Bullous pemphigoid – 1. Considering the diagnosis

- Clinical features -
  - Large tense blisters on erythematous/urticarial skin
  - Heals without scarring, although milia can be seen
  - +/- pruritus (usually+)

- Urticarial type lesions
  - Often present in early disease
  - Eczematous, serpiginous, targetoid, EM like lesions have also been reported

- Dyshidrotic like lesions
  - Localized palmar and/or plantar disease
  - “dyshidrosiform pemphigoid”

- Localized
  - Most commonly lower extremities
  - May remain localized or progress to generalized BP
  - Often responds to topicals alone
Bullous pemphigoid – 1. Considering the diagnosis

- Mucosal involvement
  - Mucosal disease is rare in bullous pemphigoid (less than 10%)
  - Typically associated with classic bullous pemphigoid findings on the skin
  - Limited to the oral mucosa
  - Rare reports of esophageal involvement

Morkenburger K et al. Gastroenterology. 2010;138:3.

Bullous pemphigoid – 1. Considering the diagnosis

- Epidemiology
  - Incidence ~7.43 per million per year
  - Increases with age
  - Has increased over the years (localized disease?)
  - Mortality ranges from 1.1-41% at 1 year
  - Poor prognosis – older age (over 80yo), higher dose of systemic steroids, low serum albumin
  - No overall difference between localized and generalized, but generalized patients had higher 1 year mortality rate (21% vs 8%)


Bullous pemphigoid – 1. Considering the diagnosis

- Disease associations
  - Neurological disease - YES
    - Case-control study of 89 patients, neurological disease was present in 42% of patients compared to 19% of controls
    - Patients with neurological disease have a higher risk of developing BP (odds ratio of 10.55), particularly those over 80 years old
    - Conditions include cerebral stroke, dementia, Parkinson’s disease


Bullous pemphigoid – 1. Considering the diagnosis

- Target antigens - BP180 and BP230

Bullous pemphigoid – 1. Considering the diagnosis

- Epidemiology -
  - Most commonly occurs in patients over 60 years old
  - Peak age of onset in the 70s
  - No racial or gender predilection

Bullous pemphigoid –
2. Work up

- Etiology – pathophysiology of blisters
  - Stepwise degradation of the BMZ that depends on complement, mast cell degranulation, neutrophil activation

Fitzpatrick’s Dermatology in General Medicine, 8th ed.

Bullous pemphigoid –
2. Work up

- Etiology – update
  - Over 85% of BP patients have IgE directed against BP180 (NC16A)
  - IgE autoantibodies play a role in eosinophil infiltration
  - Innate immune cell production of IL17 may sustain inflammation by upregulating MMP-9 and neutrophil elastase


Bullous pemphigoid –
2. Work up

- Biopsy for H&E
  - Early small blister or edge of larger blister
  - Sub-epidermal blister
  - Superficial dermal infiltrate of eosinophils, neutrophils, lymphocytes, and macrophages
  - Urticarial lesions may show eosinophilic spongiosis

Bullous pemphigoid –
2. Work up

- Biopsy for direct immunofluorescence
  - Perilesional – about 5mm away from lesion
  - IgG and C3 in a linear pattern at the BMZ
  - IgE can be seen as well in many patients

Bullous pemphigoid –
2. Work up

- Indirect immunofluorescence
  - 70% of patients have serum IgG that bind the BMZ on normal human skin
  - 1M NaCl split skin is more sensitive and can distinguish from EBA
  - Autoantibodies can also be found in blister fluid


Bullous pemphigoid –
2. Work up

- ELISA
  - Increasingly being used in both clinical and research settings
  - Sensitivity of 89% and specificity of 98%
  - ELISA titers correlate with disease activity
  - 7% of the normal population will have anti-BP180 detectable by ELISA

Bullous pemphigoid – 2. Work up

- Lab data
  - Total serum IgE levels elevated in up to 70% of untreated BP patients
  - Peripheral blood eosinophilia in 50% of BP patients and can be a marker of severity of disease


Bullous pemphigoid – 3. Management

- Waxing and waning course with occasional spontaneous remission (more often in localized disease)
- In treated patients, disease activity ranges from 9 weeks to 17 years (median 2 years)


Bullous pemphigoid – 3. Management

Treatment - Localized BP
- May respond to potent topicals alone
- May respond to more mild systemic agents


Bullous pemphigoid – 3. Management

Treatment - Extensive BP
- Typically requires prednisone
  - Usually start prednisone 60mg daily with taper by 5mg weekly holding at 30mg daily
  - Once you reach 30mg daily you can attempt an alternating day taper…
- Potent topicals such as clobetasol cream (40g/day) are also very effective and may be safer – systemic absorption?


Bullous pemphigoid – 3. Management

Treatment - Extensive BP
- Steroid sparing agents – MTX, azathoprine, mycophenolate
- MTX
  - Often at fairly low doses of 5-7.5mg weekly is effective at successfully tapering prednisone
  - Can be used as monotherapy (median time to remission 11 weeks)
  - May have particular efficacy against eosinophils


Bullous pemphigoid – 3. Management

Treatment - Extensive BP
- What to do when prednisone is not working or not tolerated?
  - IV Ig and/or wet wraps
- New approaches
  - Rituximab – anti-CD20, B cell depleting
  - Omalizumab – humanized mAb, anti-IgE Fc

Ahmed AR et al. J.AAD 2016 [Epub ahead of print].

Bullous pemphigoid – 3. Management

- Omalizumab – 6 patients treated

The parameter that was most closely associated with disease activity was eosinophil count.


Bullous pemphigoid – 3. Management

Risk of infection
- 97 patients
- Serious infectious complications occurred in 56%
- Median time from diagnosis 3 months
- 78% in the first year
- Pneumonia (37%), UTI (33%), skin and soft tissue (13%)
- 18% mortality at 1 year, 81% of deaths caused by infections
- Risk factors for infectious complications – Karnofsky score less than 60 and dementia


Bullous pemphigoid – 3. Management

Risk factors for relapse
- Prospective, multicenter, cohort study, 114 patients
- Factors predictive of relapse within 12 months after cessation of therapy were
  - High ELISA titer*
  - A positive DIF
  - One of these tests should be considered prior to discontinuation of therapy
  - Other things to consider – eosinophilia, itch


Pemphigus – 1. Considering the diagnosis

- Classic variants
  - Pemphigus vulgaris – mucosal and mucocutaneous
  - Pemphigus foliaceus

- Less common variants
  - Pemphigus vegetans (typically a PV variant)
  - Pemphigus herpetiformis (typically a PF variant)
  - IgA pemphigus


Pemphigus – 1. Considering the diagnosis

- Pemphigus vulgaris
  - Mucosal erosions
  - Flaccid bullae or superficial erosions
  - Most frequent type of pemphigus (~70% of cases)
- Two distinct subtypes
  - Mucosal PV
  - Mucocutaneous PV

- Mucosal PV
  - Mucosa is the first area involved in over 60% of cases
  - Oral mucosa is most commonly involved
  - Genital and anal involvement can occur
Pemphigus – 1. Considering the diagnosis

- Mucocutaneous PV
  - Skin involvement usually occurs after mucosal disease
  - Flaccid blisters and erosions


Pemphigus – 1. Considering the diagnosis

- Pemphigus foliaceus
  - Fragile superficial bullae and localized or generalized exfoliation
  - Rupture almost as soon as they form leaving crusting and scaling
  - NO oral involvement
  - Comprises 20-30% of pemphigus

James K et al. Dermatologic Clinics 2011;29:405-12.

Pemphigus – 1. Considering the diagnosis

- Pemphigus vegetans - atypical
  - Flaccid bullae or pustules that erode to form hypertrophic plaques with predominance in the flexures, scalp, face, and mucous membranes
  - Rare variant (2-5% of cases)


Pemphigus – 1. Considering the diagnosis

- Pemphigus herpetiformis - atypical
  - Vesicopustules, crusted erosions in annular or circinate pattern on the trunk and proximal extremities, pruritic
  - Rare (5-7% of pemphigus cases)
  - UV exposure can exacerbate disease

Tatemoto K et al. JAD 2010;63:e8-10.

Pemphigus – 1. Considering the diagnosis

- IgA pemphigus - atypical
  - Vesicles, pustules, crusted erosions in annular or circinate pattern on the trunk and proximal extremities, plaques in the axillae
  - Mucosal involvement rare
  - Two distinct subtypes
    - Intraepidermal neutrophilic
    - Subcorneal pustular dermatosis


Pemphigus – 2. Work up

- Target antigens
  - Mucosal PV
    - Antibodies to desmoglein 3
  - Mucocutaneous PV
    - Antibodies to desmoglein 3 and desmoglein 1
  - Pemphigus foliaceus
    - Antibodies to desmoglein 1
  - Antibody alone causes acantholysis (no complement needed) – steric hindrance, signaling

Pemphigus – 2. Work up
- Biopsy for H&E (small blister or edge)
  - Pemphigus vulgaris – suprabasilar acantholysis with intraepidermal blister formation
  - Pemphigus foliaceus – subcorneal acantholysis with intraepidermal blister formation
  - Atypical variants – pseudoepitheliomatous hyperplasia with neutrophilic/eosinophilic microabscesses, acantholysis variable


Pemphigus – 2. Work up
- Biopsy for direct immunofluorescence
  - Taken from perilesional tissue
    - 5 mm away from lesion on skin
    - 1 cm away from lesion on mucosa
  - ICS staining with IgG and C3


Pemphigus – 2. Work up
- Indirect immunofluorescence/ELISA
  - ICS staining with IgG and C3
  - Indirect IF titers correlate with disease activity
    - IF on monkey esophagus or normal human skin is positive in 90% of cases
    - Lower sensitivity with atypical variants


Pemphigus

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical findings</th>
<th>Histology</th>
<th>Target antigen</th>
<th>Antibody</th>
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<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>Mucosal and cutaneous erosions</td>
<td>Suprabasilar split with acantholysis</td>
<td>Dsg1</td>
<td>IgG4</td>
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<td></td>
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<td>IgG1</td>
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<tr>
<td>Pemphigus foliaceus</td>
<td>Colossal erosions</td>
<td>Subcorneal split with acantholysis</td>
<td>Dsg1</td>
<td>IgG4</td>
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<td>IgG1</td>
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<tr>
<td>Pemphigus vegetans</td>
<td>Vegetation, crusted plaques</td>
<td>Pseudoepitheliomatous hyperplasia, neutrophilic/eosinophilic microabscesses</td>
<td>Dsg1</td>
<td>IgG4</td>
</tr>
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<td></td>
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<tr>
<td>Pemphigus herpetiformis</td>
<td>Circinate vesiculopustules</td>
<td>Neurophilic/eosinophilic spongiosis and microabscesses</td>
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<td>IgG</td>
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Summary

Pemphigus – 3. Management
- Prednisone
- Immunosuppressive steroid sparing agent
  - Azathioprine or mycophenolate mofetil
  - Also cyclophosphamide, MTX
- Antibody targeted therapy (IVIg)
- B cell depleting therapies (rituximab)

Henti M et al. JADV 2015;29:405-414.
Effect of immunomodulatory agents

- Prednisone at 1mg/kg/day, higher not really better
- Adjuvant steroid sparing agent
  - Azathioprine – TPMT, 1-3mg/kg/d, steroid sparing
  - Mycophenolate – Titrato to 2-3g/d, steroid sparing
  - Cyclophosphamide – Titrato to 2-2.5 mg/kg/d, steroid sparing
  - Particularly helpful in patients with recalcitrant disease and/or vegetative plaques

Herr M et al. JADV 2015; 29:405-414.

Effect of antibody targeted therapy

- Intravenous immunoglobulin (IVIg)
  - Multiple proposed mechanisms
    - Increased catabolism of autoantibodies
    - Rapid clearance of autoantibodies and clinical improvement
      - Within 1 week new lesions ceased to form
      - Within 2 weeks 80% of lesions had healed
    - Non immunosuppressive
      - Antibody levels to other common antigens remain stable

Amagai M et al. JAAD 2009;60:595-603.

Pemphigus – 3. Management

- Upon initial presentation the patient was failing prednisone 80mg daily
- She was treated with IVIg x 1 cycle and azathioprine was started as a steroid sparing agent

Day 0 – 1:640
2 weeks – 1:320

Effect of B cell depleting therapy

Rituximab and CD20

- Chimeric murine/human monoclonal antibody that recognizes the B lymphocyte surface protein CD20
- CD20 is a transmembrane protein expressed on pre-B to mature B cells and functions to regulate B cells early in development
- CD20 is an ideal B cell target
  - Not shed from the cell surface
  - Not found in circulation
  - Does not internalize upon binding
  - Not expressed on other tissues/cells

Antibody changes following rituximab

- Specific decrease in anti-Dsg antibodies (Dsg1>Dsg3)
- Levels of IgG to HSV, tetanus toxoid, and pneumococcal capsule were stable (or increased) following rituximab

Rituximab dosing schedules

- Two approved dosing protocols
  - Lymphoma protocol
    - 375 mg/m² IV once weekly for 4 consecutive weeks
  - Rheumatoid arthritis protocol
    - 1000mg IV administered at day 0 and day 15
- Multiple off-label protocols have been used
- Often combined with other systemic therapy, such as corticosteroids, immunosuppressives, or IVig

Which protocol is better?

- Complete remission in ~85% of patients
- Time to complete remission
  - Median 2-3 months
- Relapse rate
  - 42.48% relapse (median 18 months)
- Lower doses do not seem to be as effective

Repeat dosing increases remission

- 47 patients
- 1000mg administered at day 0 and day 15
- Remission (CR or PR) in 76% after first cycle
- Repeat treatments increased remission rates to 91%


Pre-treatment vaccinations

- Vaccinations should be administered 1 month before or 6 months after treatment
  - Risk of ineffective antibody response in protein based or inactivated vaccines
  - Risk of increased infectivity in live vaccines
- Consider administering influenza, tetanus, pneumococcal, and herpes zoster vaccines at least one month prior to treatment

Giving the infusion

- Most dermatologists partner with an infusion center
- The coadministration of systemic corticosteroids, diphenhydramine and acetaminophen reduces infusion related adverse effects
- The first infusion is typically given over 5 hours with subsequent infusions given over 3-5 hours if well tolerated

Safety

Infusion reactions

- Mild – Fever, chills, headache, pruritus, urticaria
- Severe – Angioedema, bronchospasm, hypotension

Non-infusion related severe side effects

- Infection, severe
  - 7% of pemphigus patients on rituximab
  - 1st 6 months critical period
- Neutropenia
- Progressive multifocal leukoencephalopathy
  - Not yet reported in AIBD patients

Safety

153 patients

Pemphigus – 3. Management

- 31 patients failing standard therapy
- Endpoint - Complete remission off or on minimal therapy
  - 18/31 (58%) achieved the endpoint
  - Those achieving the endpoint had a lower median disease duration


Pemphigus – 3. Management

First line agent
• Five patients with contraindication to systemic steroids (PDAI 15-84)
• Given rituximab and topical steroids
• Disease control at 4 months
• 2-3 patients relapsed


Pemphigus – 3. Management

Subcutaneous anti-CD20 mAb
• Veltuzumab -
  • Patient with refractory PV achieved CRoffT
  • Relapsed at 2 years and was retreated again with CRoffT
• B cell depleting agents that target molecules other than CD20
  • Belimumab, atacicept (anti-BAFF)

Elshabouri CT et al. JAMA Dermatology 2014;150 (12):1311-5.

Pemphigus – 3. Management

• Escape from tolerance does not occur frequently
  • 3 patients followed, 2 with relapsing disease
  • Anti-Dsg3 IgG repertoire studied over time
  • Small set of non-tolerant B cell lines are responsible for disease
  • These clones are undetectable after rituximab induced disease remission
  • The same clones may return during flares


Pemphigus – 3. Management

• Consider HSV and/or VZV superinfection in patients with recalcitrant lesions or unusual flare


Pemphigus – 3. Management

Comorbidities in inpatient pemphigus patients
• Cross sectional cohort of hospitalized patients in the US
• Cushing’s syndrome, adrenal insufficiency, myasthenia gravis, herpes infection, fungal infection, insomnia
• Patients with a secondary diagnosis of pemphigus had a higher mortality compared to patients with a primary diagnosis of pemphigus

Predictors of relapse in patients in clinical remission

- 89 patients in complete remission for at least 6 months on less than 10mg prednisone/day and no immunomodulatory agents
- DIF and ELISA, 18 month follow up
- Relapse occurred in 42% of patients
- Relapse free time shorter in patients with anti-Dsg3 Ab and positive DIF

Pemphigus – Management

Daneshpazhooh M et al. JAAD 2016, Feb 17 [Epub ahead of print]

Take home messages...

- We continue to learn more about the unique clinical presentations of these diseases
- Diagnostic techniques are evolving
- As we learn more about the pathophysiology of these diseases, more targeted treatment strategies will emerge
- Keep following the literature for updates that can be incorporated into our clinical practice to improve care for our patients

Take home messages...

- The top 3 things dermatologists should do for their pemphigus and pemphigoid patients

Resources

- International Pemphigus and Pemphigoid Foundation (IPPF)
  - www.pemphigus.org

Acknowledgements

UNC Department of Dermatology
- Luis Diaz, MD
- IPPF
  - Becky Strong, RN, Outreach Coordinator

The Dermatology Foundation has supported & advanced my career.