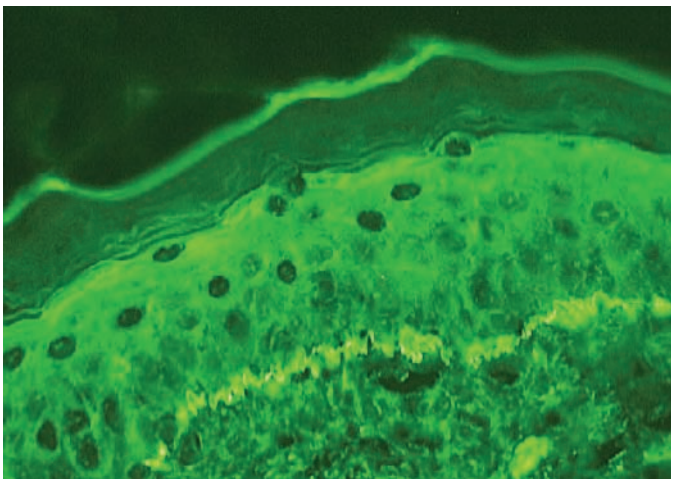

Fig. 1.7 Linear BMZ: IgG

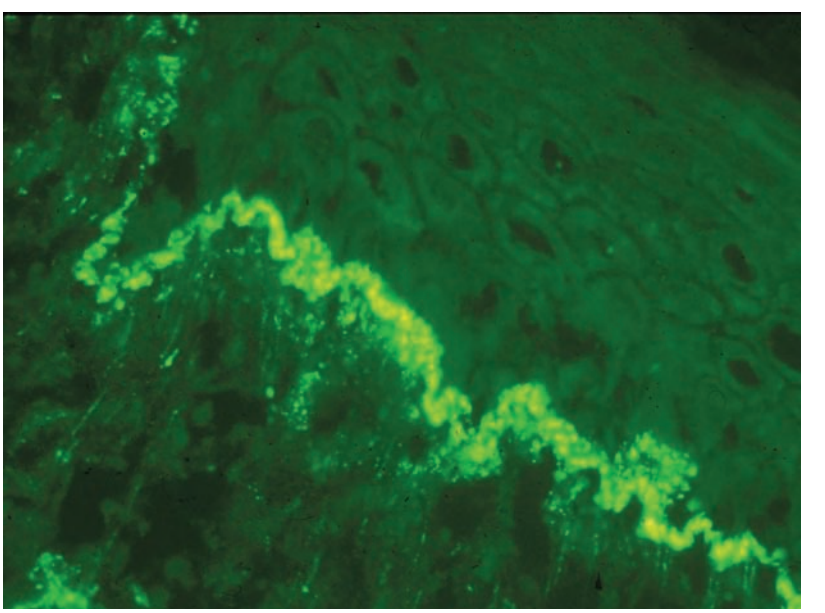

Fig. 1.8 Granular BMZ: IgG

Epidermolysis Bullosa Acquisita

Clinical

- Erosions and blisters on trauma-prone areas such as elbows, knees, acral surfaces
- Scarring and milia, postinflammatory changes
- Nail dystrophy and scarring alopecia can occur
- Other variants: BP-like presentation, cicatricial pemphigoid-like presentation with mucous membrane involvement, Brunsting-Perry cicatricial pemphigoid-like presentation

Direct Immunofluorescence

- Linear BMZ: IgG (100%) and C3; occasionally IgA (66%) or IgM (50%)

Indirect Immunofluorescence

- Linear BMZ: IgG in 50% of patients
- SSS: dermal pattern (Fig. 1.9)

Target Antigens

- Type VII collagen (290 kd)
  - NC1 domain

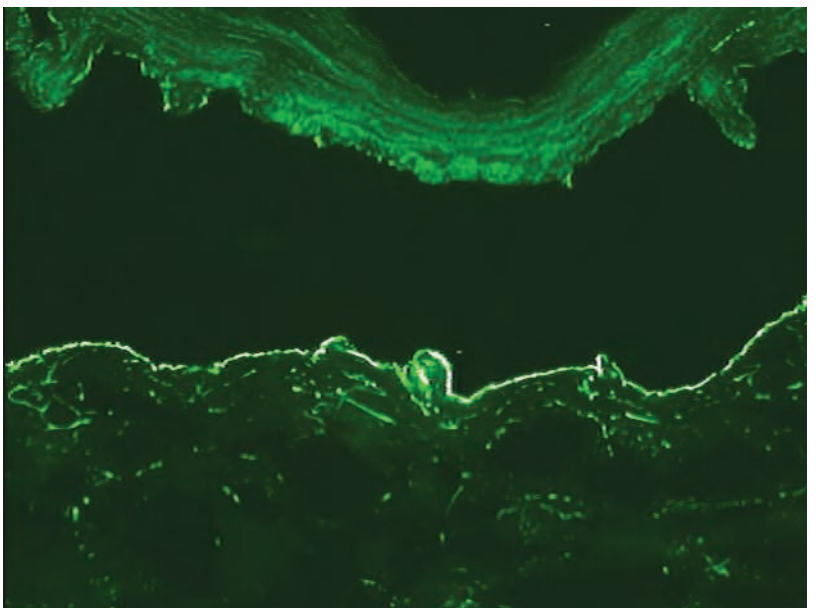

Fig. 1.9 SSS: dermal pattern

Linear IgA Bullous Dermatosis

Clinical

- Widespread vesicles and bullae on normal skin or urticarial plaques
- Most commonly involves trunk
- Annular or targetoid appearance with peripheral vesicles or bullae
- Mucous membrane involvement is common, and ocular involvement also occurs
- Same disease as chronic bullous disease of childhood
- In chronic bullous disease of childhood: perineal and perioral involvement is very common
- Grouped small vesicles forming "clusters of jewels or pearls"

Direct Immunofluorescence

- Linear BMZ: IgA needed for diagnosis (less intense linear BMZ deposition of IgG, IgM, C3 in some cases) (Fig. 1.10)

Indirect Immunofluorescence

- Linear BMZ: IgA in 30% to 50% of cases (70% in chronic bullous disease of childhood)
- SSS: epidermal, dermal, or combined

Target Antigens

- BP180 (BPAG1)
- LABD (97 kd) and LAD-1 (120 kd) represent cleavage products of BP180
- Type VII collagen (290 kd) and a 285-kd dermal antigen

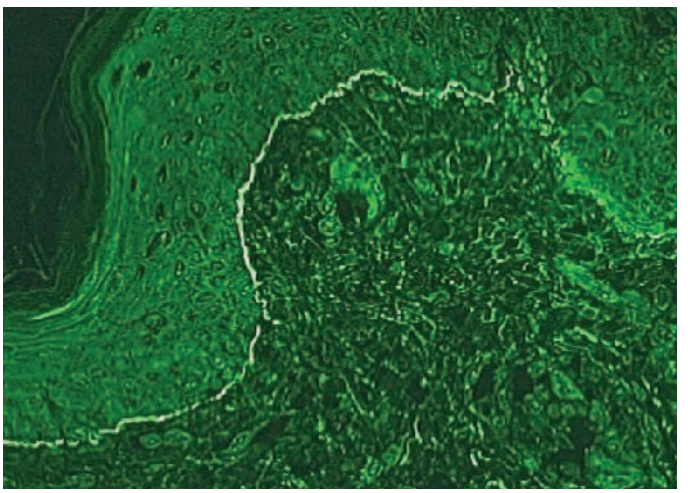

Fig. 1.10 Linear BMZ: IgA

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II

Cell Surface/Intercellular Space (ICS) Staining Pattern

A. Pemphigus Vulgaris

B. Pemphigus Vegetans

C. Pemphigus Foliaceus

D. Paraneoplastic Pemphigus

E. Pemphigus Erythematosus

F. IgA Pemphigus

Pemphigus Vulgaris

Clinical

- Most common subtype of pemphigus
- Flaccid bullae rupture, leaving denuded areas
- Oral involvement is often the initial manifestation, in approximately 60% of patients
- Positive Nikolsky sign
- Skin manifestations involve scalp, chest, back, intertriginous areas

Direct Immunofluorescence

- Cell surface/ICS pattern for IgG (90%-100%) or C3 (Fig. 2.1)

Indirect Immunofluorescence

- Cell surface/ICS pattern for IgG in 90% of active cases (Fig. 2.2)

Target Antigens

- Desmoglein 3 (130 kd)
- Desmoglein 1 (160 kd)
- Anti-desmoglein 3 (in oral pemphigus vulgaris)
- Anti-desmogleins 3 and 1 (in mucocutaneous disease)
- Enzyme-linked immunosorbent assay for desmogleins 3 and 1 available and correlates with disease activity

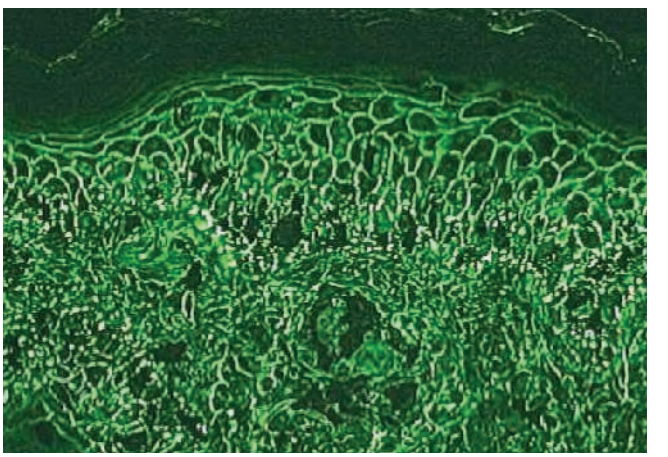

Fig. 2.1 Cell surface/ICS: IgG

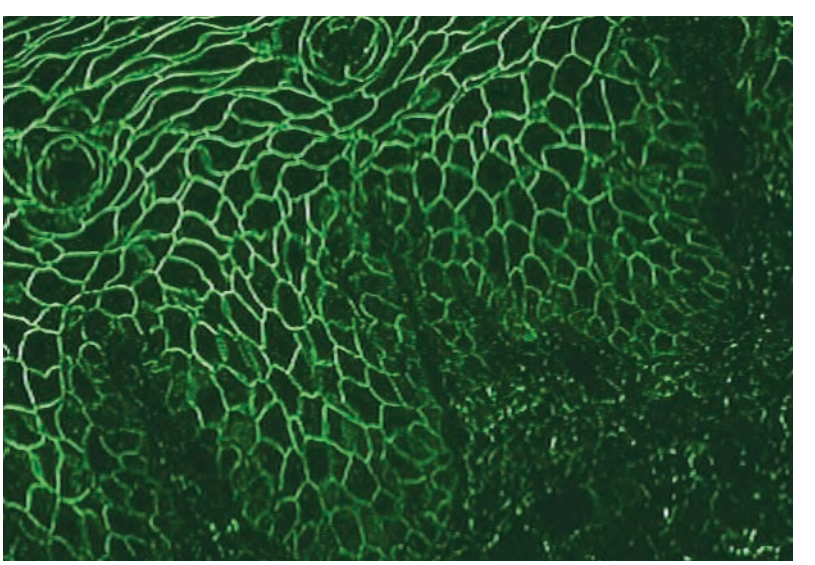

Fig. 2.2 Cell surface/ICS: IgG

Pemphigus Vegetans

Clinical

- Variant of pemphigus vulgaris
- Painful flaccid bullae that lead to vegetative granulating lesions with or without pustules
- Involves intertriginous areas predominantly

Direct Immunofluorescence

- Identical to pemphigus vulgaris

Indirect Immunofluorescence

- Identical to pemphigus vulgaris

Target Antigens

- Identical to pemphigus vulgaris

Pemphigus Foliaceus

Clinical

- Superficial vesicles or bullae that heal with superficial erosions and crusting
- Involves scalp, face, trunk
- No mucosal involvement
- Positive Nikolsky sign
- Pemphigus foliaceous variants:

  A. Fogo selvagem
  - Endemic in rural areas of Brazil
  - Correlates with blackfly (*Simulium* species) distribution
  - Increased familial tendency with increased HLA-DRB1

  B. Drug-induced pemphigus
  - More commonly associated with pemphigus foliaceus than pemphigus vulgaris (4:1)
  - Most common offending drugs: D-penicillamine, captopril

Direct Immunofluorescence

- Identical to pemphigus vulgaris (pg. 18)

Indirect Immunofluorescence

- Identical to pemphigus vulgaris (pg. 18)
- Guinea pig lip or esophagus also can be used (in addition to monkey esophagus)

Target Antigens

- Desmoglein 1 (160 kd)

Paraneoplastic Pemphigus

Clinical

- Severe oral involvement
- Polymorphic cutaneous involvement
- Acral involvement occurs
- Associated bronchiolitis obliterans
- Associated malignancy
- In two-thirds of cases, tumor exists at presentation
- In one-third of cases, paraneoplastic pemphigus precedes the tumor

Associated Neoplasms

- Chronic lymphocytic leukemia
- Castleman tumor
- Thymoma
- Spindle cell neoplasms
- Waldenström macroglobulinemia

Direct Immunofluorescence

- Weak focal cell surface/ICS pattern and linear or granular BMZ for IgG or C3 (Fig. 2.3)
- Lichenoid changes also may be seen (shaggy BMZ and cytoid bodies)
- Increased rate of false-negative results

Indirect Immunofluorescence

- Cell surface/ICS (IgG) with or without linear BMZ on monkey esophagus substrate
- Rat bladder is most sensitive substrate for paraneoplastic pemphigus (Fig. 2.4)
  - 75% sensitive
  - 83% specific

Target Antigens

- Desmoglein 3 (130 kd)
- Desmoglein 1 (160 kd)
- Plectin (>500 kd)
- Desmoplakin I (250 kd)
- BP antigen I (230 kd)
- Desmoplakin II (210 kd)
- Envoplakin (210 kd)
- Periplakin (190 kd)
- 170 kd, undetermined

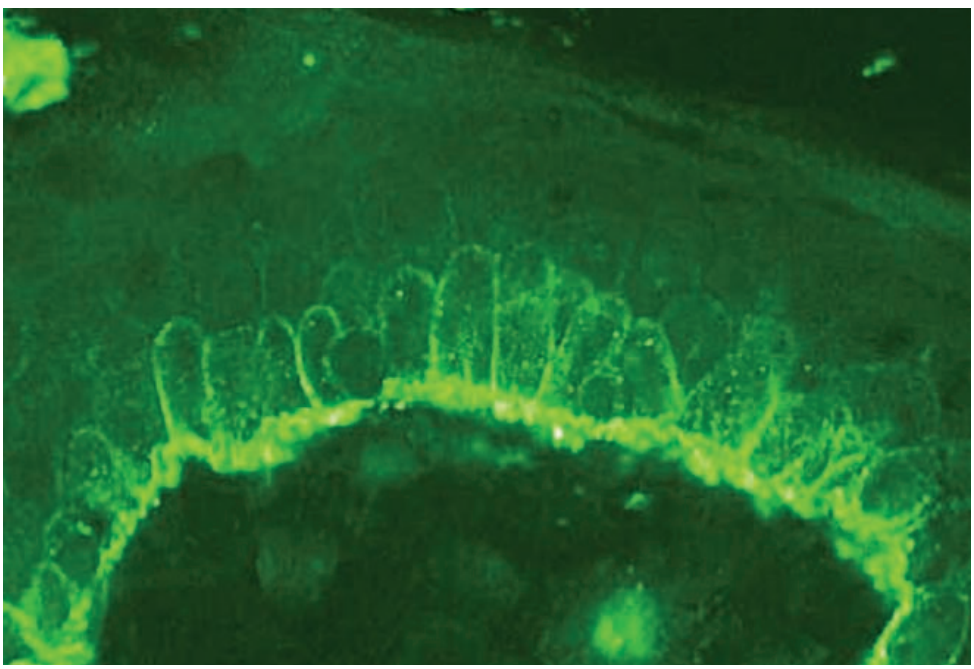

Fig. 2.3 Cell surface/ICS and linear BMZ: IgG

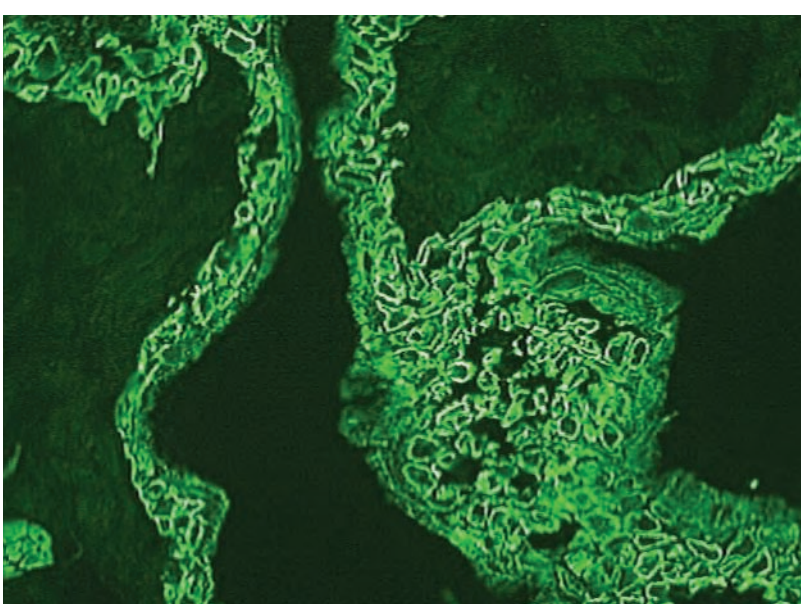

Fig. 2.4 Epithelial surface staining on rat bladder

Pemphigus Erythematosus

Clinical

- Involves seborrheic areas of face and trunk, mimicking lupus erythematosus

Direct Immunofluorescence

- Cell surface/ICS pattern (IgG or C3) and granular BMZ (IgM, C3) (Fig. 2.5 and 2.6)

Indirect Immunofluorescence

- Cell surface/ICS pattern: IgG
- ANA

Target Antigens

- Desmoglein 1 (160 kd)

IgA Pemphigus

Clinical

- Pruritic vesicles and pustules in an annular pattern
- Predilection for intertriginous areas
- Rare mucous membrane involvement
- Associated disorders
  - IgA monoclonal gammopathy
  - Crohn disease/gluten-sensitive enteropathy

Direct Immunofluorescence

- Cell surface/ICS pattern for IgA (Fig. 2.7)

Indirect Immunofluorescence

- Positive in 50% of patients

Target Antigens

- Desmocollin 1 (subset of patients target desmogleins 3 and 1)

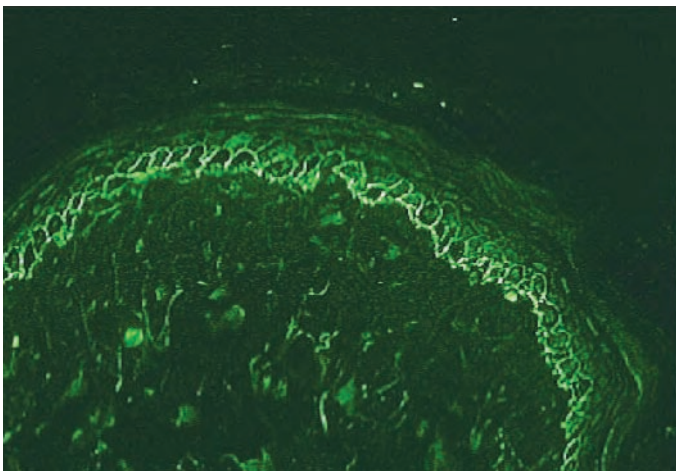

Fig. 2.5 Cell surface/ICS: IgG

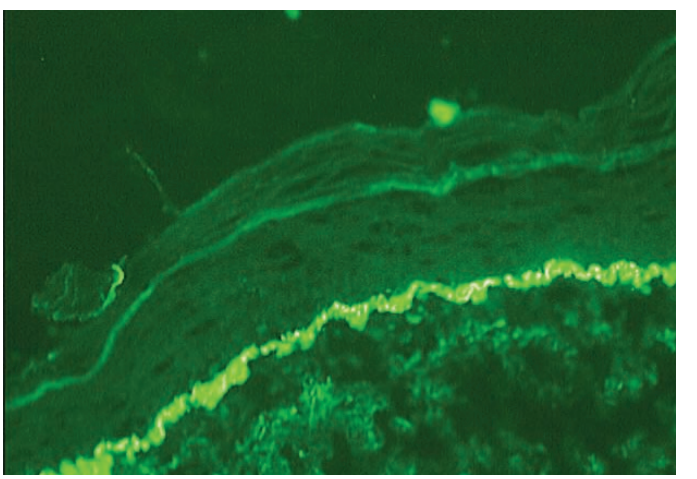

Fig. 2.6 Granular BMZ: IgM

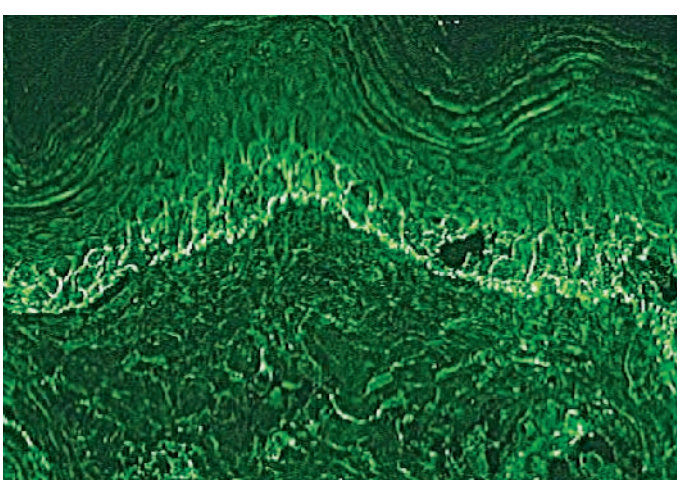

Fig. 2.7 Cell surface/ICS: IgA

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II

Granular Basement Membrane Zone Staining Pattern

A. Dermatitis Herpetiformis

B. Lupus Erythematosus
   1. Systemic Lupus Erythematosus
   2. Discoid Lupus Erythematosus
   3. Subacute Cutaneous Lupus Erythematosus

C. Mixed Connective Tissue Disease

D. Systemic Scleroderma

E. Dermatomyositis

Dermatitis Herpetiformis

Clinical

- Erythematous papules or vesicles symmetrically distributed over extensor surfaces of the elbows, knees, buttocks, back, and scalp
- Vesicles may be grouped in a herpetiform configuration
- Intensely pruritic
- Often associated with multiple erosions caused by scratching
- One part of a spectrum of gluten-sensitive disorders that includes celiac disease
- An indirect consequence of a gluten-sensitive enteropathy

Direct Immunofluorescence

- Granular BMZ pattern for IgA, with stippling of dermal papillae (100%) (Fig. 3.1)
- Occasionally C3 (50%); IgG and IgM less often

Indirect Immunofluorescence

- IgA class endomysial antibody staining demonstrated in 76% of persons receiving a normal gluten-containing diet (Fig. 3.2)
- Endomysial antibody testing is recommended to identify a gluten-sensitive enteropathy and to monitor response to a gluten-free diet

Target Antigens

- Tissue transglutaminase in gluten-sensitive diseases
- Recent literature describing epidermal transglutaminase in skin lesions of dermatitis herpetiformis
- Circulating IgA antibody testing to tissue transglutaminase by enzyme-linked immunosorbent assay is recommended to identify the presence of a gluten-sensitive enteropathy and to monitor response to a gluten-free diet

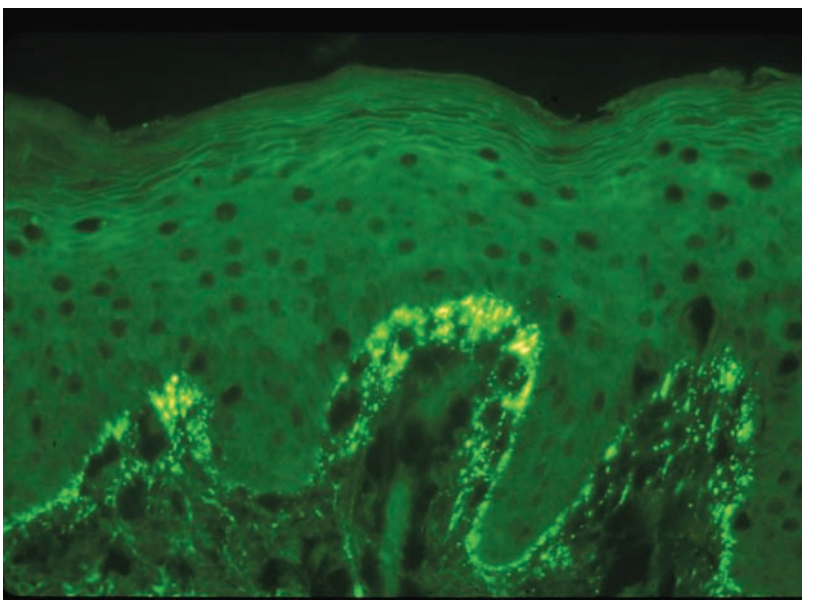

Fig. 3.1 Granular BMZ with stippling of dermal papillae: IgA

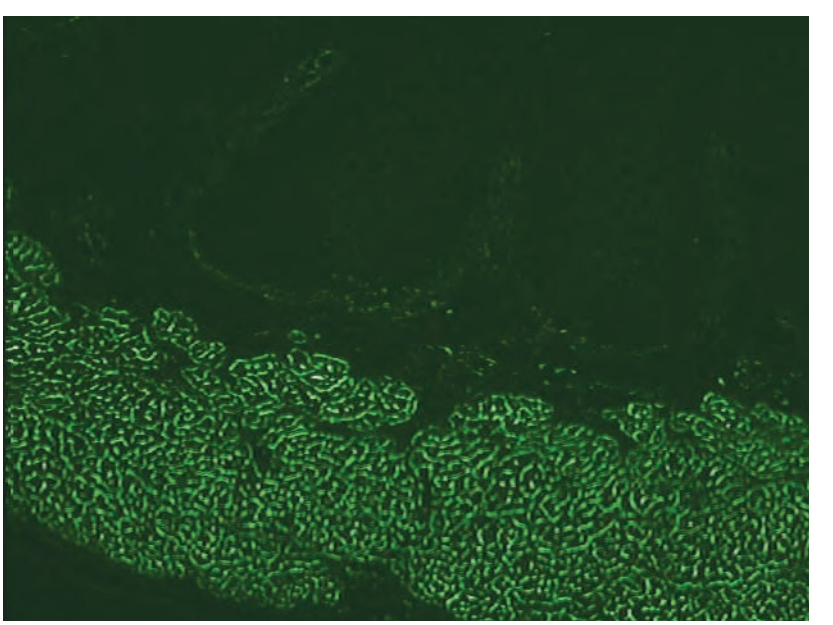

Fig. 3.2 Endomysial antibody: IgA

Systemic Lupus Erythematosus

Clinical

- Malar "butterfly" rash
- Exacerbated by ultraviolet light
- Waxes and wanes with underlying systemic lupus erythematosus disease activity
- Discoid rash may occur at some point in the disease
- Photosensitivity
- Painless oral ulcers
- Nonerosive arthritis involving two or more peripheral joints
- Serositis
- Central nervous system involvement
- Nephritis
- Anemia, leukopenia, lymphopenia, thrombocytopenia
- See American College of Rheumatology's revised criteria for the classification of systemic lupus erythematosus (Tan et al, 1982)

Immunologic Disorder

- ANA in abnormal titer
- Anti–double-stranded DNA in abnormal titer
- Presence of anti-Sm antibody
- IgG or IgM anticardiolipin antibodies

Direct Immunofluorescence

- Granular BMZ pattern for IgG, IgM, IgA, C3 (Fig. 3.3) (sun-exposed involved skin >90%; sun-exposed nonlesional skin 50%; non–sun-exposed nonlesional skin 30%)
- Speckled epidermal nuclei pattern for IgG in 10% to 15% (Fig. 3.4)
- High yield with systemic lupus erythematosus–specific skin lesions: malar rash, erythematous edematous plaques, and active disease

Indirect Immunofluorescence

- ANA

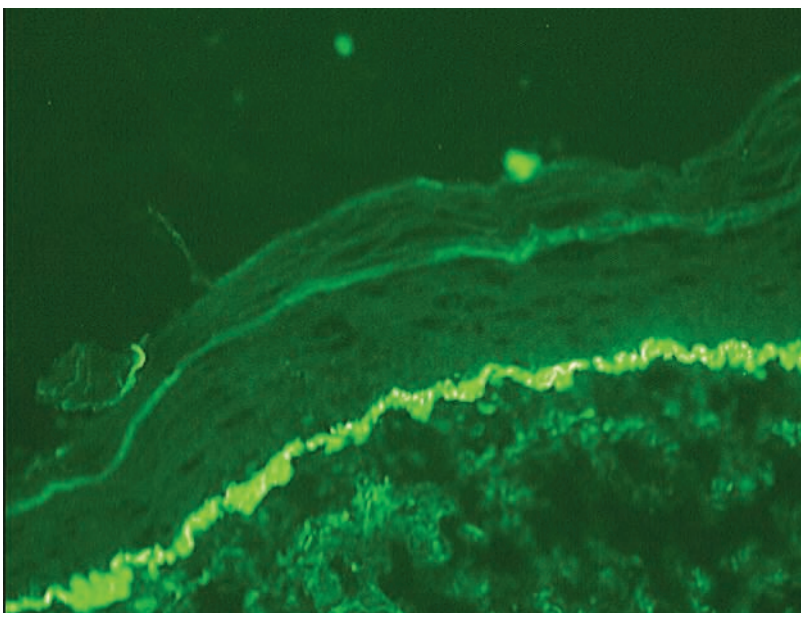

Fig. 3.3 Granular BMZ: IgM

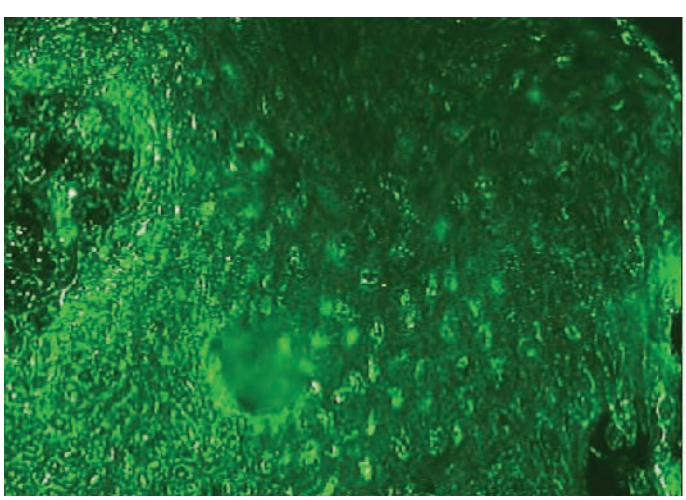

Fig. 3.4 Speckled epidermal nuclei: IgG

Discoid Lupus Erythematosus

Clinical

- Discoid rash typically presents as sharply demarcated, erythematous, indurated plaques with hyperkeratosis, atrophy, telangiectasia, and follicular plugging
- Hypopigmentation or hyperpigmentation may be prominent
- Most frequently involves the face, scalp, ears, V area of the neck, and extensor aspects of the arms
- Scalp involvement may lead to scarring alopecia

Immunologic Disorder

- Antibodies to single-stranded DNA may be present
- ANA present in low titers in 30% to 40% of patients
- Ro/SS-A and La/SS-B autoantibodies are rare
- Antibodies to double-stranded DNA are uncommon

Direct Immunofluorescence

- Granular BMZ pattern for IgG and IgM (Fig. 3.5) (involved skin >90%)
- May have shaggy, thick BMZ with fibrinogen
- Cytoid bodies with IgM and IgA

Indirect Immunofluorescence

- None (ANA rarely)

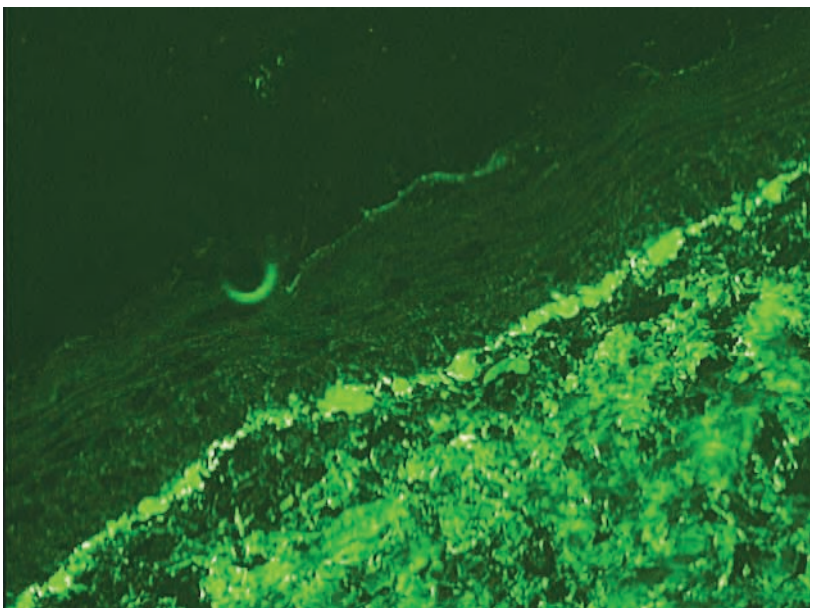

Fig. 3.5 Granular BMZ and cytoid bodies: IgM

Subacute Cutaneous Lupus Erythematosus

Clinical

- Erythematous macules and papules that evolve into hyperkeratotic papulosquamous polycyclic and annular plaques
- Photosensitivity
- Less common on the face
- Heals without scarring
- May resolve with leukoderma and telangiectasias
- About 50% of patients meet the American College of Rheumatology's revised criteria for the classification of systemic lupus erythematosus

Immunologic Disorder

- Autoantibodies to Ro/SS-A ribonucleoprotein present in 70% to 90% strongly support the diagnosis
- Autoantibodies to La/SS-B present in 30% to 50%
- ANA present in 60% to 80%

Direct Immunofluorescence

- Granular BMZ pattern for IgG, IgM, C3
- Epidermal/keratinocyte intracytoplasmic particulate deposition with IgG (Fig. 3.6)
- Cytoid bodies for IgM and IgA

Indirect Immunofluorescence

- ANA

Mixed Connective Tissue Disease

Clinical

- Combined features of lupus erythematosus, scleroderma, and myositis

Immunologic Disorder

- High titers of antibody to the extractable nuclear antigen

Direct Immunofluorescence

- Granular BMZ pattern rare (15%)
- Speckled epidermal nuclei for IgG in 46% to 100%

Indirect Immunofluorescence

- ANA

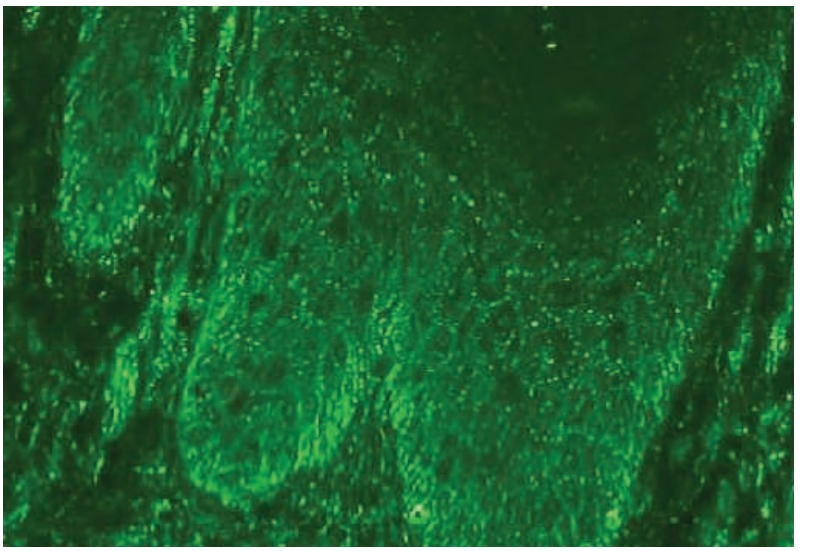

Fig. 3.6 Epidermal/keratinocyte intracytoplasmic particulate deposition: IgG

Systemic Scleroderma

Clinical

- Skin tightening extends from fingers to upper extremities, trunk, face, and, finally, lower extremities
- Raynaud phenomenon
- Nail-fold capillary changes (giant or sausage-shaped loops)
- Edema of the hands and fingers
- Flexion contractures and sclerodactyly with waxy, shiny, atrophic skin
- Ulcers on fingertips and over knuckles
- Masklike, expressionless face, with loss of normal facial lines
- Small, sharp nose, thinning of lips and hair
- Microstomia with radial furrowing around the mouth
- Matlike telangiestasias on face and upper trunk
- Esophageal dysfunction in more than 90%
- Pulmonary fibrosis
- Myocardial fibrosis in 50% to 70%
- Renal involvement with hypertension

Immunologic Disorder

- Anticentromere antibodies only in 12% to 25% of patients (present in 50%-96% of patients with CREST syndrome)
- Scl-70 autoantibodies (30%)

Direct Immunofluorescence

- Granular BMZ pattern for IgM (sun-exposed 60%)
- Speckled epidermal nuclei pattern in 20%
- Shaggy BMZ with fibrinogen (Fig. 3.7)

Indirect Immunofluorescence

- ANA

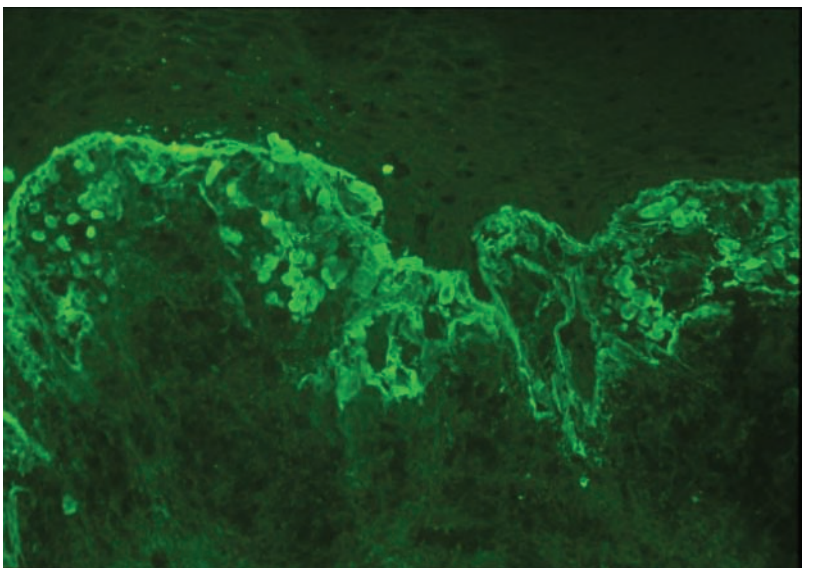

Fig. 3.7 Shaggy BMZ: fibrinogen

Dermatomyositis

Clinical

- Erythematous, violaceous papules over the dorsal aspect of the interphalangeal or metacarpophalangeal joints (termed Gottron papules)
- Symmetric, confluent, violaceous erythema over the interphalangeal or metacarpophalangeal joints, olecranon process, medial malleoli, and patella (termed Gottron sign)
- Periorbital, violaceous (heliotrope) erythema and edema
- Periungual telangiectasia with or without cuticular hemorrhage and dystrophic cuticles
- Violaceous erythema over dorsal aspect of arms, posterior aspect of shoulder and neck (shawl sign)
- Poikiloderma atrophicans
- Pruritus can be severe
- Cutaneous calcification is more common in juvenile form (40%-50%)
- Symmetric proximal muscle weakness
- Skeletal muscle-derived enzymes increased in 90% of cases of classic dermatomyositis at some point of the disease
- Abnormal muscle biopsy specimen
- Abnormal electromyographic results
- Higher-than-expected risk for malignancy (ovarian cancer), especially in patients 50 years or older

Immunologic Disorder

- Increased ANA levels on human tumor cell substrates (60%-80%)
- Anti-Jo-1 (20% of cases of classic dermatomyositis and 40% of cases of polymyositis)

Direct Immunofluorescence

- Granular BMZ pattern for IgM, IgG, and C3 (low intensity)
- Cytoid bodies for IgM (Fig. 3.8) and IgA, shaggy BMZ with fibrinogen (Fig. 3.9)

Indirect Immunofluorescence

- ANA

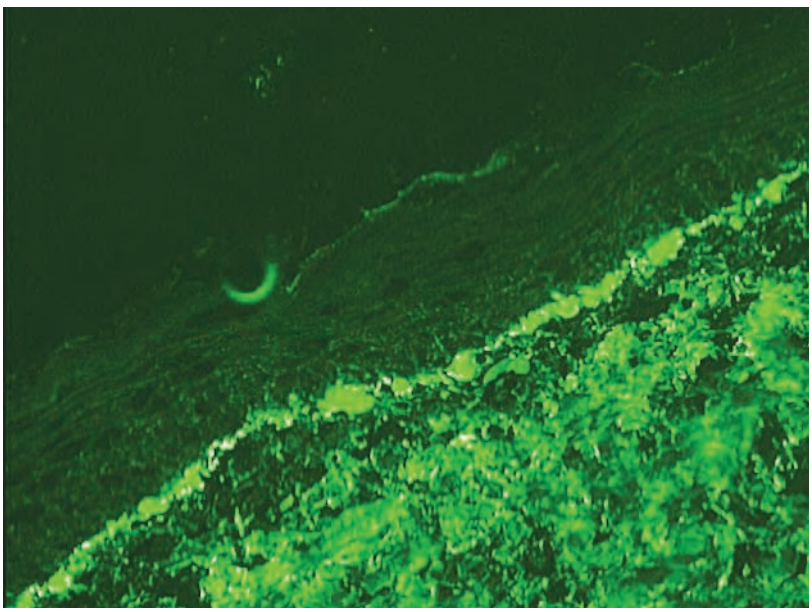

Fig. 3.8 Granular BMZ and cytoid bodies: IgM

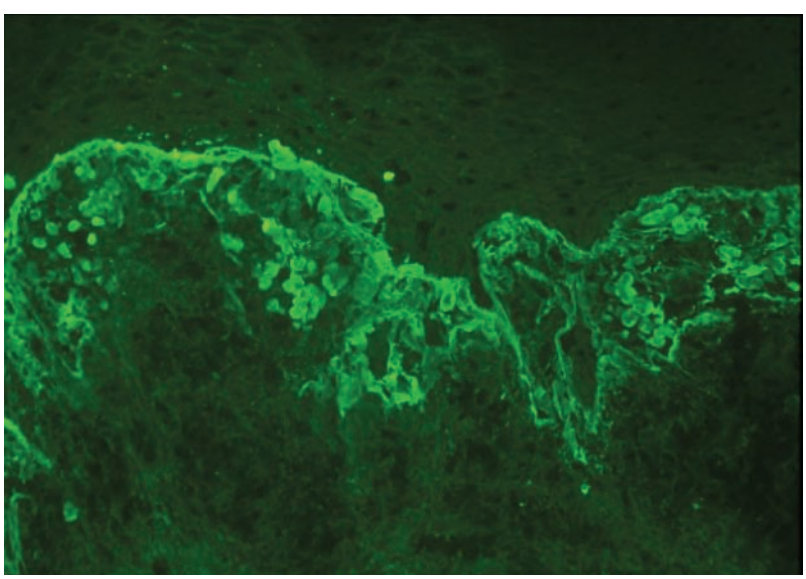

Fig. 3.9 Shaggy BMZ: fibrinogen

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IV

Shaggy Basement Membrane Zone Staining Pattern

A. Lichenoid Tissue Reactions
   1. Lichen Planus
   2. Lupus Erythematosus and Other Connective Tissue Disorders
   3. Drug Reactions
   4. Photodermatoses

Lichenoid Tissue Reactions

Clinical

Lichen planus

- Erythematous to violaceous, flat-topped, polygonal papules with fine, whitish reticulations termed Wickham striae
- Distributed symmetrically over flexural areas of extremities
- Pruritus usually present
- Hypertrophic lichen planus extremely pruritic
- Presence of Koebner phenomenon
- White, reticulated pattern occurs with oral involvement
- Nail pterygium or complete loss of nail plate

Lupus erythematosus and other connective tissue disorders

- See Chapter III

Lichenoid drug reactions

- Initiated by many drugs, such as β-adrenergic blockers (latent period of 1 year), penicillamine (latent period of 2 months-3 years), angiotensin-converting enzyme inhibitors, especially captopril (latent period of 3-6 months)
- Usually resolves 2 to 4 months after discontinuation of offending drug

Lichenoid photodermatoses

- Lesions appear eczematous with a photodistributed pattern
- Drugs that induce a photodistributed lichenoid reaction include carbamazepine, chlorpromazine, ethambutol, quinine, tetracyclines, thiazide diuretics, and furosemide
- Generally resolve 3 to 4 months from discontinuation of offending drug

Direct Immunofluorescence

- Shaggy BMZ pattern for fibrinogen (Fig. 4.1)
- Cytoid bodies for IgM and IgA, occasionally IgG, C3, and fibrinogen (Fig. 4.2)

Indirect Immunofluorescence

- ANA for lupus erythematosus

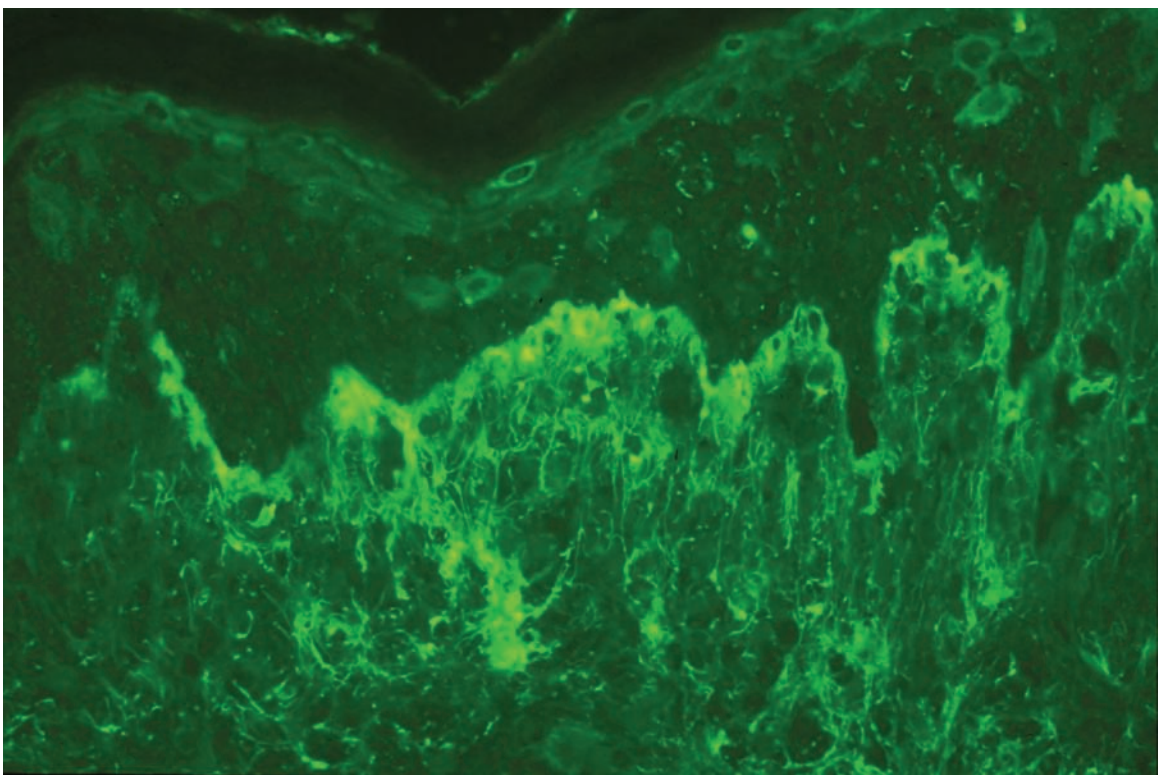

Fig. 4.1 Shaggy BMZ: fibrinogen

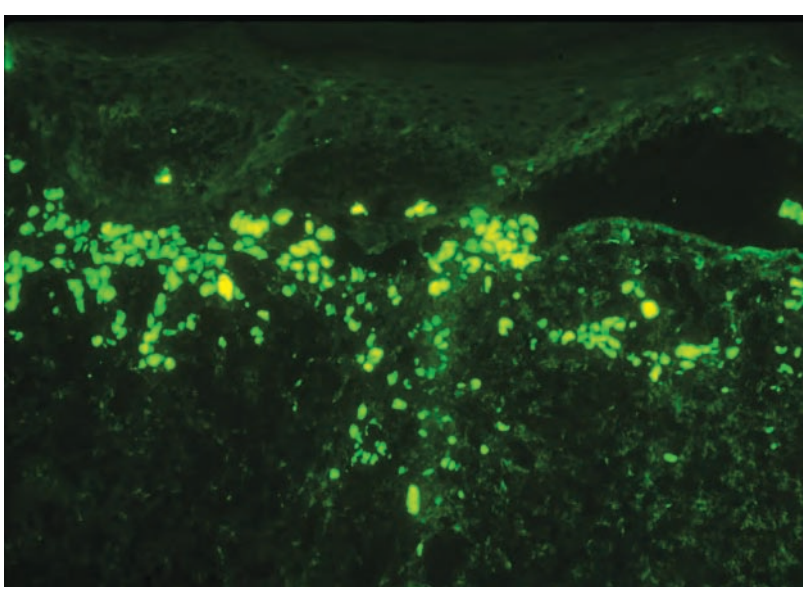

Fig. 4.2 Scattered and clumped cytoid bodies: IgM

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V

Vascular Staining Pattern and Others

A. Porphyria

B. Henoch-Schönlein Purpura

C. Vasculitis

Porphyria

Clinical

Porphyria cutanea tarda

- Most common porphyria
- Photosensitivity, fragile skin
- Vesicles, bullae, erosions, crusts, milia, scarring, hypertrichosis on sun-exposed areas
- Usually occurs in third or fourth decade of life
- Most often acquired, but autosomal dominant in 20% of cases
- Associated with use of oral contraceptives, alcohol, chemicals (hexachlorobenzene, chlorinated phenols)

Pseudoporphyria

- Clinically identical to porphyria cutanea tarda
- Associated with chronic renal failure with hemodialysis, systemic lupus erythematosus, hepatoma, hepatitis C, sarcoidosis, drugs
- Offending drugs include nonsteroidal anti-inflammatory drugs, tetracyclines, nalidixic acid, furosemide, diazide, cyclosporine

Direct Immunofluorescence

- Dermal vessels: homogeneous thick staining pattern for IgG, ± IgA, C3, fibrinogen (Fig. 5.1)
- Granular BMZ for C3, IgM
- Weak, thick linear BMZ for IgG, IgA

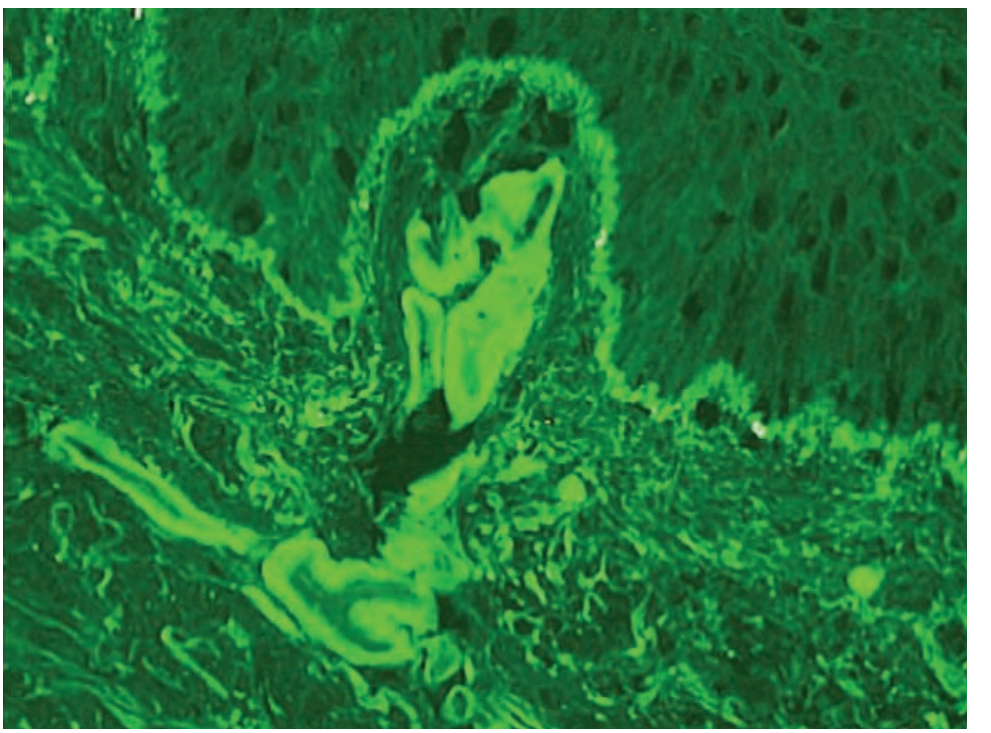

Fig. 5.1 Homogeneous thick dermal blood vessels: IgG, IgA, IgM, C3, fibrinogen

Henoch-Schönlein Purpura

Clinical

- Predominantly occurs in children but can occur in adults
- Palpable purpura over the feet, ankles, lower extremities
- Recent upper respiratory tract infection in 75% of cases
- Abdominal pain, gastrointestinal bleeding, or intussusception
- Arthralgia, arthritis
- Glomerulonephritis

Direct Immunofluorescence

- Strong dermal vessels with IgA (± other conjugates) (Fig. 5.2)

Vasculitis

Clinical

- Palpable purpura
- Macules, urticaria, pustules, vesicles, ulcers, necrosis, and livedo reticularis may be present
- Most often involves lower extremities or other dependent areas
- Specific diagnosis is dependent on the organ pattern involvement and histopathologic findings

Direct Immunofluorescence

- Strong dermal vessels with IgM, IgG, C3, fibrinogen (Fig. 5.3)

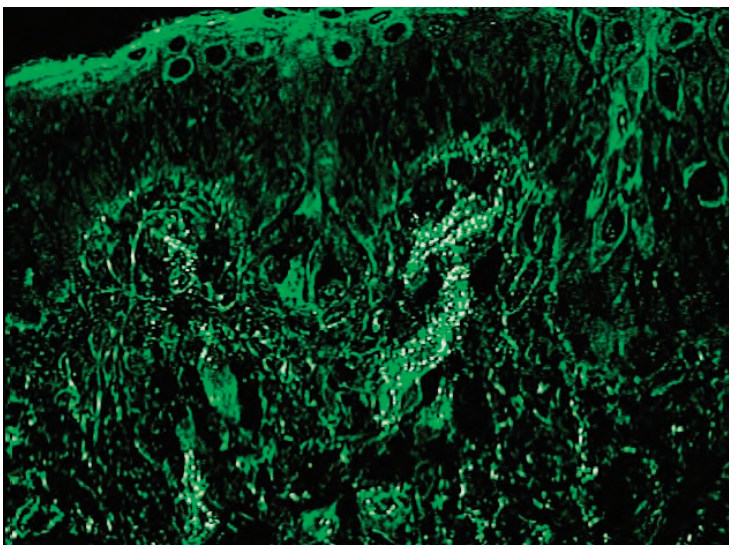

Fig. 5.2 Strong dermal blood vessels: IgA

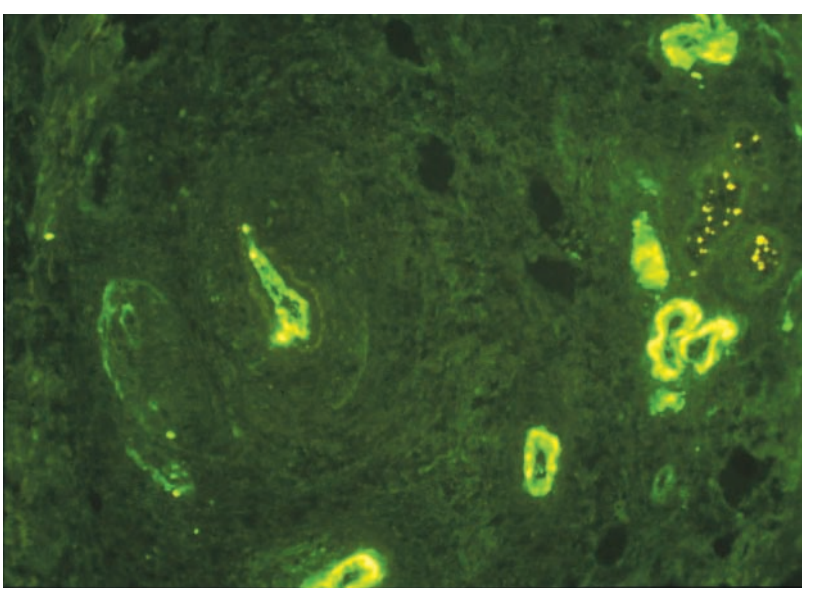

Fig. 5.3 Strong dermal blood vessels: IgM

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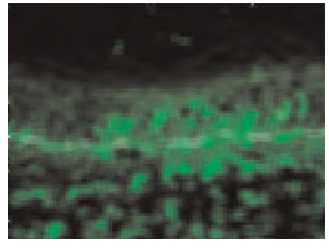
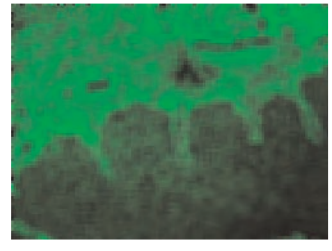
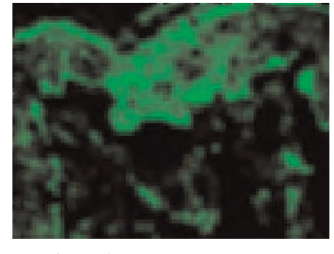
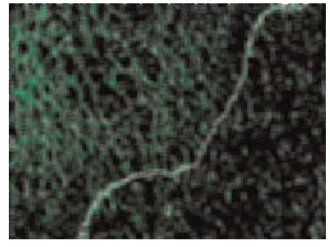
VI Summary

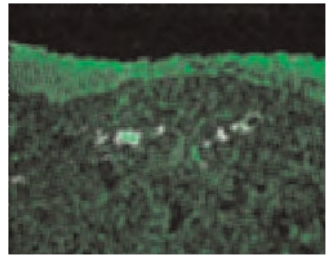
Summary Table

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Linear BMZ staining pattern			
Bullous pemphigoid	Linear BMZ: IgG (90%) and C3 (>90%, nearly all)  *Linear BMZ (IgG)*	BMZ antibodies (IgG) in 75% SSS: epidermal pattern (shown below), occasionally combined epidermal-dermal pattern  *BMZ antibodies (IgG)*  *Epidermal pattern (IgG)*	BP230 BP180 ■ NC16A
Pemphigoid gestationis (herpes gestationis)	Linear BMZ: C3 (100%); IgG (approximately 25%)	BMZ antibodies (IgG) in <25% HG factor in 50% SSS: epidermal pattern	BP230 BP180 ■ NC16A

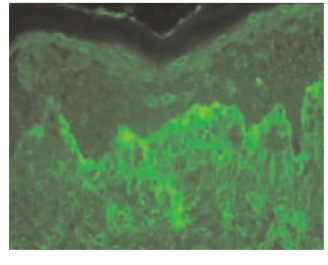
Lichen planus pemphigoides	Linear BMZ: IgG and C3 with changes of lichen planus (cytoid bodies with IgM, IgA, C3, and shaggy BMZ with fibrinogen)	BMZ antibodies (IgG) in 50% SSS: epidermal pattern	BP230 BP180 ■ NC16A



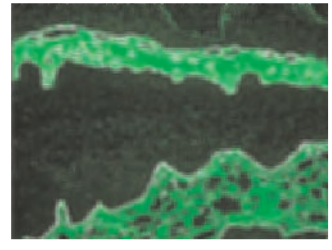
Linear BMZ (IgG)

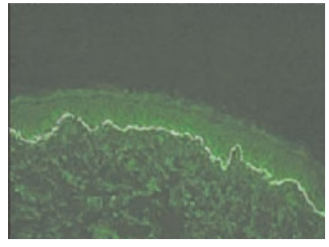
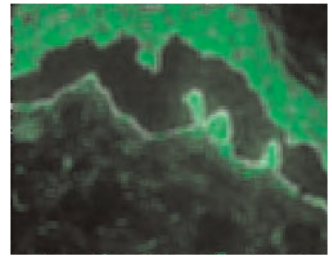
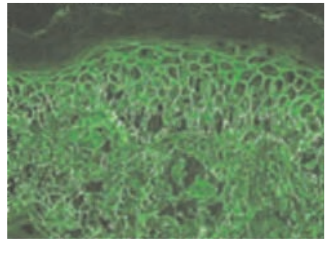
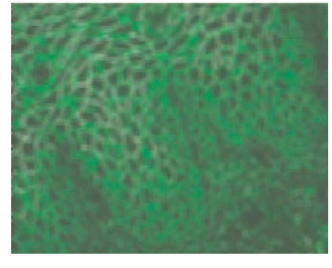


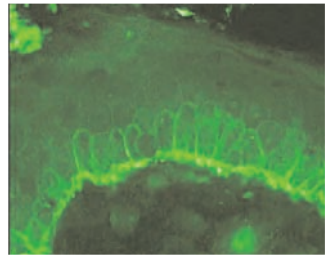
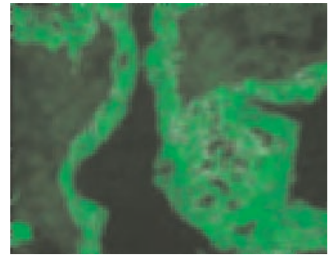
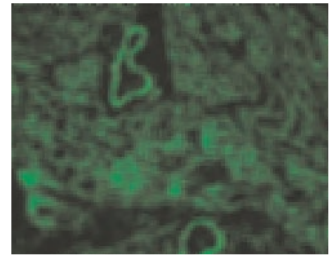
Cytoid bodies (IgA)



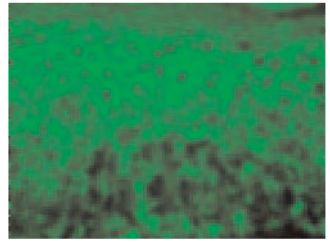
Shaggy BMZ (fibrinogen)

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Linear BMZ staining pattern			
Mucous membrane pemphigoid	Linear BMZ: IgG, C3, or IgA	BMZ antibodies (IgG) in 15%-20% SSS: epidermal, dermal, or combined  *Dermal pattern (IgG)*	BP230 BP180 ■ C-terminus and some NC16A β_4 integrin subunit Laminin-5 (also called epiligrin, nicein, kalinin, BM600) Laminin-6 Type VII collagen (290 kd)
Bullous lupus erythematosus	Linear BMZ: IgG and C3; IgM and IgA also	ANA BMZ antibodies not detected on monkey esophagus can be detected on SSS (dermal pattern)	Type VII collagen (290 kd) ■ NC1 domain
Epidermolysis bullosa acquisita	Linear BMZ: IgG (100%) and C3; occasionally IgA (66%) or IgM (50%)	BMZ antibodies (IgG) in 50% SSS: dermal pattern	Type VII collagen (290 kd) ■ NC1 domain

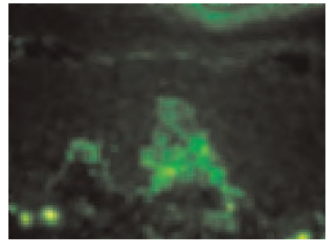
Linear IgA bullous dermatosis	Linear BMZ: IgA needed for diagnosis; less intense deposition of IgG, IgM, and C3 in some cases  *Linear BMZ (IgA)*	BMZ antibodies (IgA) in 30%-50% (70% in chronic bullous disease of childhood) SSS: epidermal, dermal, or combined  *Dermal pattern (IgA)*	BP180 LABD (97 kd) and LAD-1 (120 kd) represent cleavage products of BP180 Type VII collagen (290 kd) and a 285-kd dermal antigen
Cell surface/ICS staining pattern			
Pemphigus vulgaris and vegetans	ICS: IgG (90%-100%) or C3  *ICS (IgG)*	ICS antibodies (IgG) in 90% of active cases  *ICS (IgG)*	Desmoglein 3 (130 kd) Desmoglein 1 (160 kd)
Pemphigus foliaceus	ICS: IgG (90%-100%) or C3	ICS antibodies (IgG) Guinea pig lip or esophagus: ICS antibodies (IgG)	Desmoglein 1 (160 kd)

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Cell surface/ICS staining pattern			
Paraneoplastic pemphigus	ICS: IgG (90%-100%) and C3 BMZ: linear or granular (C3, IgG) May have lichenoid changes (cytoid bodies with IgM and IgA, rarely C3 and shaggy BMZ with fibrinogen)  *ICS and linear BMZ (IgG)*	ICS antibodies (IgG); BMZ antibodies (IgG) Rat bladder epithelium (best screening: 83% specific, 75% sensitive). ICS antibodies, occasionally BMZ  *Rat bladder (IgG)*  *Mouse liver, portal ducts (IgG)*	Desmoglein 1 (160 kd) Desmoglein 3 (130 kd) Plectin (>500 kd) Desmoplakin I (250 kd) BP antigen I (230 kd) Desmoplakin II (210 kd) Envoplakin (210 kd) Periplakin (190 kd) 170 kd, undetermined

Pemphigus erythematosus	ICS: IgG or C3 BMZ: granular IgM, C3	ICS antibodies (IgG) ANA	Desmoglein 1 (160 kd)

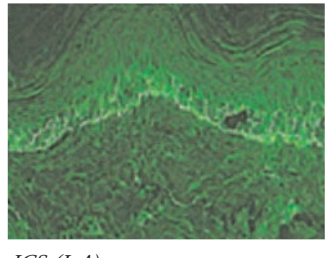


ICS (IgG)

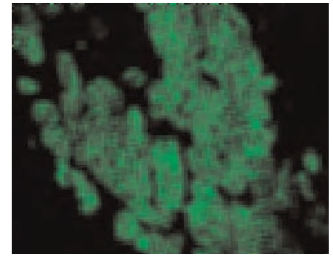


Granular BMZ (IgM)

IgA pemphigus	ICS: IgA	ICS antibodies (IgA) in 50%	Desmocollin 1 (subset of patients target desmogleins 3 and 1)



ICS (IgA)

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Granular BMZ staining pattern			
Dermatitis herpetiformis	Granular BMZ: IgA, with stippling of dermal papillae (100%); occasionally C3 (50%), IgG and IgM less often  *Granular BMZ with stippling of dermal papillae (IgA)*	IgA class endomysial antibodies in 76% of those on a normal gluten-containing diet  *Endomysial antibody (IgA)*	Tissue transglutaminase in gluten-sensitive diseases Recent literature describing epidermal transglutaminase in skin lesions of dermatitis herpetiformis Circulating IgA antibody testing to tissue transglutaminase by enzyme-linked immunosorbent assay is recommended to identify the presence of a gluten-sensitive enteropathy and to monitor response to a gluten-free diet

Lupus erythematosus

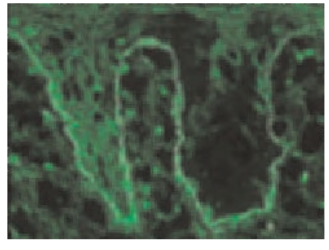
Systemic lupus erythematosus

Granular BMZ: IgG, IgM, IgA, C3 (sun-exposed involved skin >90%; sun-exposed nonlesional skin 50%; non–sun-exposed nonlesional skin 30%)

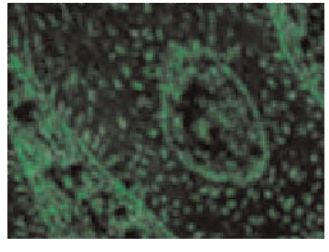
ANA

Epidermal nuclei, speckled (IgG) in 10%-15%

High yield with systemic lupus erythematosus–specific skin lesions: malar rash, erythematous edematous plaques, and active disease

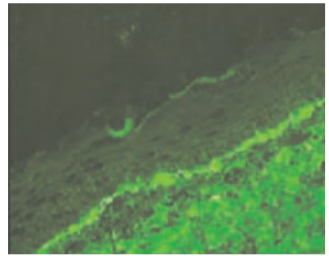


Granular BMZ (IgM)



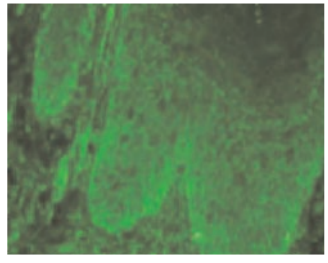
Epidermal nuclei (IgG)

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Granular BMZ staining pattern			
Discoid lupus erythematosus	Granular BMZ: IgG and IgM (involved skin >90%) May have shaggy thick bands Cytoid bodies with IgM and IgA	None (ANA rarely)	



Thick granular BMZ (IgM)

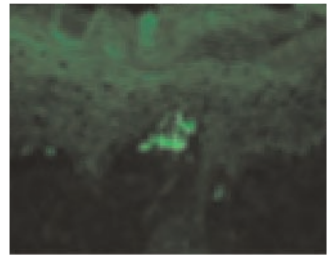
Subacute cutaneous lupus erythematosus	Granular BMZ: IgG, IgM, C3 Epidermal/keratinocyte intracytoplasmic particulate deposition (IgG) Cytoid bodies (IgM and IgA)	ANA



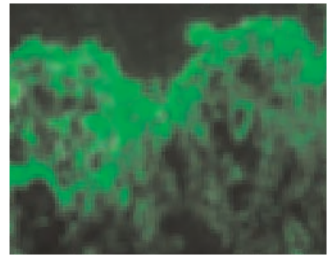
Intracytoplasmic particulate deposition (IgG)

Mixed connective tissue disease	Granular BMZ: rare (15%) Epidermal nuclei, speckled (IgG) in 46%-100%	ANA
Systemic scleroderma	Granular BMZ: IgM (sun-exposed 60%) Epidermal nuclei, speckled, in 20%	ANA
Dermatomyositis	Granular BMZ: IgM, IgG, and C3 (low intensity) Cytoid bodies, IgM and IgA	ANA

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Shaggy BMZ staining pattern			
Lichenoid tissue reactions **Lichen planus** **Lupus erythematosus** **Drug reactions** **Photodermatoses**	Shaggy BMZ: fibrinogen	None	
	Cytoid bodies (IgM and IgA, occasionally IgG, C3, and fibrinogen)	ANA for systemic lupus erythematosus	

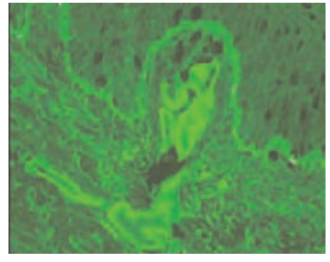


Cytoid bodies (IgM)



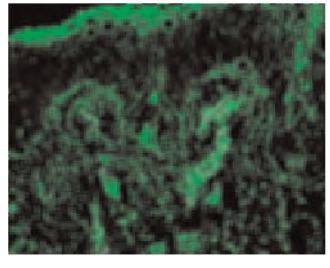
Shaggy BMZ (fibrinogen)

Porphyria	Dermal vessels: homogeneous IgG, granular C3 BMZ: weak, thick linear BMZ	None



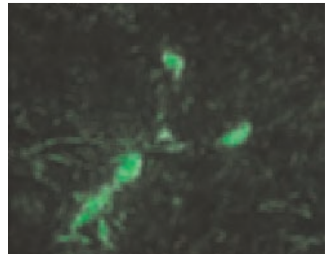
Homogeneous thick dermal blood vessels: IgG, IgA, IgM, C3, fibrinogen

Henoch-Schönlein purpura	Strong dermal vessels: IgA	

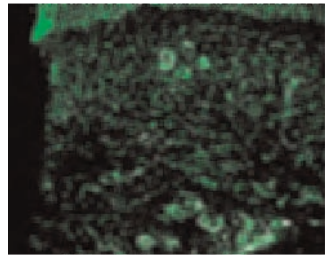


Dermal vessels (IgA)

Disease	Direct immunofluorescence	Indirect immunofluorescence	Target antigens
Vascular staining pattern and others			
Vasculitis	Strong dermal vessels: IgM ± C3, IgG		



Dermal vessels (IgM)



Dermal vessels (C3)

Immunofluorescence Flowchart

1. Linear BMZ (DIF)

Linear BMZ: IgG, C3 ± IgA

- IIF on SSS
  - Epidermal pattern:
    i. Bullous pemphigoid and its variants
    ii. Mucous membrane pemphigoid
    iii. Lichen planus pemphigoides
  - Dermal pattern:
    i. Bullous systemic lupus erythematosus
    ii. Epidermolysis bullosa acquisita
    iii. Mucous membrane pemphigoid
    iv. Brunsting-Perry cicatricial pemphigoid

Linear BMZ: IgG, C3

+ lichenoid changes (cytoid bodies with IgM and IgA and shaggy BMZ with fibrinogen)
i. Lichen planus pemphigoides

Linear BMZ: IgA ± IgG, C3

- IIF with IgA may show an epidermal, dermal, or combined pattern
  i. Linear IgA bullous disease or chronic bullous disease of childhood

Linear BMZ: C3 ± IgG

- HG factor:
  i. Pemphigoid (herpes) gestationis

2. ICS/cell surface (DIF)

ICS: IgG, C3

- IIF with monkey esophagus
  - Positive:
    i. Pemphigus vulgaris
    ii. Pemphigus vegetans
    iii. Pemphigus foliaceus
- IIF with guinea pig esophagus/lip
  i. Pemphigus foliaceus

ICS: IgG, C3

+ linear/granular BMZ (C3, IgG) + lichenoid changes (cytoid bodies with IgM and IgA and shaggy BMZ with fibrinogen)
i. Paraneoplastic pemphigus

ICS: IgG, C3

+ granular BMZ (IgM ± other conjugates) ± ANA
i. Pemphigus erythematosus

ICS: IgA

i. IgA pemphigus

3. Granular BMZ (DIF)

Granular BMZ: IgA, with stippling of the dermal papillae

i. Dermatitis herpetiformis (confirm with tissue transglutaminase ELISA or IIF with endomysial antibody)

Granular BMZ: IgG, IgM, C3

± epidermal nuclear fluorescence (speckled) ± lichenoid tissue reaction ± epidermal intracytoplasmic particulate deposition
i. Lupus erythematosus

4. Shaggy BMZ (DIF)

Shaggy BMZ: fibrinogen

+ cytoid bodies (IgA, IgM)
- Lichenoid tissue reactions
  i. Lichen planus
  ii. Lichenoid drug reactions
  iii. Connective tissue diseases

Shaggy BMZ: fibrinogen (mucosa)

i. Lichenoid tissue reaction
ii. Oral lichen planus
iii. Lichenoid drug reactions
iv. Oral lupus erythematosus

5. Epidermal nuclear fluorescence (anti-U1RNP) (DIF)

i. Mixed connective tissue disease (47%-100%)
ii. Systemic scleroderma (20%)
iii. Systemic lupus erythematosus (10%-15%)

6. Epidermal/keratinocyte intracytoplasmic particulate staining with IgG (anti-Ro/SS-A) (DIF)

i. Subacute cutaneous lupus erythematosus
ii. Sjögren syndrome
iii. Mixed connective tissue disease

7. Thickened BMZ and dermal vessels (DIF)

Thickened linear BMZ: IgG

+ homogeneous vessels (IgG) and granular vessels (C3)
i. Porphyria

8. Strong dermal vessels (DIF)

Dermal blood vessels: IgG or IgM or IgA or C3 (2 or more conjugates required)

i. Vasculitis

Dermal blood vessels: IgA

i. Henoch-Schönlein purpura

DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence.

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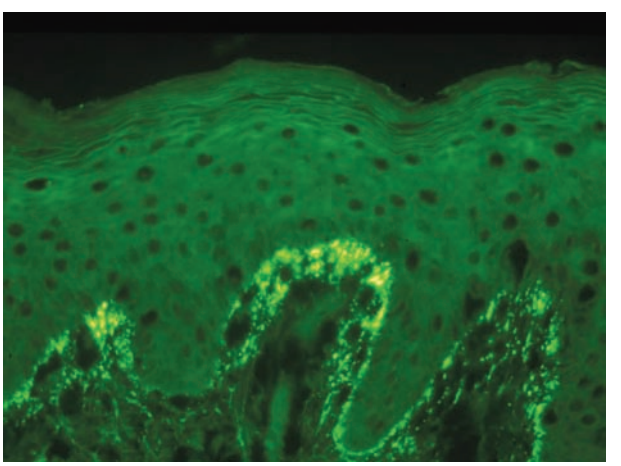
Practice Questions for Board Exams

1. **A 55-year-old man presents with multiple flaccid bullae on his trunk which are short-lived and develop crusts. He does not have mucosal involvement. The patient most likely has:**

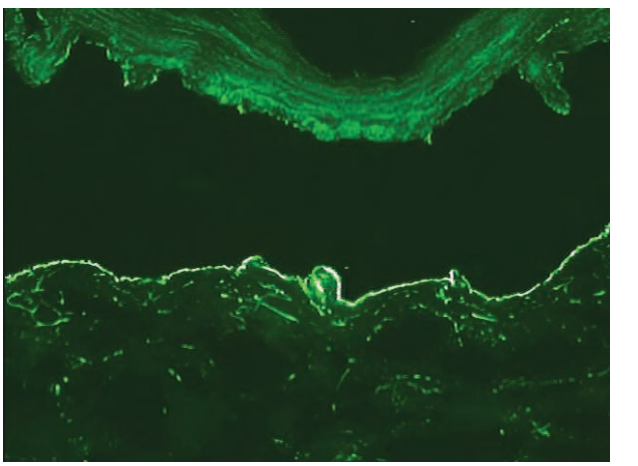
   a. Bullous pemphigoid
   b. Cicatricial pemphigoid
   c. Pemphigus vulgaris
   d. Pemphigus foliaceus
   e. Dermatitis herpetiformis

2. **The following immunofluorescence pattern is with fluorescein-labeled IgA. The patient's diagnosis is:**



   a. Linear IgA bullous dermatitis
   b. Dermatitis herpetiformis
   c. IgA pemphigus
   d. Cicatricial pemphigoid
   e. Lupus erythematosus

3. **The following indirect immunofluorescence pattern on SSS can be found in:**

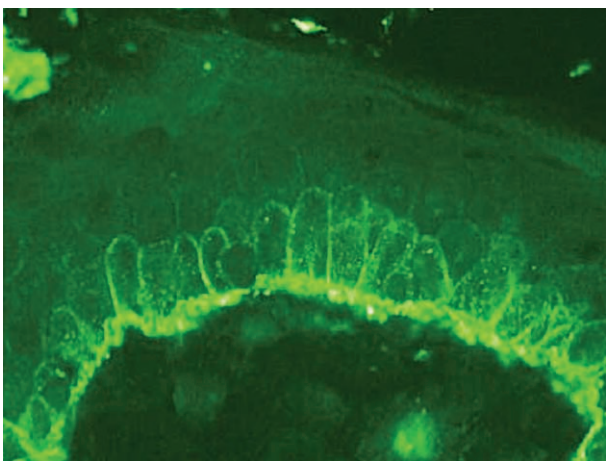


   a. Pemphigus vulgaris
   b. Pemphigus foliaceus
   c. Bullous pemphigoid
   d. Pemphigoid gestationis
   e. Epidermolysis bullosa acquisita

4. **In a 30-year-old woman, a vesicular eruption develops on her trunk 2 days post partum. The most specific diagnostic pattern on direct immunofluorescence is:**

   a. Strong granular BMZ with IgG
   b. Cell surface/ICS pattern with C3
   c. Strong linear BMZ with C3
   d. Shaggy BMZ staining with fibrinogen
   e. Cytoid bodies with IgM

5. The following immunofluorescence pattern is seen with IgG. The most likely diagnosis is:

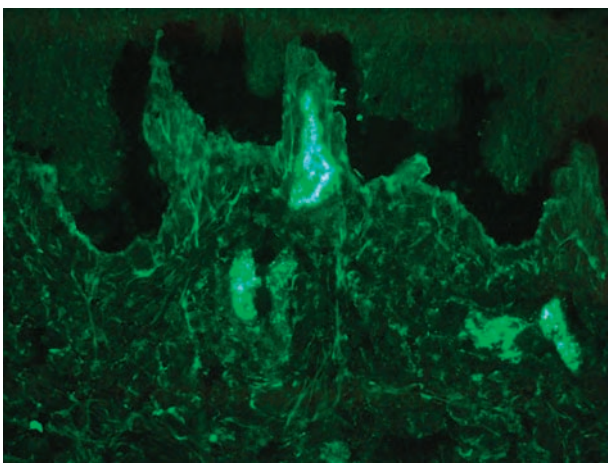


a. Bullous pemphigoid
b. Mucous membrane pemphigoid
c. Pemphigus foliaceus
d. Paraneoplastic pemphigus
e. Pemphigus vulgaris

6. A patient has only positive desmoglein-1 antibodies. The patient has:

a. Pemphigus vulgaris
b. Pemphigus foliaceus
c. Paraneoplastic pemphigus
d. IgA pemphigus
e. Bullous pemphigoid

7. The following immunofluorescence pattern is seen with IgA. The patient has:

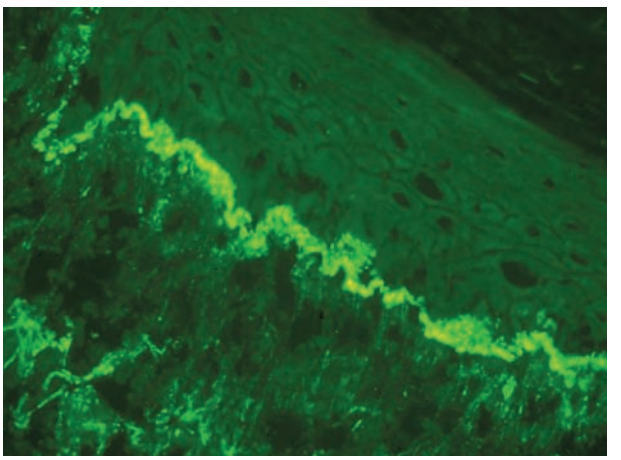


a. Dermatitis herpetiformis
b. Linear IgA bullous dermatitis
c. IgA pemphigus
d. Henoch-Schönlein purpura
e. Porphyria

8. A 45-year-old woman presents with photosensitivity and bullae. She has autoantibodies directed against:

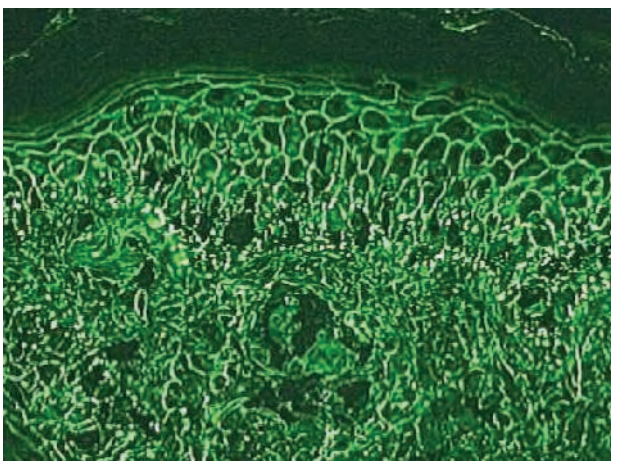
a. BP180
b. Desmoglein 3
c. Desmoglein 1
d. Desmogleins 3 and 1
e. Type VII collagen

9. The following immunofluorescence pattern is seen with IgM. The patient most likely has:



a. Bullous pemphigoid
b. Lupus erythematosus
c. Cicatricial pemphigoid
d. Epidermolysis bullosa acquisita
e. Dermatitis herpetiformis

10. The following immunofluorescence pattern is seen with IgA. The patient's autoantibodies are most likely to react against:

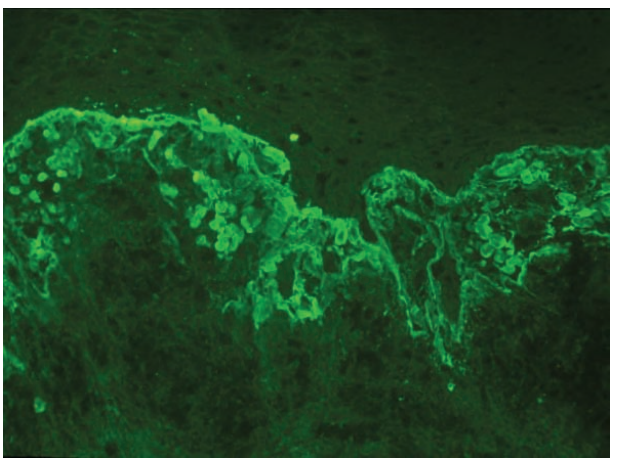


a. Desmoglein 3
b. Desmoglein 1
c. Desmocollin 1
d. Desmogleins 3 and 1
e. Periplakin

11. A 59-year-old woman has a linear dermal pattern with IgG on SSS and an associated malignancy. The diagnosis is most likely:

a. Paraneoplastic pemphigus
b. Antiepiligrin cicatricial pemphigoid
c. Bullous pemphigoid
d. Celiac disease
e. Epidermolysis bullosa acquisita

12. The following direct immunofluorescence photograph shows staining with fibrinogen. The most likely diagnosis is:



a. Bullous pemphigoid
b. Pemphigus vulgaris
c. Systemic lupus erythematosus
d. Epidermolysis bullosa acquisita
e. Lichen planus

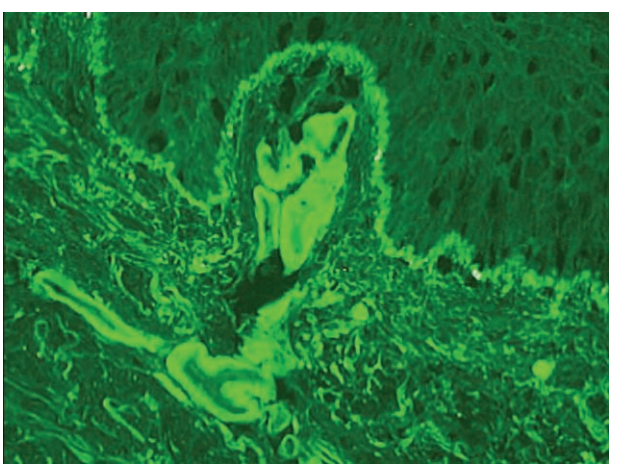
13. The most sensitive substrate for the diagnosis of paraneoplastic pemphigus by immunofluorescence is:

a. Rat bladder
b. Monkey esophagus
c. Guinea pig esophagus
d. SSS
e. Guinea pig lip

14. An 80-year-old patient presents with multiple tense bullae. The most important autoantibodies are targeting:

a. BP230
b. BP180
c. NC16A domain of BP180
d. NC1 domain of type VII collagen
e. Desmogleins 3 and 1

15. The following immunofluorescence pattern is seen with IgG. The most likely diagnosis is:



a. Leukocytoclastic vasculitis
b. Henoch-Schönlein purpura
c. Bullous pemphigoid
d. Porphyria
e. Epidermolysis bullosa acquisita

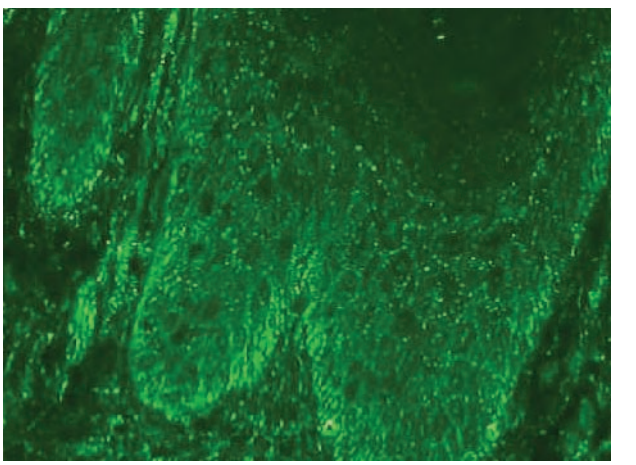
16. The target antigen in antiepiligrin cicatricial pemphigoid is:

a. Desmoglein 3
b. Desmoglein 1
c. Desmogleins 3 and 1
d. Laminin 5
e. Type VII collagen

17. A 45-year-old patient presents with an annular skin eruption characterized by peripheral vesicles. The characteristic immunofluorescence pattern seen on a direct immunofluorescence biopsy is:

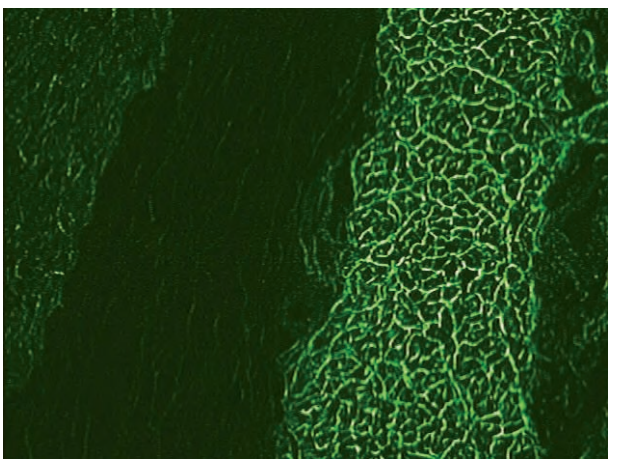
a. Linear BMZ staining for IgG
b. Cell surface staining for C3
c. Linear BMZ staining for IgA
d. Linear BMZ staining for C3
e. Granular BMZ staining for IgM

18. The following staining pattern for IgG on direct immunofluorescence is most commonly seen in:



a. Subacute cutaneous lupus erythematosus
b. Epidermolysis bullosa acquisita
c. Discoid lupus erythematosus
d. Pemphigoid gestationis
e. Cicatricial pemphigoid

19. The following staining pattern seen for IgA is characteristic of:



a. Pemphigus vulgaris
b. Celiac disease
c. Pemphigus foliaceus
d. Paraneoplastic pemphigus
e. Bullous pemphigoid

20. The following is a target antigen recognized in paraneoplastic pemphigus:

a. BP230
b. Type VII collagen
c. NC16A domain of BP180
d. Desmocollin 1
e. Periplakin

Answers

1. d
2. b
3. e
4. c
5. d
6. b
7. d
8. e
9. b
10. c
11. b
12. e
13. a
14. c
15. d
16. d
17. c
18. a
19. b
20. e

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