Vesiculobullous Diseases

Dylan Alston, DO   Robert Lin, DO
Sarah Gracie, DO   Gregory Polar, DO

Program Director: Alpesh Desai, DO FAOCD
South Texas Osteopathic Dermatology
University of North Texas Health Science Center
Basic Science

- Keratin intermediate filaments
  - K5, 14
- Hemidesmosome
  - Plectin
  - BPAG I
  - BPAG II
  - Integrins
- Lamina lucida
  - Anchoring filaments
    - Laminin 5
    - Type XVII collagen (BPAG II)
- Lamina densa
  - Type IV collagen
- Sub-Lamina Dense
  - Type VII collagen
Pemphigus Vulgaris

• Potentially fatal autoimmune bullous disease of the skin and mucous membranes

• Clinical Features:
  • Flaccid vesicles/bullae which rupture leaving large, painful erosions with bleeding and crusting
  • Erosions may also be in nose, mouth, larynx, pharynx, vagina
  • + Nikolsky sign, + Asboe-Hansen sign (pressure to surface of blister causes lateral spread)
Pemphigus Vulgaris
Pemphigus Vulgaris

• Autoantigen:
  • Cadherin family, desmosomal protein
    • Desmoglein 3 (mucosal)
    • Desmoglein 1 (mucocutaneous)

• Drug-induced:
  • Thiol drugs - penicillamine, captopril, enalapril, lisinopril, piroxicam
  • Pyrazolone derivatives - phenylbutazone, oxyphenylbutazone
  • Antibiotics - penicillin derivates, cephalosporin, rifampicin
Pemphigus Vulgaris

- Histology:
  - Suprabasal cleavage with acantholytic keratinocytes
  - “Tombstone Row” of basal cells attached to basement membrane
  - perivascular lymphocytes and eosinophils
  - acantholysis may involve hair follicles
Pemphigus Vulgaris

• Direct Immunofluorescence:
  • Intercellular IgG4 > C3 (net-like pattern in epidermis, more pronounced in lower epidermis)

• Indirect Immunofluorescence:
  • Monkey esophagus - Positive in 80–90% cases, titer correlates with disease activity

• Treatment:
  • Oral corticosteroid, methotrexate, azathioprine, mycophenolate mofetil, plasmapheresis, IVIG, rituximab
IgA Pemphigus

- Blistering disease with intraepidermal IgA deposits

- Clinical Features:
  - Subcorneal pustular dermatosis:
    - Serpiginous vesicles or pustules, may be associated with underlying IgA gammopathy
  - Intraepidermal neutrophilic type:
    - Flaccid pustules and bullae involving intertriginous locations which enlarge forming annular or polycyclic arrangement
IgA Pemphigus
IgA Pemphigus

- **Histology:**
  - Intraepidermal pustule or vesicles containing neutrophils, no acantholysis

- **Direct Immunofluorescence:**
  - Intercellular IgA deposition

- **Indirect Immunofluorescence:**
  - Positive in 50%, intercellular IgA

- **Treatment:**
  - Dapsone
  - Oral corticosteroid
Bullous Pemphigoid

• Most common autoimmune bullous disorder with chronic nature, typically in patients over 60

• Clinical Features:
  • Presents with initial urticarial lesions which evolve into large, tense bullae over medial thighs, groin, abdomen, and legs
  • +/- pruritus initially with tenderness
  • No constitutional symptoms unless extensive disease
  • 10-35% with oral involvement
Bullous Pemphigoid
Bullous Pemphigoid

• Autoantigen:
  • BPAG2: 180 kDa, transmembrane hemidesmosomal protein
  • BPAG1: 230 kDa, cytoplasmic plaque protein

• Drug Induced:
  • furosemide, NSAIDs, PCN derivates, gold, captopril, D-penicillamine, sulfasalazine
Bullous Pemphigoid

• Histology:
  • Subepidermal bulla with increased eosinophils and lymphocytes in papillary dermis, +/- neutrophils

• Direct Immunofluorescence:
  • Linear C3 and IgG at BMZ

• Indirect Immunofluorescence:
  • Positive in 60-80%
  • IIF on salt split skin shows binding to epidermal side (roof)
Bullous Pemphigoid

- Treatment: (Good Prognosis)
  - Oral corticosteroid
  - Steroid sparing agent (azathioprine, mycofenolate, etc)
  - Dapsone
  - TCN + nicotinamide
Linear IgA Bullous Dermatosis

- Rare, subepidermal blistering disease with IgA deposition at BMZ; likely identical to chronic bullous disease of childhood

- Clinical Features:
  - Annular or grouped vesicles/bullae over extensor extremities and buttock typically in herpetic arrangement, mucosal involvement
Linear IgA Bullous Dermatosis
Linear IgA Bullous Dermatosis

- **Autoantigen:**
  - LAD-1 (120 kDa, part of BPAG2); LAD-1 cleavage results in second autoantigen, LABD97 (97 kDa)

- **Drug Induced:**
  - Vancomycin, captopril, cephalosporin, PCN, NSAIDs, phenytoin, sulfonamide

- **Histology:**
  - Subepidermal bullae with rich neutrophilic infiltrate in papillary dermis (may resemble DH)
Linear IgA Bullous Dermatosis

- Direct Immunofluorescence:
  - Linear IgA (+/- C3) deposition at BMZ

- Indirect Immunofluorescence:
  - Positive in 60% cases, IIF on (SSS) shows binding to epidermal side of split (roof)

- Treatment:
  - Dapsone or sulfapyridine
  - Low dose oral corticosteroid
Dermatitis Herpetiformis

- Recurrent chronic pruritic disease associated with gluten sensitive enteropathy
- Clinical Presentation:
  - Erythematous grouped papules or vesicles over elbows, knees, buttocks, intensely pruritic, primary lesions not visible due to excoriations
- Associated with:
  - HLA-DQ2 (strongest)
  - HLA-B8
Dermatitis Herpetiformis

• Autoantigen:
  • Epidermal Transglutamininase (TG-3)
  • Tissue Transglutaminase (Endomysial)

• Labs:
  • Anti-gliadin/antiendomysial antibodies in DH/celiac disease
Dermatitis Herpetiformis

• Histology:
  • Neutrophilic microabscesses in dermal papillae
  • +/- subepidermal vesicles

• Direct Immunofluorescence:
  • Granular IgA>C3 deposition in dermal papillae

• Indirect Immunofluorescence:
  • Negative
Dermatitis Herpetiformis

• Comorbidities:
  • Increased incidence thyroid disease (Hashimoto’s thyroiditis)
  • Insulin Dependent Diabetes Mellitus
  • Enteropathy-associated T cell lymphoma

• Treatment:
  • Dapsone (immediate skin improvement)
  • Referral to GI (>90% with gluten sensitive enteropathy and risk of small bowel lymphoma)
Biopsy Techniques

- Bullous Pemphigoid & Pemphigus Vulgaris
  - Biopsy the edge of an active blister or erythematous skin
  - Avoid having the epidermis come off, ulcers and distal extremities
- Dermatitis Herpetiformis
  - Biopsy normal appearing skin 3 mm from a blister
  - May require multiple biopsies
  - Avoid active lesions
- Specify to dermatopathologist whether biopsy comes from involved or uninvolved skin