Pemphigus & Pemphigoid from the Microscope to the Bedside
Learning Objectives

- Pemphigus vulgaris
- Paraneoplastic pemphigus
- Bullous pemphigoid
  - Pathophysiology, clinical features, histology
  - Evaluation and management
Pemphigus and Pemphigoid: Overview

- Distinct set of autoimmune blistering disorders
- Autoantibodies target cell adhesion molecules
- Disadhesion results in chronic blistering
- Level of split determines the major category
  - intraepidermal split: pemphigus group
  - subepidermal split: pemphigoid group
Classification

- Pemphigus vulgaris
  - Pemphigus vegetans
- Pemphigus foliaceus
  - Pemphigus erythematousus (Senear-Usher)
  - Endemic Pemphigus foliaceus (Fogo Selvagem)
- Paraneoplastic pemphigus
- IgA pemphigus
- Drug-induced pemphigus
Pemphigus vulgaris
Epidemiology

- Most common form of pemphigus
- Both sexes affected equally
- Mean age of onset is 50-60
- HLA class II genes confer susceptibility
  - ~0.75-5 new cases per million per year
  - ~16-32 in Ashkenazi Jewish population
IgG autoantibodies target desmosomal adhesion molecules (desmogleins)

↓

Loss of cell to cell adhesion

↓

Acantholysis

↓

Blistering
Desmogleins

- Cadherin superfamily
  - Calcium-dependent adhesion proteins

- 3 isoforms: desmoglein 1-3
  - 1 (160 kd): superficial layers of SSE
  - 2: all desmosome-possessing tissues
  - 3 (130 kd): suprabasilar layers of SSE
Desmoglein Compensation Theory

- Desmoglein 1 and 3 expression in skin and mucosa differ and are compensatory.
- The specific desmoglein(s) targeted determines the localization of blisters.
- The clinical features of pemphigus are determined by the autoantibody profile.

Skin and mucosa:
Desmoglein Expression Patterns: Mucosa

- **Desmoglein 1**
  - low quantity
- **Desmoglein 3**
  - high quantity
Desmoglein Expression Patterns: Skin

- **Desmoglein 1**
  - superficial layers
- **Desmoglein 3**
  - basal layers
Mucosal Dominant: Desmoglein 3
Mucocutaneous:
Desmogleins 1 and 3
Diagnostic Criteria

- **Clinical findings**
- **Histopathology**
- **Autoantibodies**
Clinical Features

- Insidious onset
- Oral erosions
- Skin blisters/erosions
- Remissions/relapses
- Mucosal Dominant
  - Dsg 3
- Mucocutaneous
  - Dsg 3 and 1
- Painful oral erosions
- Presenting sign
- Irregular
- Ill-defined borders
- Blisters are rare
- Buccal, palatine and gingival mucosa
Any mucosa covered with SSE is vulnerable
Flaccid vesicles/bullae → erosions
Nikolsky and Asboe-Hansen Signs
Head/neck $\rightarrow$ trunk/flexures $\rightarrow$ generalizes
Biopsy Material

- H&E: early, intact vesicle
- DIF: normal, perilesional skin
- IIF: serum
Direct Immunofluorescence

- Detects *in vivo* bound IgG on patients’ skin or mucosa
- High sensitivity
- Intercellular, suprabasilar IgG4
- Variable C3 deposition
- No deposition at BMZ
Indirect Immunofluorescence

- Examines patients’ sera for circulating Ab
- Autoantibodies specifically bind to SSE
  - Monkey esophagus substrate
- 80-90% with active disease have circ Ab
- Correlates well with disease activity
ELISA

- Detects antibodies to desmogleins in serum
- Serum added to desmoglein-coated plates
- Enables serological distinction between subtypes
- Scores parallel clinical fluctuations
- Sensitive and specific
- *If Ab levels are high, results are not quantitative*
• Relentless and progressive
• < 50%: sustained med-free remission
• Loss of epidermal barrier function
  • Metabolic imbalance; superinfection
• Mortality, pre-prednisone
  • 50% at 2 years, ~100% at 5 (sepsis)
• Mortality today is < 5%
  • Often due to complications of therapy
Treatment Objectives

*Reduce autoantibody synthesis*

*Achieve long-term remission*

*Minimize side effects of therapy*
Management Approach

1. Confirm the diagnosis
2. Assess for comorbid conditions
   - PUD, TB, DM, HTN, lipids, osteoporosis
3. Baseline evaluation
   - CBC, CMP, HBV/HCV, HIV, CXR/PPD
   - Bone densitometry
   - Serum antibodies by IIF or ELISA
   - Pneumonia and influenza vaccine
Management Approach

4. Systemic treatment
5. Wound care
6. Supportive care
7. Close clinical/laboratory monitoring
Management Principles

**Early systemic treatment is key**
- Less chance of *epitope spreading*
- Greater chance of better control and prolonged remission

Limited disease **will** generalize
Management Principles

Goal: Reduce autoantibody production

- Limited number of agents
- Specific antibody suppression is impossible
- Basis of therapy is *nonspecific immunosuppression*
Treatment Efficacy

1. Clinical parameters
   - New lesions
   - Healing of existing lesions
   - Nikolsky sign

2. Laboratory monitoring
   - Antibody levels via IIF
   - Less reliable than clinical exam
   - Goal: absence of circulating and bound Ab
Treatment Considerations

- The disease
  - Severity, duration, sites of involvement
- The patient
  - Age, comorbidities, drug tolerance, quality of life
- The drugs
  - Mechanism, onset of action, safety, cost, practicality
1. Get control
   ✓ Correct drug at the correct dose
2. Keep control
   ✓ Steady dosing during healing
3. Maintain control
   ✓ Lowest dose necessary
Combination Therapy

systemic corticosteroids + systemic immunosuppressives ↓ maximizes efficacy & minimizes side effects
Therapeutic Choices

Rapid Onset
- Systemic steroids
- IVIG
- Plasmapheresis

Delayed Onset
- Immunosuppressives
  - Azathioprine
  - Mycophenolate
  - Cyclophosphamide
  - Methotrexate
  - Others...
Get Control

Prednisone 1 mg/kg/d
- 1st line initial therapy
- Alone or in combo
- Dosing frequency varies
- Goal: halt disease progression/remission
Adjuvant Therapies

- If disease is progressing despite prednisone or as initial adjuvant therapy with prednisone
  - Mycophenolate mofetil (40 mg/kg/d; 2-3g/d)
  - Azathioprine (2-4 mg/kg/d)
  - Cyclophosphamide (2-3 mg/kg/d)
If improving / remitting

- Maintain regimen until most lesions have healed
- Continue nonsteroidal agent
- Taper steroids

If not improving / deteriorating

- Assure compliance, look for infection
- Continue prednisone at max dose
- Transition or dose-adjust immunosuppressive
- Consider plasmapheresis, IVIG
Keep Control

- Maintain the meds/dosages needed to control disease until lesions have healed
- Slow healing signals inadequate treatment or complicating factors
Maintain Control

- Goal: off all drugs
- Taper meds to lowest suppressive dose
- Taper one medication at a time
- Clinical and serologic factors guide taper
Prednisone

- Achieves *early* control in most cases
- Long term control at this dose is rare
- **Majority** will require additional agents
- BID: better control; more SE (HPA axis)
- qOD: less side effects (except osteoporosis)
Prednisone Tapering
(if use exceeds 2-3 weeks)

- Change dose no more than once weekly
- Decrease by 10 mg/d until dose is 40 mg/d
- From 40-20 mg, taper by 5 mg/week
- From 20-10 mg, taper by 2.5 mg/week
Prednisone Tapering

- Alternate day dosing
  - can start at 40mg
  - + and - by 10 on alternate days until qod
    - 50/30 x 1 week
    - 60/20 x 1 week
    - 70/10 x 1 week
    - 80 qod, then taper per prior schedule
Prednisone Tapering

- Below 10 mg, taper by 1mg/week until 3-5 mg/day
- Check 8 am serum cortisol
  - >10ug/dl: continue taper to off
  - <10ug/dl: continue current dose, check monthly
- Stress dose steroids required for one year
Prednisone Prophylaxis Regimens

- **Osteoporosis**
  - Calcium 1500 mg/d and vit D 800 IU/d
  - Bisphosphonates (alendronate)
  - HRT per PCP
  - Bone densitometry every 6-12 months
  - Alternate day dosing does not decrease risk
Prednisone Prophylaxis Regimens

- Pneumocystis carinii pneumonia
  - TMP-SMX if 15mg/d pred used > 2 months
  - Alternate day dosing decreases risk
- Screen regularly for:
  - Diabetes, hypertension, peptic ulcers
  - Glaucoma, cataracts
- Alternate day dosing does not protect against cataracts
Mycophenolate mofetil

- Purine synthesis inhibitor: B and T cells
  - Dosing: 35-45 mg/kg/d (2-3 g/d ÷ BID)
  - Onset of action: 2-3 months
  - Reports of efficacy as *monotherapy*
  - Favorable safety profile: GI distress
  - Neutropenia, infection, lymphoma
Azathioprine

- Purine synthesis inhibitor
- Complex metabolism
  - Dosing: 2-4 mg/kg/day
  - Effective as *adjuvant* therapy
- Safety profile is “middle of the road”
  - versus cytoxan and MMF
Azathioprine

- Bone marrow suppression → leukopenia
- Hepatotoxicity; GI intolerance
- Hypersensitivity syndrome; drug fever
- Advantages for younger patients:
  - Lower lifetime risk of malignancy and sterility
Azathioprine → 6-mercaptopurine

- **Hypoxanthine-Guanine Phosphoribosyltransferase**
  - Anabolizes 6-MP to **active** purine analogs

- **Thiopurine Methyltransferase**
  - Catabolizes 6-MP to **inactive, nontoxic metabolites**
  - Functional enzyme assay for level of activity
  - Low activity: ↑ risk of pancytopenia
  - High activity: ↓ efficacy

- **Xanthine Oxidase**
  - Catabolizes 6-MP to **inactive, non-toxic metabolites**
  - Allopurinol inhibits
Cyclophosphamide

- Alkylates DNA → apoptosis
- Reduces B > T cells
- ↓ total antibody production
- Differentiated lymphocytes targeted
- Dosing: 2-3 mg/kg/d, single am dose
- Excellent adjuvant efficacy in pemphigus
Cyclophosphamide

Unfavorable safety profile

- Significant short term risks:
  - Myelosuppression → leukopenia
  - Hemorrhagic cystitis → aggressive hydration

- Long term risks:
  - Leukemia, lymphoma, bladder cancer
  - Amenorrhea; azoospermia → sterility
Plasmapheresis

- Physically removes serum antibodies
- Efficacy is controversial
- Not recommended as 1\textsuperscript{st} line therapy
- Results in \textit{rebound increase in antibodies}
- Use \textit{in combo} with an alkylating agent
Intravenous Immunoglobulin

- Purified human IgG from pooled plasma
- 2 g/kg/cycle
- 3 = doses over 3 days
- q month until remission +/- maintenance
- Exact MOA unknown
- Baseline labs/pre-Rx meds
- AE: thrombosis, anaphylaxis, infectious risk
IVIg Indications
(Arch Dermatol. 2003;139:1051-1059)

- Failure of conventional therapy
- Significant AE of conventional therapy
- Contraindications to conventional therapy
- Progressive or uncontrolled disease
- Age and pregnancy
Other Agents

- **Chlorambucil**
  - Alkylating agent, toxic

- **Methotrexate**
  - Inconsistent, poor as monotherapy

- **Cyclosporine**
  - Adjuvant therapy
  - Jury is still out

- **Immunoablative cyclophosphamide**

- **Gold**
  - Inferior efficacy
  - No carcinogenicity/infertility

- **Dapsone**
  - Fairly effective in PF
  - Unclear efficacy in PV

- **Anti-CD20 mAb** (rituximab)
Paraneoplastic Pemphigus
Autoimmune blistering disease associated with an underlying neoplasm
(B cell lymphoproliferative disorder)

Mucocutaneous ulcerations

Polymorphous eruption
Mucosal Ulcerations

- Severe intractable stomatitis
- Pseudomembranous conjunctivitis
  - Scarring, obliteration of conjunctival fornices
- All mucosal sites are vulnerable
  - Esophageal, tracheobronchial $\Rightarrow$ morbidity
Polymorphous Skin Lesions

- Blisters and erosions
- Targetoid (EM-like)
- Lichenoid
- Palms and soles
  - distinguish PNP from PV
- Ulcerative paronychia
Associated Neoplasms

- 2/3: pre-existing neoplasm
- 1/3: neoplasm detected after presentation
- 3 most common neoplasms:
  1. Non-Hodgkin’s Lymphoma (42%)
  2. Chronic Lymphocytic Leukemia (29%)
  3. Castleman’s Disease (10%)
Associated Neoplasms

- Thymoma, malignant or benign (6%)
- Waldenstrom’s Macroglobulinemia (6%)
- Spindle Cell Sarcoma (6%)

Striking absence of association with common tumors
Target Antigens

Plakin Gene Family

- 500 kd Plectin
- 250 kd Desmoplakin 1
- 230 kd BP Antigen 1
- 210 kd Envoplakin
- 190 kd Periplakin

Undetermined

- 170 kd transmembrane

Desmosomal Antigens

- 160 kd Desmoglein 1
- 130 kd Desmoglein 3
Theories of Pathogenesis

- Antitumor immune response cross reacts with epithelial proteins

- Cytokine secretion by tumor induces B cell differentiation and Ig production, resulting in autoimmunity
H&E: vesicular lesions

- Epidermal acantholysis
- Suprabasilar clefting
- Keratinocyte necrosis and dyskeratosis
- Vacuolar interface change in the basal layer
- Exocytosis of inflammatory cells
Direct Immunofluorescence

- Epidermal intercellular IgG/C3 and granular-linear complement along BMZ
- False negatives are common
  - Repeat biopsies are often necessary
Indirect Immunofluorescence

- Circulating IgG binds SSE and non-SSE
- Substrates:
  - Monkey esophagus: SSE
  - Rodent bladder: NSSE
Lane, J. E. et al. Pediatrics 2004;114:e513-e516
Lane, J. E. et al. Pediatrics 2004;114:e513-e516
Diagnostic Criteria

- Clinical findings
- Histopathology
- Pathogenic Autoantibodies
Paraneoplastic Pemphigus and Benign Neoplasms

- Remove resectable neoplasms
- Substantial clearance or complete remission in the majority
- Time to clearance is variable (6-18 mos)
Paraneoplastic Pemphigus and Malignant Neoplasms

- Prognosis is grave
- 90% mortality despite aggressive Rx
- Course of autoimmunity ≠ malignancy
- Rx of neoplasm ≠ clearance of disease
Paraneoplastic Pemphigus and Malignant Neoplasms

- Skin responds first
- Mucosal disease is particularly refractory
- Pulmonary involvement is prognostic
  - Progressive respiratory failure
  - Cause of death in ~30%
Paraneoplastic Pemphigus and Malignant Neoplasms

- Combination therapy is best
- Prednisone plus adjunctive agent
  - High dose immunoablative cyclophosphamide
  - Anti-CD20 mAb (rituximab)
  - Plasmapheresis
Bullous Pemphigoid
Bullous Pemphigoid

- Primarily affects the elderly
- Antibodies target hemidesmosomal proteins
- Subepidermal separation $\rightarrow$ tense bullae
- Wide clinical spectrum
Major Pemphigoid Variants

- Bullous Pemphigoid
- Gestational Pemphigoid
- IgA Pemphigoid
- Mucous Membrane Pemphigoid
- Most common AIBD
- Onset typically after 60
- Rarely in children
- No geographic nor gender predilection
- HLA Class II alleles may predispose
Antigenic Targets

- Components of the hemidesmosome
  - Mediate epithelial-stromal adhesion
  1. BP Ag 1, 230 kd
  2. BP Ag 2, 180 kd (type XVII collagen)
- Cytoplasmic protein, plakin family
- Transmembrane protein with a collagenous extracellular domain
Pathogenesis

Humoral and cellular immune responses

- Autoreactive CD$_4^+$ T cells respond to BP 180
- Cytokine cascade stimulates B cells
- Plasma cells $\rightarrow$ pathogenic autoantibodies
Pathogenesis

- Circulating autoantibodies bind:
  - BP Ag 2, NC16A domain (extracellular)
  - BP Ag 1, C-terminal region (intracellular)

- Complement activation $\rightarrow$ inflammatory cascade $\rightarrow$ tissue disadhesion $\rightarrow$ blistering
Non-bullous Phase

- Nonspecific and of variable duration
- Intractable pruritus is common
- Wide spectrum of clinical presentations
- Urticarial, eczematous, or papular lesions
- May remain as sole disease manifestation
Bullous Phase

- Tense bullae on nl or inflamed skin
- Flexures, lower trunk, thighs, legs
- Urticarial and infiltrated papules/plaques
- Annular or figurate patterns
• Oral mucosa involved in ~10-30%
• Other mucosal sites rarely involved
• Peripheral blood eosinophilia in ~50%
Clinical Variants

- Localized
- Dyshidrosiform
- Vesicular
- Pemphigoid Nodularis
- Erythrodermic
- Gestational
- Childhood
Disease Associations

Malignancy
- Likely related to advanced age
- Screen if symptomatic/atypical presentation

Autoimmune Disorders
- Genetically predisposed?
Disease Associations

Chronic Inflammation/Trauma/Burns
- Epitope spreading

Drugs
- Trigger in genetically predisposed?
- Modify immune response or alter antigens
H&E

- Eosinophilic spongiosis
- Subepidermal
- Blister cavity:
  - Fibrin/variable
  - Eosinophils
- EM:
  - split occurs at the *lamina lucida*
Direct Immunofluorescence

Perilesional skin

- Linear IgG and/or C3 along BMZ
Indirect Immunofluorescence

Serum:
- 60-80% have detectable circulating IgG / C3
- Variable correlation with clinical disease

Salt split nl human skin:
- Substrate of choice
- Ab bind epidermal side
Course & Prognosis

- Chronic with exacerbations/remissions
- Self-limited, remits within 5-10 years
- Morbidity limited but *can* be significant
  - Intractable pruritus, impetiginization, fluid/electrolytes
  - Quality of life
- Mortality
  - Estimated mortality during 1st year: 10-40%
  - Age and drug-related side effects contribute
Treatment Principles

- Consider the patient
- Aggressive vs. conservative approach
- Balance risk to benefit ratio of therapies
- Aim for reduction, not complete suppression
- Inflammation is a key pathogenic element
- Utilize synergistic mechanisms
  - Decrease antibody synthesis
  - Decrease inflammation
Treatment Options
Corticosteroids: 1st line

- Anti-inflammatory & immunosuppressive
- Intraleisonal
- Topical
- Systemic
  - 0.5-1 mg/kg/d (lean body weight)
If disease is limited or steroids are not tolerated/ contraindicated

Non-steroidal anti-inflammatory drugs:
- Antimetabolites (methotrexate)
- Calcineurin Inhibitors (cyclosporine)
- Antibiotics (tetracycline, erythromycin)
- Dapsone
Good Response:

• Healing of lesions
• Cessation of new blisters

Begin steroid taper
Poor Response:

- Persistent or progressive

Continue steroid

add steroid sparing agent

- MMF
- Azathioprine
- Alkylating agents rarely
Monitoring and Follow-Up

- Until remission is achieved and off all meds
- Frequently to review efficacy/adverse effects
- Clinical is best, IF is of limited value