• We have no relevant disclosures
Topics of Discussion

• Subcorneal Vesiculobullous Disorders
  – Pemphigus foliaceous
  – Pemphigus erythematosus
  – Subcorneal pustular dermatosis (Sneddon-Wilkinson Disease)
  – Acute Generalized Exanthematous Pustulosis

• Intraepidermal Vesiculobullous Disorders
  – Pemphigus vulgaris
  – Pemphigus vegetans
  – Hailey-Hailey Disease
  – Darier’s Disease
  – Grover’s Disease
  – Paraneoplastic Pemphigus
  – IgA Pemphigus
Topics of Discussion (Continued)

• Pauci-inflamatory Subepidermal Vesiculobullous Disorders
  – Porphyria Cutanea Tarda (PCT)
  – Epidermolysis Bullosa Acquisita (EBA)
  – Pemphigoid Gestationis

• Inflammatory Subepidermal Disorders
  – Bullous Pemphigoid
  – Cicatricial Pemphigoid
  – Dermatitis Herpetiformis
  – Linear IgA
Subcorneal Vesiculobullous Disorders

- Pemphigus foliaceous
- Pemphigus erythematosus
- Subcorneal pustular dermatosis (Sneddon-Wilkinson Disease)
- AGEP
Pemphigus Foliaceous

- IgG Ab to desmoglein 1 (Dsg-1, 160 kDa)
- Peak onset middle age, no gender preference
- Endemic form – Fogo selvagem in Brazil and other parts of South America
- Pemphigus erythematous - Localized variant of pemphigus foliaceous with features of lupus erythematous
Pemphigus Foliaceous

Clinical

Overview
Pemphigus Foliaceous
Pemphigus Foliaceous

Net-like deposition of IgG within epidermis
Pemphighus Foliaceous

- Topical and systemic steroids
- Mycophenolate mofetil
- Azathioprine
- Dapsone
- Rituximab
- IVIG
Subcorneal Pustular Dermatosis

- Aka, Sneddon-Wilkinson Disease
- Etiology unclear
- Cultures from the pustules are sterile
- More common in women and >40 y/o
- Some cases are associated with a monoclonal gammopathy (usually IgA)
Subcorneal Pustular Dermatosis
Subcorneal Pustular Dermatosis
Subcorneal Pustular Dermatosis

- Negative – if positive, most likely IgA Pemphigus
Subcorneal Pustular Dermatosis

- Treatment of choice: Dapsone
- Alternatives: retinoids, NBUVB, colchicine, topical steroids, cyclosporine
Acute Generalized Exanthematous Pustulosis (AGEP)

- Acute febrile pustular eruption
- Causes: Drugs, Hg ingestion, bacterial/viral infection
- Pustules begin on face/intertriginous areas—> widespread within a few hours
- B/W reveals marked neutrophilia; pustules may show heavy S. aureus on culture
AGEP
AGEP
AGEP

• Negative
AGEP

- Symptomatic treatment
- Antihistamines
- Topical tx of *S. aureus* with mupirocin
- Reassurance
Intraepidermal Vesiculobullous Disorders

- Pemphigus Vulgaris
- Hailey-Hailey
- Darier’s Disease
- Grover’s Disease
- Paraneoplastic Pemphigus
- IgA Pemphigus
Pemphigus Vulgaris

- Ab against desmoglein 1 and/or 3

- Drug-induced: thiol drugs (penicillamine, captopril, enalapril, lisinopril, piroxicam), pyrazolone derivatives (phenylbutazone, oxyphenylbutazone), antibiotics (penicillin derivatives, cephalosporin, rifampicin)

- Pemphigus Vegetans - Rare vegetative variant of Pemphigus Vulgaris (Neumann and Hallopeau type)
Pemphigus Vulgaris
Pemphigus Vegetans

Overview

Clinical

H&E

DIF

Treatment
Pemphigus Vulgaris
Pemphigus Vulgaris

• Treatment:
  – Oral corticosteroid
  – Methotrexate
  – Azathioprine
  – Mycophenolate mofetil
  – Plasmapheresis
  – IVIG
  – rituximab
Hailey- Hailey

- Benign familial pemphigus
- AD, ATP2C1 gene (encodes Golgi-associated Ca2+ ATPase hSPCA1), results in abnormal intracellular calcium signaling
- Onset typically 2\textsuperscript{nd} to 3\textsuperscript{rd} decade
- Presents with flaccid vesicles initially on erythematous base over intertriginous areas, ruptures easily, and gives rise to macerated or crusted erosions
Hailey- Hailey
Hailey- Hailey
Hailey- Hailey
Hailey- Hailey

- Negative DIF
Hailey- Hailey

- Avoid triggers (sweating, friction, tight clothing)
- Topical corticosteroids
- Topical antibiotics (clindamycin, mupirocin)
- Topical calcineurin inhibitors
- Oral antibiotics (tetracycline, minocycline)
- Anticholinergics (glycopyrrolate)
- Intra-lesional corticosteroids
- Botulinum toxin
- Lasers (CO2, Er:YAG, PDL)
Darier’s Disease

- AD, ATP2A2; SERCA2 calcium-dependent ATPase
- Impaired cell cohesion, increased apoptosis
- Onset puberty (6-20 yrs)
  - Chronic & unremitting
- Exacerbated by sun, heat, lithium therapy
- Superinfection - bacterial, fungal, HSV
  - Kaposi’s varicelliform eruption - vesicular eruption w/ fever
Darier’s Disease

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Darier’s Disease

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Treatment
Darier’s Disease
Darier’s Disease

- Negative DIF
Darier’s Disease

- Light-weight clothing and sunscreen
- Antimicrobial cleanser, keratolytics
- Topical steroids, topical retinoids
- Isotretinoin and acitretin
  - Very effective however relapse when stopped
- Prompt oral acyclovir or valacyclovir (HSV)
Grover’s Disease
(Transient Acantholytic Dermatosis)

- Intensely pruritic papulovesicular eruption occurring as scattered eroded lesions usually on the trunk of a well-appearing male > 40 years old.
- Self limited variant (transient acantholytic) vs chronic relapsing variant (persistent acantholytic)
- Associated with AD, ACD/ICD, and astematotic eczema
- Exacerbated by heat, friction and sweat
Grover’s Disease

Clinical

Overview
Grover’s Disease

Overview
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Treatment
Grover’s Disease

• Negative DIF
Grover’s Disease

• Avoidance of exacerbating factors, loose clothing, topical steroids, topical antibiotics, calcipotriol, urea, zinc oxide, antihistamines

• Refractory cases may respond to dapsone, isotretinoin, oral corticosteroids, PUVA or NBUVB
Paraneoplastic Pemphigus

- First sign: Severe stomatitis
- Erosions and ulcerations can affect oropharynx and extend onto vermilion lip
- Palm and soles involvement is common
- Pseudomembranous conjunctivitis
- Bronchiolitis obliterans
Paraneoplastic Pemphigus

- Associated underlying neoplasms
  - Non-Hodgkin lymphoma (40%)
  - CLL (30%)
  - Castleman’s disease (10%)
  - Malignant and benign thymomas (6%)

- Autoimmunity
  - IgG autoantibodies target members of the plakin family and desmogleins
  - Autoantibodies detected by indirect immunofluorescence on rodent urinary bladder epithelium
Paraneoplastic Pemphigus

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Paraneoplastic Pemphigus

**Overview**

**Clinical**

**H&E**

**DIF**

**Treatment**

Suprabasilar clefting with "tombstoning"

Interface process with satellitosis and necrotic keratinocytes
Paraneoplastic Pemphigus

Overview

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Treatment
Paraneoplastic Pemphigus

- Resistant to most therapies
- Treatment is aimed at the underlying malignancy
- Reduction in antibodies
  - Corticosteroids, azathioprine, cyclosporine, photopheresis, mycophenolate mofetil, IVIG
- Rituximab
  - CD20 monoclonal antibody, has been used to treat cases with an underlying CD20+ lymphoma
IgA Pemphigus

- Intraepidermal IgA deposits, 2 clinical types
  - Subcorneal pustular dermatosis (SPD) variant
    - IgA ab to desmocollin 1
  - Intraepidermal neutrophilic (IEN) type
    - IgA ab to desmoglein 1 or 3
- Avg onset 6th decade, slight female predominance
IgA Pemphigus
IgA Pemphigus
IgA Pemphigus

Subcorneal pustule
IgA Pemphigus
IgA Pemphigus

- Oral and topical corticosteroids
- Dapsone
- Isotretinoin/acitretin
- Mycophenolate mofetil
- Adalimumab
Subepidermal vesiculobullous disorders: pauci-inflammatory subepidermal conditions

- Porphyria cutanea tarda
- Epidermolysis bullosa acquisita
Porphyria cutanea tarda (PCT)

- Acquired (T I) or AD (T II)
- Deficiency of uroporphyrinogen decarboxylase in the heme biosynthetic pathway (enzyme 5 of 8)
- Liver disease major causative/contributing factor
- Skin lesions develop due to sun exposure (400-410 nm)
- Urine “glows” - orange-red fluorescence with acetic acid/10% HCl
PCT

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PCT

- Sun avoidance/ Zinc Oxide or Titanium Dioxide
- Eliminate ETOH
- Serial phlebotomy +/- chelation therapy
- Antimalarials: hydroxychloroquine
Epidermolysis Bullosa Acquisita (EBA)

- Rare acquired autoimmune blistering disease to NC-1 domain of collagen VII
- Non-inflammatory or pauci-inflammatory tense bullae affecting trauma-prone extensor skin surfaces
- Lesions heal with significant scarring and milia
- Resembles the inherited form of dystrophic epidermolysis bullosa with lack of family history
- Exclusion of all other bullous diseases
EBA

Overview

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Treatment
EBA
EBA
EBA

- Supportive care
- Systemic steroids
- Dapsone
- Imuran
- Cellcept
- IVIG, cyclosporine, methotrexate, rituximab, colchicine, photopheresis & anti-TNFα biologics for severe or recalcitrant disease
Pemphigoid Gestationis

- Self-limited, rare: 1 in 50,000 pregnancies
- Typically 3rd trimester or immediate postpartum period
- Antibody: anti-BP180 (NC16A domain of BP 180)
- HLA-DR3, HLA-DR4 associations
- Maternal risk: Grave’s disease
- Fetal risk: prematurity, small gestational age, up to 10% risk of skin involvement
Pemphigoid Gestationis

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Pemphigoid Gestationis

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Treatment
Pemphigoid Gestationis

- 0.5 mg/kg of prednisolone daily; taper as soon as blister formation suppressed
- Delivery usually precipitates flare → increase dose
- Cyclosporine
- Mild cases: potent topical steroids + emollients & antihistamines (usually ineffective)
Inflammatory Subepidermal Conditions

- Bullous pemphigoid
- Cicatricial pemphigoid
- Dermatitis herpetiformis
- Linear IgA dermatosis
Bullous Pemphigoid

• Most common autoimmune bullous disorder with chronic nature
• Typically seen in patients over age 60
• Autoantigens: BPAG2 (180 kDa) and BPAG1 (230 kDa)
• 10-35% with oral involvement
• Drug-induced: furosemide, NSAIDs, PCN-derivatives, phenactin, gold, potassium iodide, captopril, enalapril, D-penicillamine, sulfazalazine
Bullous Pemphigoid
Bullous Pemphigoid
Bullous Pemphigoid

- Oral corticosteroids
- Steroid sparing agents
  - Azathioprine
  - Mycophenolate mofetil
  - Thalidomide
  - Methotrexate
  - Cyclophosphamide
- Tetracycline + nicotinamide
- Dapsone
- IVIG for refractory cases
Cicatricial Pemphigoid

• Rare autoimmune disease involving the mucous membrane → scarring

• Autoantigens:
  – BPAG2 (180 kDa): mucosa & skin
  – β4 (subunit of α6β4): pure ocular form
  – Laminin 5 (epiligrin): increased risk of malignancy
Cicatricial Pemphigoid

- Drug-induced (similar to BP)
  - Thiol-containing drugs
  - Captopril, gold thiosulfate, D-penicillamine
  - NSAIDS (Indomethacin)
  - β-blockers (practolol)
  - Clonidine
  - Sulfadoxine
Cicatricial Pemphigoid

Overview

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Treatment
Cicatricial Pemphigoid
Cicatricial Pemphigoid
Cicatricial Pemphigoid

• Treatment of choice:
  – Dapsone

• Alternatives:
  – Topical/intralesional/oral corticosteroids
  – Cyclophosphamide
  – Azathioprine
Dermatitis Herpetiformis

• Aka: Duhring’s Disease
• Recurrent pruritic chronic disease associated with gluten-sensitive enteropathy
• Gluten: storage proteins found in wheat, rye, barley
  – Gliadin: soluble fraction; likely antigenic component
• Autoantigen: epidermal transglutaminase (TG-3), tissue transglutaminase (endomysial)
• Labs: anti-gliadin/anti-endomysial antibodies
Dermatitis Herpetiformis

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Dermatitis Herpetiformis

- Dapsone
- Sulfapyridine
- Gluten-free diet
- Referral to Gastroenterology: gluten-sensitive enteropathy and increased risk of small bowel lymphoma
- Referral to Endocrinology: increased incidence of thyroid disease (Hashimoto’s thyroiditis) and IDDM
Linear IgA Bullous Dermatosis

- Rare; likely identical to chronic bullous disease of childhood
- Autoantigens:
  - LAD-1 is cleaved and yields LABD97
- Drug-induced
  - Vancomycin, captopril, cephalosporin, PCN, NSAIDs, phenytoin, sulfonamide
Linear IgA Bullous Dermatosis

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Linear IgA Bullous Dermatosis

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Treatment
Linear IgA Bullous Dermatosis
Linear IgA Bullous Dermatosis

- Dapsone
- Sulfapyridine
- Prednisone
- Azathioprine
- Mycophenolate mofetil
Conclusion

- Vesiculobullous diseases can be inherited or acquired
- These conditions may be antibody or cell-mediated
- The involved intracellular adhesion molecules determine subcorneal, intraepidermal or subepidermal splitting
- Direct immunofluorescence and salt splitting can help determine diagnosis