AUTOIMMUNE BLISTERING DISEASES; WINDOW TO SYSTEMIC DISEASE

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Disclosures

- I have no conflict of interest to declare
- I will be talking about off-label use of medications
Learning Objectives

• To define mechanisms of autoimmune blistering diseases (AIBD)
• To understand that bullous diseases can provide insight into systemic disease
• To review treatments for both bullous diseases and related systemic diseases
Autoimmune Blistering Diseases

**Epidermal**

- Pemphigus foliaceus
  - Endemic
  - P. Erythematosus
  - IgA Pemphigus
  - P. Herpetiformis

- Pemphigus vulgaris
  - P. Vegetans

Paraneoplastic Pemphigus

**Subepidermal**

- Bullous pemphigoid
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita
- Bullous systemic lupus
- Linear IgA disease
- Pemphigoid gestationis
- Dermatitis herpetiformis
- Lichen planus pemphigoides
- p200/Laminin γ-1-pemphigoid
Schmidt and Zillikens, The Diagnosis and Treatment of Autoimmune Blistering Diseases, Dtsch Arztebl Int 2011; 108(23): 399–405.
Pemphigus

Hertl M, Journal of Clinical Investigation, 2006
Pemphigus Foliaceus
Pemphigus Vulgaris

Another oral photo
Pemphigus Vulgaris
Direct Immunofluorescence—Intercellular IgG (IgA), C3

Pemphigus

Blister
Efficacy of Rituximab Therapy in Pemphigus

- Meta-analysis from 30 studies; 578 patients
- Complete Remission (CR) rates after one cycle: 76%
- Mean time to CR 5.8 months
- CR duration 14.5 months
- Relapse rate 40%
- Major adverse events: 3.3%

Wang HH et al, Acta Derm Venereol 2015
Bullous Pemphigoid

IL-6, IL-8
Chemokines, proteases
Mast cells
Chemokines
Neutrophils
eosinophils
macrophages
T cell
Proteases
ROS
MMP-9
α1-PI
NE
BP180 and DEJ

Schmidt E, Zillikens D, Lancet 2013
Bullous Pemphigoid
Bullous Pemphigoid
Role of IgE in Bullous Pemphigoid?

Role for IgE Directed Therapies - Omalizumab?

Ujiie H, J of Dermatological Science, 2015
Mucous Membrane Pemphigoid
Mucous Membrane Pemphigoid +/- Ocular Cicatricial Pemphigoid
Linear IgG (IgA/IgM)/C3 at Basement Membrane Zone

Subepidermal Blistering Diseases
Development of Autoimmunity

Genetic Susceptibility
- Activation of autoreactive T and B cells
- Formation of self DNA or RNA complexes

Biologic Therapies
- Activation of cells producing IFN-I
- Amplification of autoimmune responses

Tomasello E et al, Front Immunology, 2014
Pathways to Peripheral Tolerance

Activated T Cell
Indifferent T Cell
Dead T Cell
Sleeping T Cell
Suppressed T Cell
# Genetic Susceptibility for Autoimmune Diseases

*Survey based registry; 61/393 (15.5%) Patients with Pemphigus*

<table>
<thead>
<tr>
<th>Thyroid Disease</th>
<th>59%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>24.6%</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>13.1</td>
</tr>
<tr>
<td>Diabetes Type 1</td>
<td>8.2</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>3.3</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>3.3</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>1.6</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Prevalence of Autoimmunity

• 295 pemphigus patients
• Comparing to age-standardized prevalence ratios (SPRs) in Canadian general population
  • Higher prevalence in pemphigus group
    • Thyroid disease: 1.53 (1.08-2.10)
    • Diabetes: 2.20 (1.64-2.87)
    • Inflammatory Bowel Disease: 1.48 (0.4-3.80)
  • Lower prevalence in pemphigus group
    • Rheumatoid arthritis: 0.74 (0.36-1.36)

Heelan K et al, Clin, Exp Dermatology 2015
Coexistence of AIBD and Psoriasis

- Retrospective cohort of 145 cases in Japan

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>BP</th>
<th>Laminin γ1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis vulgaris</td>
<td>122</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td>Pustular psoriasis</td>
<td>13</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Psoriatic erythroderma</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Ohata C, et al, JAAD 2015
Bullous Pemphigoid

- Data from National Inpatient Sample, 2002-2012 (~72 million adults)
  - 2180 Primary diagnosis; 11234 Secondary Diagnosis
  - Commonly associated autoimmune diseases (Odds ratios/OR)
    - Cushing syndrome 10.72 (1.5-76.73)
    - Hidradenitis suppurativa 6.76 (1.68-27.17)
    - Systemic lupus erythematosus 8.68 (4.77-15.79)
    - Multiple sclerosis 4.07 (3.22-5.14)
    - Rheumatoid arthritis: 1.26 (1.12-1.42)
    - Hypothyroid: 1.21 (1.13-1.30)

Ren Z et al, British Journal of Dermatology, 2017
Autoimmune Phenomenon

**Targeted Biologic Therapies:**
Checkpoint Inhibitors Targeting PD-1 and PD-L1
- Bullous pemphigoid
Following Rituximab Therapy for Pemphigus
- Psoriasis
- Sarcoid
- Multiple Sclerosis*

Guidelli G, Rheumatol Int 2013
Nadoo J et al, Cancer Immunology Research 2016
*Unpublished observations
Skin Windows

“Bullous Window to Systemic Disease”

Case History

- 66 year old male presented with worsening skin rash and oral erosions
  - History of chronic lymphocytic leukemia in 2008
  - Treated with fludarabine, cyclophosphamide and rituximab
  - Remission until Spring 2013
  - Developed axillary lymphadenopathy along with diffuse erythematous rash with areas of blistering
  - Retreated with rituximab in June 2013
  - Oral erosions with severe lip involvement; admitted for possible Steven’s Johnson syndrome
  - Skin biopsies inconclusive
  - Treated with tapering courses of systemic corticosteroids
Paraneoplastic Pemphigus (PNP)

- Pemphigus in setting of malignancy:
  - NHL, CLL, Castleman disease, Thymoma, Retroperitoneal sarcomas
- Painful mucosal erosions with refractive mucositis
- Polymorphous skin eruptions
  - Blistering
  - Urticaria
  - Erythema multiforme
  - Lichen planus
- Cicatrizing conjunctivitis
- “Paraneoplastic autoimmune multiorgan syndrome”
- Confirm by histology--immunofluorescence

Can Look like both pemphigus and pemphigoid!

Epidermis

Dermis

PNP

Paraneoplastic Pemphigus

- Pulmonary involvement later in course of disease in ~30% of patients
  - Respiratory failure
  - Features of bronchiolitis obliterans
  - Functional obstructive or restrictive bronchiolitis
  - Mostly irreversible

- Link with Pemphigus??

Respiratory Epithelium in PNP

Loss of Cellular Adhesion, Similar to pemphigus

Autoantibodies Deposited by immunofluorescence

Nousari HC, et al, NEJM, 1999
Increased Desmoglein 3 in areas of Squamous Metaplasia!

Hata T, et al., J Immunology, 2013
Bullous Window to Systemic Disease

- Increased skin injury from autoantibodies
- Induction of various cytokines—Interleukin-22?
- Downstream effects on respiratory epithelium—Squamous metaplasia?
- Induction of ectopic expression of Desmoglein 3 in respiratory epithelium
- Humoral attack—similar to classic pemphigus
- Respiratory failure
Case History

• 44 year old African American male
• Referred for worsening blisters mostly on extremities
• Diagnosed with Crohn’s disease shortly before blistering began
• Previously treated with courses of prednisone and sulfasalazine
Linear IgG/C3 at Basement Membrane

Epidermis

Dermis

Subepidermal Blistering Diseases
Adhesion Molecules in the Skin

Schmidt E and Zillikens D, *Dtsch Arztebl Int*, 2011
Epidermolysis bullosa acquisita

- Autoantibodies bind to collagen VII in the dermis
- Potential for scarring
- Link with Inflammatory Bowel Disease?

Kim JH, JEADV 2012
Type VII Collagen is Present in Skin and Colon

Serum autoantibodies to type VII collagen

Bullous Window to Systemic Disease

- Tissue injury, inflammation in skin or gastrointestinal tract, exposing epitopes on collagen VII
- Development of cross reactive antibodies?
- Exposure of other antigens during inflammation, development of other AIBD
  - Bullous pemphigoid--CD/UC
  - Linear IgA disease--UC
  - Dermatitis herpetiformis-Celiac disease
- EBA most commonly associated with CD
- Inflammatory bowel disease tends to precede AIBD

Shipman AR, et al, Clinical Experiment Dermatology 2012
Reddy H et al, Clinical Experimental Dermatology 2013
Case History

• 40 year old female
• 5 years post kidney/pancreas transplant for diabetes
• On prednisone and mycophenolate
• Attempted to wean down mycophenolate
• Creatinine levels increased to 3.3
• Developed widespread pruritic rash
• Subsequently developed tense blisters
Linear IgG/C3 at Basement Membrane Zone

Serum ELISA
Elevated anti-BP180 antibodies
(BPAG2/Collagen XVII)
Bullous Window to Systemic Disease

• Bullous pemphigoid in the setting of renal allograft failure?
• Usually with reduction in dose of immunosuppression
• Injury to glomerular basement membrane, epitope spreading?
• Common antigen between glomerular basement membrane zone and cutaneous? Collagen XVII, IV?

Cavaliere G et al, Eur J Dermatol 2014
Bullous Window to Systemic Disease

Collagen XVII expressed in human and mouse glomerulus

Antibodies against Type IV Collagen: Skin and Renal Glomerulus

Case History

• 74 year old Caucasian female
• Diagnosed with Lewy Body Dementia in 2011
• Developed worsening pruritus in 2013
• Treated with antihistamines and topical steroids
• Developed gingival erosions and blisters on lower extremities
• Biopsied by oral surgery—inconclusive
• Seen by dermatology in 2014—widespread erosions on gingiva and across her abdomen and back
Linear IgG/C3 at Basement Membrane Zone

Tissue Bound Antibodies

Loss of Cellular Adhesion

Epidermis

Dermis
Case History

- Bullous pemphigoid
- Bullous pemphigoid disease area index (BPDAI)
  - Cutaneous: 34/120
  - Oral: 16/120
- Age of onset >70 years
- Disease relationship with underlying dementia??
Bullous Pemphigoid

• Data from National Inpatient Sample, 2002-2012 (~72 million adults, cont)

Neuropsychiatric disorders!
• Demyelinating disorders: 3.57 (1.48-8.61)
• Presenile Dementias: 2.63 (1.34-5.18)
• Parkinson’s disease: 1.86 (1.65-2.10)
• Epilepsy: 1.67 (1.41-1.98)
• Other neurological disorders: 1.98 (1.86-2.11)

Ren Z et al, British Journal of Dermatology, 2017
Bullous Pemphigoid

- Significant increase in odds of developing BP in people with neurological diseases diagnosed more than 12 months previously
  - Dementia and Parkinson’s-- 3 fold increase
  - Stroke and Epilepsy--2 fold increase
- Neurological disease precedes the BP
- Patients with Parkinson’s have circulating autoantibodies to collagen XVII and localize to neurons

Laffitte E, et al, Br Journal of Dermatology, 2004
BPAG1 in the Central Nervous System?

- Knockout mice for BPAG1/BP230
  - Develop skin fragility as expected
  - Dystonia, ataxia?
  - Severe neurodegeneration and myelin abnormalities in CNS and peripheral nervous system?

Guo L et al, Cell 1995
Expression of BPAG1 (BP230)

- Brain, Spinal Cord
- Striated muscle, bone cartilage
- Epidermis

“Dystonin”; peripheral sensory neurons, motor neurons, oligodendrocytes, Schwann cells

*BPAG2/Collagen XVII is also expressed in the Brain

Bousquet O and Coulombe P, Current Biology 1996
BP patients with neurological diseases recognize BPAG 1 protein in the brain

- Serum samples from BP and neurological diseases (BPND) compared with serum from BP without neurologic disease (BP)
  - Recognized BPAG1—epidermal extracts:
    - 72% BP/ND vs 50% BP
  - Recognized BPAG1—brain extracts:
    - 55% BP/ND vs 9% BP

Chen J et al, Gerontology, 2011
Bullous Window to Systemic Disease

- Neurological disorders cause damage to blood brain barrier?
- Loss of immune privilege—inappropriate exposure of brain antigens—BPAG1 or BPAG2?
- Develop cross reactive autoantibodies to skin??
BP and Venous Thromboembolism

- **INVENTEP**
  - Incidence of VENous ThromboEmbolism in bullous Pemphigoid study
  - Cohort of 432 patients
  - BP patients have four-fold increased risk of VTE compared to age, sex matched controls
  - Increased during acute phase of disease up to 15-fold

  Cugno M et al, Thrombosis and Haemostasis, 2015
BP and Venous Thromboembolism

• Mechanism?
  • Related to increased expression of tissue factor by proinflammatory cytokines and eosinophils
  • Elevation of prothrombin fragments—coagulation activation
  • Anticoagulate patients with active disease?

Zebrowska Z et al, Mediators Inflammation, 2015
• AIBD can be window into systemic inflammation/injury of multiple organ systems
Conclusion

- Bullous diseases fascinating group of autoimmune diseases
- Diagnostic and therapeutic decisions potentially affected
THANKS FOR THE INVITE!

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