Introduction to Pemphigus

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Disclosures

I am a B cell immunologist by training
I spend hours thinking about pemphigus every day
I feel that every patient deserves to understand their disease at a deeper level
I am a bit of a Pollyanna
What is pemphigus?!
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- An autoimmune disease that can affect the skin and mucous membranes
- It is caused by antibodies that attack the proteins that hold the skin cells together
- There are multiple forms of pemphigus
- It is one of the most severe skin diseases
What is pemphigus?!

• An autoimmune disease that can affect the skin and mucous membranes

• Okay...then what is an autoimmune disease?!

• We have to start with a review of a healthy immune system...
Introduction to pemphigus

- The healthy immune system
- How the immune system goes haywire in pemphigus
- Subtypes of pemphigus
The healthy immune system

- Elegantly designed system to protect and defend the body from foreign invaders (bacteria, viruses, fungi, etc.) that cause infection = military
- Cells and proteins in the blood and tissues = soldiers and weapons
- Organs = training camps and forts/bases
The healthy immune system

White blood cells (soldiers)
- Lymphocytes
  - B cells
  - T cells
- Neutrophils
- Monocytes
- Eosinophils
B lymphocytes

- Generated in the bone marrow (birthplace and early training camp)
- B cells go through a series of stages during which each B cell develops a unique specificity
- Specificity of each B cell is determined by the B cell receptor
B lymphocytes

- Many different specificities are generated
- B cells are tested at different checkpoints to ensure that they don’t recognize self proteins
  - Recognize self – under programmed death or inactivated or fixed
  - No self recognition – move on
B lymphocytes

- B cells migrate out from the bone marrow to the blood, lymph nodes, spleen, tissues
- When the B cell encounters its target it is activated to make antibodies
B lymphocytes

- Antibodies = weapons or flags that mark the target
- Antigen = target of the antibody
B lymphocytes

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- Antibodies = weapons or flags that mark the target
- Antigen = target of the antibody

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<th>Constant region</th>
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Antibodies

- B cells produce a quick first round of antibodies
- ...but...then B cells divide and expand making tweaked clones of itself (best soldier)
- Clones go through additional training where they become even more zeroed in on and specific for their antigen (or protein target)
- Concept of clonal expansion and affinity maturation → memory
Antibodies

- Plasma cell is the end stage of B cell development
- An antibody factory
*This is the concept that vaccination is based on!*
What goes wrong in pemphigus?

- What if the B cell just happens to recognize a self protein/antigen instead of a bacterial or viral protein?
- What if that self protein is one of the proteins that hold the skin cells together?
What goes wrong in pemphigus

Bone Marrow

Pro-B  Pre-B

Immature  Mature

Spleen

Germinal Center

Plasma.cell

Memory

Plasmablast

Bone Marrow

Y  Y  Y Y
What goes wrong in pemphigus

Bone Marrow
- Pro-B
- Pre-B

Spleen
- Immature
- Mature
- Germinal Center
  - Ag
  - Memory
  - Y

Plasma cell

Plasmablast

Bone Marrow
What goes wrong in pemphigus

- Bone Marrow
  - Pro-B
  - Pre-B

- Spleen
  - Immature
  - Mature
  - Germinal Center
  - Ag
  - Memory

- Bone Marrow
  - Plasma cell
  - Plasmablast
Pemphigus target antigens

- Target antigens
  - Proteins that hold the skin cells together
  - AKA keratinocyte adhesion proteins

- Skin anatomy review
Skin anatomy review

Stratum Corneum
Epidermis
Dermis

Stratum:
- corneum
- lucidum
- granulosum
- spinosum
- basale
Pemphigus target antigens

- Target antigens
  - Desmoglein proteins
    - Desmoglein 1 (Dsg1)
    - Desmoglein 3 (Dsg3)
  - Acetylcholine R
    - $\alpha_9$ AChR
  - Possibly others…

*Antibodies directly cause the disease by binding to keratinocyte adhesion proteins and causing the skin cells to pull apart from their neighbor cells = acantholysis.
Making the diagnosis

- Biopsy for regular microscopy (H&E)
  - Pemphigus vulgaris - suprabasilar acantholysis with intraepidermal blister formation
  - Pemphigus foliaceus – subcorneal acantholysis with intraepidermal blister formation

Making the diagnosis

- Biopsy for direct immunofluorescence (DIF)
  - Taken from normal intact skin near a blister
  - IgG staining in a chickenwire pattern

Making the diagnosis

- Blood for indirect immunofluorescence (IIF)
  - Serum is separated from the blood
  - Diluted and placed over tissue substrate
  - ICS staining with IgG and C3
  - Indirect IF titers correlate with disease activity
    - IIF on monkey esophagus or normal human skin is positive in 90% of cases
  - Lower sensitivity with atypical variants
  - New multivariate ELISA validated

vан Beek N et al. JAAD 2016; Dec 28 Epub ahead of print.
What does pemphigus look like

- Classic variants
  - Pemphigus vulgaris
    - Mucosal predominant
    - Mucocutaneous
  - Pemphigus foliaceus

- Atypical variants
  - Pemphigus vegetans
  - Pemphigus herpetiformis
  - IgA pemphigus
  - Endemic pemphigus
Pemphigus vulgaris

- Pemphigus vulgaris
  - Mucosal erosions
  - Flaccid blisters or erosions on skin
  - Most frequent type of pemphigus (~70% of cases)

- Two distinct subtypes
  - Mucosal predominant PV
  - Mucocutaneous PV
Pemphigus vulgaris

- **Mucosal PV**
  - Mucosa is the first area involved in over 60% of cases
  - Oral mucosa is most commonly involved
  - Nasal, pharyngeal, esophageal, genital and anal involvement can occur
  - About 40% of patients will stay with mucosal disease only
  - Antibodies to Dsg3

Pemphigus vulgaris

- Mucocutaneous PV
  - Skin involvement usually occurs after mucosal disease
  - Flaccid blisters and erosions
  - Antibodies to Dsg3 AND Dsg1

Pemphigus foliaceus

- 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
  - Antibodies to Dsg1 alone

James K et al. Dermatologic Clinics 2011;29:405-12.
Pemphigus vegetans – atypical variant of PV

- 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 herpetiformis

- **Pemphigus herpetiformis** – atypical variant of PF
  - Small blisters and pustules, crusted erosions in annular pattern on the trunk and extremities, pruritic
  - Rare (5-7% of pemphigus cases)
  - UV exposure can exacerbate disease

Tateishi C et al. JAAD 2010;63:e8-10.
IgA Pemphigus

- IgA pemphigus - atypical
  - Vesicles, pustules, crusted erosions in annular or circinate pattern on the trunk and proximal extremities, plaques in the axilla
  - Two distinct subtypes
    - Intraepidermal neutrophilic
    - Subcorneal pustular dermatosis
  - Antibodies to desmocollin 1

Endemic pemphigus foliaceus

- **Fogo Selvagem**
  - Tropical and subtropical areas of interior Brazil
  - Typically affects younger population, seborrheic areas (1/3 cases before age 20)

- Columbia and Tunisia also have endemic foci of pemphigus foliaceus


Fogo Selvagem means “wildfire” in Portuguese, as the lesions burn in the sun.
Endemic pemphigus foliaceus

- Prevalence is 3.4% - wow!
  - Evidence of genetic predisposition
  - Environmental trigger (?)sand fly salivary gland antigen)
  - Anti-Dsg1 antibodies from FS patients also recognize these proteins
  - ?Salivary gland antigen looks like Dsg1?
    - Molecular mimicry

Autoimmune disease affecting the skin and mucous membranes

Mediated by autoantibodies that bind to keratinocyte adhesion molecules

Characterized by acantholysis and blister formation

Genetic predisposition and likely an environmental trigger

Different clinical variants or presentations
Acknowledgements

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