Introduction to Pemphigoid: Spectrum of Disease & Treatment

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SPECTRUM OF PEMPHIGOID

BULLOUS PEMPHIGOID (BP180, BP230) **HIGH MORTALITY**

ANTI-LAMININ GAMMA 1 PEMPHIGOID (LAMININ GAMMA-1)

**ORAL PEMPHIGOID (ALPHA-6 INTEGRIN)**

Limited to specific Sites

**OCULAR PEMPHIGOID (BETA-4 INTEGRIN)**

MUCOUS MEMBRANE PEMPHIGOID (BETA-4 INTEGRIN)

ANTI-LAMININ 332 PEMPHIGOID (LAMININ 332)

PREVIOUSLY LAMININ 5 **HIGH MORTALITY**
SPECTRUM OF PEMPHIGOID

Bullous Pemphigoid

Involvement: Skin Only

Mucosal & Skin

NO SCARRING

Laminin Gamma 1

Mucous Membrane Pemphigoid

Involvement: Mucous Membrane

CANCER

SCARRING

Laminin 332
Overall Survival, %

Years From Diagnosis

Expected

Observed

P<.001

Pemphigoid

Bullous & Mucous Pemphigoid Membrane
Bullous Pemphigoid
Bullous Pemphigoid
Bullous Pemphigoid
Urticarial Variety
Bullous Pemphigoid Histology

Low Power

High power
IIF USING SALT SPLIT SKIN SERA FROM PATIENTS WITH MMP/OCP

Direct IF of fresh bullae on skin showing BMZ Staining
IIF Monkey Esophagus Substrate – Binding of Antibody to BMZ
Bullous Pemphigoid Histology

BP Pt. perilesional skin

Normal human skin
Bullous Pemphigoid
Indirect Immunofluorescence
ELISA

• BPAg1(BP230)(intracellular)
• BPAg2(BP180)(intracellular)
  - Role in diagnosis
  - Usefulness in treatment & F/U
Mucous Membrane Pemphigoid
MUCOUS MEMBRANE PEMPHIGOID
aka Cicatricial Pemphigoid

- Rare disease
- Incidence 1.16 (France) & 0.87 (Germany) per million
- Currently considered a phenotype as a consequence of autoantibody mediated damage to epithelium basement membranes
- Not a single disease but several subsets
- Last 15 years different investigators
  - Autoantibodies to different autoantigens
  - Autoantibodies in a patient retain specificity
  - Autoantigens are important adhesion proteins in BMZ
MUCOUS MEMBRANE PEMPHIGOID
aka Cicatricial Pemphigoid

Clinical Subsets

- Generalized Mucous Membrane Pemphigoid (MMP)
- Ocular Cicatricial Pemphigoid (OCP)
- Oral Pemphigoid (OP)
- Anti-epiligrin-laminin 5 Cicatricial Pemphigoid
  (AECP - MMP) (laminin new name laminin 332)
MUCOUS MEMBRANE PEMPHIGOID
aka Cicatricial Pemphigoid

Serological Subsets

- Anti human β4 integrin autoantibody MMP/OCP
- Anti human α6 integrin autoantibody- Oral Pemphigoid - OP
- Anti epiligrin cicatricial pemphigoid – AECP
  Anti-laminin 332 pemphigoid
- Anti-laminin γ-1 pemphigoid (P200)
## Spectrum of Cicatricial Pemphigoid

<table>
<thead>
<tr>
<th></th>
<th>Anti epiligrin</th>
<th>Anti β4 integrin</th>
<th>Anti α6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Profile</strong></td>
<td>Mucosal and cutaneous</td>
<td>Mucosal and cutaneous</td>
<td>Oral only</td>
</tr>
<tr>
<td><strong>IIF – SSS</strong></td>
<td>Floor</td>
<td>Roof</td>
<td>Roof</td>
</tr>
<tr>
<td><strong>Response to Rx</strong></td>
<td>Poor</td>
<td>Favorable</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Guarded</td>
<td>Good- variable</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Association with Malignancies</strong></td>
<td><strong>Very high</strong></td>
<td>&lt; normal</td>
<td>&lt; normal</td>
</tr>
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</table>
Mucous Membrane Pemphigoid
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MUCOUS MEMBRANE PEMPHIGOID
aka
CICATRICIAL PEMPHIGOID
- Blisters heal w/Scarring
  - Except Oral Cavity
Mucous Membrane Pemphigoid

Sub-epidermal Blister
Mucous Membrane Pemphigoid

Histology of Sub-Epithelial Blister
Association of Cancer With Mucous Membrane Pemphigoid

Direct IF of Perilesional Skin showing BMZ Staining
ANTI-EPILIGRIN
CICATRICIAL PEMPHIGOID
Laminin 332 Pemphigoid
(new nomenclature)
- Heals w/Scarring
Mucous Membrane Pemphigoid
Anti-epiligrin (Laminin 5/332)

IIF- Antibodies bind to the floor of the blister of salt split skin
Immunoblotting using laminin 5 purified from keratinocyte extract as the substrate for patient 1 showed that the IgG antibodies reacted with 140-kDa polypeptides identical to the β3 subunit of the laminin 5 molecule.

Mucous Membrane Pemphigoid
Anti-epiligrin (laminin 5/332)

SCARRING
# Association of MMP with Cancer

## Table I. Clinical spectrum in MMP patients

<table>
<thead>
<tr>
<th>Ag/Ab</th>
<th>Disease</th>
<th>Clinical Profile</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrin α6 subunit</td>
<td>OP</td>
<td>Erosions limited to oral cavity only, No extra-oral disease</td>
<td>Self limiting, no long-term sequelae or hazards</td>
</tr>
<tr>
<td>Integrin β4 subunit</td>
<td>Generalized MMP</td>
<td>Generalized erosions in all mucous membranes, including oral cavity, esophagus, larynx, vagina, and the skin</td>
<td>Incidence of malignancy lower than normal (our unpublished data)</td>
</tr>
<tr>
<td></td>
<td>OCP</td>
<td>Erosions limited to conjunctiva, resulting invariably in scarring</td>
<td>Reasonable, if early intervention and if response to therapy is good</td>
</tr>
<tr>
<td>Laminin 5/Antiepiligrin</td>
<td>AECP</td>
<td>Similar to generalized MMP</td>
<td>Scarring can cause blindness, laryngeal, esophageal, vaginal, and anal stenosis</td>
</tr>
</tbody>
</table>

*Clinical spectrum, prognosis, and association with malignancy observed in subsets of MMP patients.*
Association with Malignancies

- 30% patients solid tumors (lung, stomach, colon, uterus - adenocarcinomas)
- Within first years of onset of AECP
- National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCI SEER) database
  - expected vs observed rate = relative risk 15.4 similar to adult dermatomyositis

*Medicine (Baltimore) 82: 177-186, May 2003*
61 patients observed between 1985-2000
32 females 29 males
Mean age 67 years (38-92)
Longitudinal follow up mean 86 mths (12-264)
Association with malignancies, 3 patients only
National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCISEER) database → expected 10.37 cases for age & sex specific observation period
Relative risk for cancer 0.29 (95% confidence interval 0.09-0.90)
• Lower Risk for Cancer than general population
ANTI HUMAN α6 INTEGRIN ANTIBODY
ORAL PEMPHIGOID ASSOCIATION WITH CANCER

- 72 patients
- 45 F, 25 M
- Mean age 54 years (26-76)
- Longitudinal follow up mean 9.1 years (3.9-15.8)
- Association with malignancies, 3 patients only

National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCI SEER) database → expected 8.83 cases for age & sex specific observation period
Relative risk for cancer 0.34 (95% CI 0.07-0.99)

Statistically significant lower (<0.01) than age, sex matched controls

*J Oral Pathol Med 2007; 36:1-5*
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID

New subset of pemphigoid previously known as anti-p200 pemphigoid

Autoantibodies target 200kD A protein in BMZ. Molecularly identified as laminin gamma-1

Clinical profile highly variable – vesicles and bullae, may resemble several AIBD
- no specific presentation
- 50% like bullous pemphigoid
- 9% like DH
- 7% like vesicular pemphigoid
- 2% EBA

20% have 1 or more mucosal involvement such as 60% oral, 40% genital, 20% eyes, 10% anal canal

Treatment – prednisone, dapsone, azathioprine, cyclosporine, methotrexate

Scarring rarely observed.

Follow-up – mean duration of disease – 30 months
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID

No Scarring
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID
ANTI-LAMININ GAMMA-1 (P200) PEMPHIGOID

DIF (IgG)

ss-IIIF (IgG)
Diagnosis possible only on immunoblot
Treatment of Bullous Pemphigoid

1. Topical Care
2. Anti-Inflammatory
   1. Antibiotics (Lancet 2017)
   2. Low dose prednisone
   3. Dapsone
   4. Sulfapyridine
3. Immunosuppressive agents
   1. Azathioprine
   2. Mycophenolate Mofetil
   3. Methotrexate
4. IVIg
5. Biologics - rituximab
Treatment of Mucous Membrane Pemphigoid

1. Topical Care
   1. Separate for each mucosal surface

2. Anti-inflammatory agents
   1. Dapsone-drug of choice
   2. Prednisone – limited use--only for acute episodes
   3. Sulfapyridine

3. Immunosuppressive Agents
   1. Azathioprine
   2. Cellcept
   3. Methotrexate
   4. Cyclophosphamide – often recommended---serious side effects

4. IVIG
5. Biologics- rituximab
12 patients – failed conventional therapy, 5/12 failed previous rituximab therapy with the lymphoma protocol

End point – control of disease, complete remission (no disease, no drugs). Achieved in all.

Follow-up – no relapses, no hospitalizations, no infections, no deaths.
   - Mean follow-up since D/C of RTX & IVIg – 6 years

Laboratory – autoantibodies to BMZ decrease and undetectable
   - B cells become zero shortly after therapy. Reach normal levels in 4 – 5 years.

Combination of Rituximab and Intravenous Immunoglobulin for Recalcitrant Ocular Cicatricial Pemphigoid: A Preliminary Report

C. Stephen Foster, MD, FACS, Peter Y. Chang, MD, A. Razzaque Ahmed, MD
Use of Rituximab in Treating Pemphigus

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Mucosal & Skin

NO SCARRING

Laminin Gamma 1

Mucosal & Skin

Laminin 332

CANCER

Mucous Membrane Pemphigoid

Involvement: Mucous Membrane SCARRING
More information can be found at our website for the Center for Blistering Diseases.

http://centerforblisteringdiseases.com
"There is a voice that doesn't use words. Listen."
- Kumi

THANK YOU