Pemphigus and Pemphigoid – The Unique Role of the Dental Professional

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Sign In: pemphigus.org/form

The International Pemphigus & Pemphigoid Foundation (IPPF) kindly asks all attendees to sign-in using the link provided. The above sign-in link is optional and NOT required to receive CE credits (if being offered). Information collected will be used by the IPPF.

www.PutItOnYourRadar.org
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The International Pemphigus & Pemphigoid Foundation (IPPF) advises audience members of the risks of using limited knowledge gained from this course when in practice.

VISION
To find a cure for pemphigus and pemphigoid

EARLY DIAGNOSIS AWARENESS PROGRAM
It takes the average pemphigus / pemphigoid patient 5 healthcare providers and 10 months to obtain a correct diagnosis.

Help us reduce diagnostic delays!
PATIENT SUPPORT SERVICES

- Physician Referral List
- Peer Health Coaches
- Patient Education Calls
- Support Group Meetings
- Quarterly Newsletter
- Annual Patient Education Conference

www.pemphigus.org

RESOURCES FOR DENTAL PROFESSIONALS

- CE Courses
- Patient speakers at dental schools
- Educational materials
- Comprehensive disease information

www.PutItOnYourRadar.org

PLEASE STOP BY THE IPPF EXHIBIT BOOTH #008
Meet a patient and learn more

Thank You!
Key Concepts

• Oral lesions may be the first or only sign of vesiculobullous diseases, including pemphigus and pemphigoid:
  “First to show and last to go”
• Biopsy is required to establish a definitive diagnosis. Proper technique and sampling is critical.
• Treatment of oral lesions may include topical corticosteroids initially or to treat breakthrough lesions; systemic therapy is almost always needed for disease control
• Other entities can mimic pemphigus and pemphigoid- if don’t get expected results, consider pemphigus
• Consult with Oral Medicine or Oral Pathology, Dermatology, Oral Surgery

DIAGNOSTIC DELAYS

Diagnostic pathway for pemphigus/pemphigoid patients:
• 5 HCPs and 10 months for correct diagnosis
• 10% see more than 10 HCPs
• 23% of patients see dentist first
• 46% see dentist at some point

Data Source: In October 2011, KJT Group was commissioned by the International Pemphigus & Pemphigoid Foundation to conduct an awareness and diagnostic pathways survey.

DIAGNOSTIC DELAYS

Of patients who saw a dentist:
• 46% reported they were not knowledgeable about their pemphigus/pemphigoid symptoms
• 40% reported being referred to another HCP
• 13% received a diagnosis

Data Source: In October 2011, KJT Group was commissioned by the International Pemphigus & Pemphigoid Foundation to conduct an awareness and diagnostic pathways survey.
CLINICAL PRESENTATION

Think of PV/MMP when there is a combination of:
- Multiple oral lesions
- Ulcerations preceded by bullae
- Chronic lesions
- Primary lesions
- Lesions may also occur outside of the mouth
- A lesion can follow minor trauma: Nikolsky sign

Initial Presenting Features of Pemphigus and Pemphigoid:
Recurrent and/or Persistent Oral Ulceration

Diagnostic Approach to Oral Ulcers

- History
  - Solitary episode or recurrent? Acute or chronic?
  - Precipitating factors?
  - Medications?
  - Dental products
  - Review of systems for other disease; other sites affected
    - Other mucosa
    - Skin
- Physical Findings
  - Location
  - Unilateral vs. bilateral
  - Keratinized vs. non-keratinized oral mucosa
  - Blisters? Erosions? Ulcers?
  - Size
  - Color
  - Associated signs and symptoms
Recurrent Oral Ulceration

- Differential Diagnosis-
  - Review of more common conditions
- Laboratory tests
  - When is a biopsy useful?
  - Blood studies?
  - Other diagnostic tests?
- Pharmacotherapeutics
  - Choices and how to prescribe
  - Mechanism of action
- Dental Management

Recurrent Oral Ulceration

- Aphthous stomatitis
- Erythema multiforme
- Recurrent Herpes simplex
- Erosive Lichen planus
  - Other lichenoid mucosities
    - GVHD, lichenoid drug reaction, Lupus
    - Lichenoid dysplasia
- Mucous membrane pemphigoid
- Pemphigus vulgaris
  - Paraneoplastic pemphigus

PEMPHIGUS VULGARIS (PV) & MUCOUS MEMBRANE PEMPHIGOID (MMP)

Rare, autoimmune, blistering diseases

PV

MMP
PEMPHIGUS VULGARIS (PV)

- Most common form of pemphigus
- Leads to intraepithelial, mucocutaneous blistering
- Predominantly manifests orally
- Autoantibody profile

Pemphigus Vulgaris

- Desquamating condition of oral mucosa and skin
  - Oral lesions “the first to show and last to go”
- Auto-antibodies to proteins of the desmosomes leads to “Acantholysis”
  - Loss of adhesion between cells in zone above basal layer: “Suprabasilar bullae formation”
- Can be life-threatening if not treated!

- Intracellular protein in desmosomes - Desmoplakin
- Extracellular proteins – Cadherins
  - Desmogleins 1 and 3 is a cadherin - the target antigen
- Detect autoantibodies in circulation, fluctuate with disease process
  - Indirect immunofluorescence
- Ethnic predisposition – genetics?
Pemphigus Vulgaris

- 50-60 year-old peak prevalence
- More common in Mediterranean and Ashkenazi Jew descent
- More common with certain MHC genotypes
- Drugs, malignancy- similar presentation
- Primarily skin of torso involved, in 50% with skin lesions, oral lesions preceded them
- Other mucous membranes – nasal, esophagus, vagina, cervix can also be involved
- Bullae common on skin, rare in mouth
- Intraoral lesions –soft palate, gingiva, buccal mucosa
- Usually bullous stage undetected, presents as eroded, erythema, pain
- Skin – brief blisters, collapses, red crust

What causes Pemphigus?

- Unknown etiology, genetic predisposition
  - Certain MHC class II molecules, alleles of HLA DR4
  - Often seen in patients with other autoimmune diseases such as myasthenia gravis
- Older age is associated (peak 50-60)
- Rarely caused by medications
  - ACE inhibitors
  - Penicillamine
  - Some antibiotics
  - NSAIDs
  - Rifampin (for TB)

NIH Genetic and Rare Diseases Information Center

Pemphigus Vulgaris
Oral Pemphigus Vulgaris

- Treatment:
  - Prolonged high dose of systemic steroids 150-360 mg daily for 6-10 weeks
  - Steroid-sparing regimens combine with other immunosuppressant drugs
    - Azathioprine
    - Cytoxan
    - Combination protocols
    - Rituximab

MUCOUS MEMBRANE PEMPHIGOID (MMP)

- Mouth and eyes most often affected
- Also known as Cicatricial Pemphigoid (CP)
- Disease onset usually between 40 and 70 yrs

Mucous Membrane Pemphigoid

- Vesiculobullous condition of mucous membranes
- Autoimmune reaction at the basement membrane
- Commonly affects the gingiva
  - “Desquamative gingivitis”
  - “Cicatricial pemphigoid”
- At least twice as common as pemphigus
- Older adults
- Females 2:1 Males
Mucous Membrane Pemphigoid

- Antibodies to BP-1 antigen, found in hemidesmosomes
  - BP-1 antigen:IgG antibody complex precipitates C3 to produce disease. Linear deposits along basement membrane as shown by direct immunofluorescence
    - Presence of IgA and IgG may indicate more severe disease
- Differential Diagnosis:
  - Pemphigus vulgaris and Erosive Lichen Planus

Immunofluorescence Studies

Fluorescein labeled anti-human IgG

Patient biopsy (auto Ab in tissue) +

Patient serum (w autoAb) +

Control Tissue

DIRECT IF

INDIRECT IF

Mucous Membrane Pemphigoid

- Lesions first appear on attached and free gingiva, irregular patches of erythema, loss of stippling
- Minor trauma results in blood-filled blisters, sloughing of epithelium
  - Rub on tissue, blister forms in 1-2 minutes:
    - Positive Nikolsky sign
- Eventually progress to involve buccal mucosa, palate, FOM, pharynx, esophagus
- Eye lesions can lead to blindness
  - Erythema, ulceration, adhesive tissue bands: “symblepharon”
  - Up to 25% with oral lesions develop eye lesions
  - Scarring – entropion, dry eyes
- Other mucosal sites may be involved
Mucous Membrane Pemphigoid
“Desquamative gingivitis”

Symblepharon – MMP

Mucous Membrane Pemphigoid
Treatment

- Low risk patients
  - Disease only in oral mucosa or combined with skin
  - Topical corticosteroid of mid to high potency (2-3 times per day)
  - Custom tray for gingival lesions is an option
  - Tetracycline 1-2 gram/day and Nicotinamide 2-3 gram/day can be used as an alternative regimen
  - If not satisfactory, change to dapsone 50-200 mg/day
    - Alternative, prednisone 20-40 mg/day in am, with or without low dose of azathioprine 50 mg/day
    - If not satisfactory, consider going to high risk regimen
Mucous Membrane Pemphigoid: Treatment

- High Risk Patients – ocular, nasopharyngeal, esophageal, laryngeal and/or genital mucosa
- Milder disease
  - Initial treatment with dapsone (50-200 mg/day) for 2-3 days
  - If not satisfactory, prednisone 0.5-0.75 mg/kg/day and cyclophosphamide 0.5-1 mg/kg/day
- Severe disease
  - Prednisone and cyclophosphamide, managed by team of physicians expert in this
  - Mycophenolate mofetil (Cellcept)
  - Other medications as alternatives

Mucous Membrane Pemphigoid

- Diagnosis: Biopsy
  - Routine histopathology – lesional tissue, AND
  - Direct immunofluorescence–nonlesional tissue
  - Splitting occurs at level of basement membrane, because antigen is located in there

Biopsy Technique
BIOPSY TECHNIQUES

Here are some guidelines:

• Do not sample the bed of an ulcer
• Must contain intact epithelium
• Should be taken from perilesional (within 1 cm) or normal appearing tissue
• Avoid separation of the epithelium from underlying connective tissue

BIOPSY TECHNIQUES

• Two specimens must be taken for:
  ○ Routine hematoxylin and eosin (H&E) stain (storing specimen in 10% formalin); **AND**
  ○ Direct immunofluorescence testing in Michel's transport medium (Order in advance)
    ■ Send to pathology laboratory as quickly as possible (identify lab in advance)

Summary of Vesiculobullous Diseases
Differential Diagnosis of Recurrent/Persistent Oral Ulceration

Recurrent Aphthous Stomatitis “RAS”

- “Canker sores”
- 15-20% world population affected
- Some populations up to 40% affected
- Ulcers may be present in other sites
- Can occur in association with systemic conditions
- Arise on non-keratinized mucosa: labial and buccal mucosa, soft palate, floor of mouth, ventral tongue
- Minor aphthae < 1 cm
- Major aphthae > 1 cm, deep, heal with scarring

Minor Aphthae

- < 1 cm, shallow yellow ulcers, with intense erythematous halo
- Smooth, round or ovoid
- Very painful!
- Heal in 7-10 days
RAS-Associated Systemic Conditions

• Most patients are completely healthy, but associated with
  – Behcet Disease
  – Crohn’s Disease - Orofacial granulomatosis (persistent linear ulcers)
  – Celiac Disease – gluten sensitive enteropathy
  – HIV/AIDS
  – Cyclic Neutropenia – cyclic oral aphthae
  – Other autoimmune diseases and rare primary immunodeficiencies

Aphthous ulcers– possible etiologic factors

• Ingestion of certain foods – nuts, chocolate, tomatoes ?
• Lysine deficiency ?
• Hematonic deficiencies
  – Iron, B12, folic acid
• Drug reactions – NSAIDS, nicorandil, Cellcept
• Allergies
• Menstrual period (?), stress and anxiety (?), family history (40%–family hx)
• Viral?
• Local physical trauma
• Smoking protective

Aphthous Major

• Uncommon
• Large lesions –5-20 mm. One or more at a time
• Mucosa of the lips, and posterior soft palate/anterior fauces
• Deeper than minor lesions
• Last for up to 6 weeks
• Severe pain, affects daily living
• Deep and persistent lesions can be secondarily infected
• Heal with scarring
Major Aphthae

- > 1cm
- Deep, heal with scarring
- Persist for 3-6 weeks
- More likely to be associated with systemic conditions such as Behcet’s; HIV/AIDS and immunodeficiency

Behcet Disease

- Uncommon systemic multifactorial condition
- Many have circulating antibodies to Herpes
- Genetics? –
- 60-70% HLA-B*51!

- Intraoral ulcers similar to aphthae
  - Most consistent feature, found in almost 100%
  - Genital ulcers (90% total pts) and erythema nodosum (47.6% of all pts) more prevalent in females
  - Skin, thrombophlebitis, ocular, neurologic, pulmonary and vascular involvement more common in males
  - Colchicine used to treat the systemic manifestations

Behcet’s International Study Group Guidelines

- Diagnosis cannot be made without the presence of oral aphthae
- RAS plus at least 2 of the following:
  - Recurrent genital ulceration
  - Eye lesions
  - Skin lesions
  - Positive pathergy test
**Behcet’s Disease**

Possible triggers: NSAIDS and other drugs
Recurrent HSV infection

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**Erythema Multiforme**

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**Erythema Multiforme**
Recurrent intraoral varicella zoster

- Can mimic a toothache before lesions appear
- May start as blisters, rapidly rupture to form coalescent shallow ulcers
- Stops abruptly at the midline
- Palate a common intraoral site
- Rare case reports of associated sloughing of necrotic bone containing the teeth
- More common in debilitated, immunocompromised patients

Lichen Planus

- A skin disease common in oral cavity
  - Cutaneous and oral surfaces 40%
  - Cutaneous alone 35%
  - Oral mucosa alone 25%
- Etiology unknown
- Relationship to dysplasia?
  “Lichenoid dysplasia”
  - Reticular
  - Plaque/Bullous
  - Atrophic/Erosive
    - Desquamative gingivitis
  - Pigmented

Lesions that look like lichen planus

- Lichenoid drug reaction
- Lichenoid dysplasia (?)
- Graft vs. Host Disease
- Cicatricial/mucous membrane pemphigoid, Pemphigus vulgaris
  - Desquamative gingivitis
- Chronic Hyperplastic Candidiasis
  - Looks like reticular LP
- Atrophic Candidiasis
  - Looks like erosive/atrophic LP
- Oral ulcers of Lupus erythematosis
Reticular Lichen Planus

Wickham’s striae

Erosive Lichen Planus

Erosive Lichen Planus

• Mixture of erythematous and white pseudomembranous areas
• May have whitish peripheral zone, between affected and normal tissue
• May have sore mouth, esp. spicy foods
• Pain and bleeding on palpation
• DDx: Candidiasis, pemphigoid, pemphigus, lupus
Lichenoid Mucositis and Candidiasis occurring together

Biopsy showed lichenoid mucositis with Candidal hyphae
After 2 weeks of clobetasol gel t.i.d and Nystatin swish and spit q.i.d.

Erosive Lichen Planus

Cinnamon Reaction
Lichenoid Mucositis
Lichen Planus – Bullous form

- Rare form
- Large bullae ranging from 4 mm to 2 cm
- Bullae of brief duration, rupture, loss of epithelium
- Becomes erosive lichen planus
- Most common on posterior buccal mucosa

Erosive and Bullous Lichen Planus

Lichen Planus

- Treatment:
  - Symptomatic cases only
  - Topical corticosteroids, tacrolimus(?)
  - Resistant cases of erosive, may use prednisone; intralesional injections of steroids; or systemic immunomodulators
Lichenoid Drug Reaction

- Increasing prevalence
- Antibiotics, antihypertensives – ACE inhibitors and thiazides, antimalarials, diuretics, gold compounds, NSAIDS, tetracyclines
- Resembles erosive lichen planus
- Posterior buccal mucosa
- Painful, central erythematous area of erosion, radiating striae
- Treatment with topical steroids and removal of offending drug

Lichenoid Dysplasia

- A series of case reports of squamous cell carcinoma arising in previously diagnosed oral lp
- Retrospective review showed that most of these were lesions exhibiting epithelial dysplasia and a lichenoid inflammatory pattern
- Nevertheless, if there are features of dysplasia in cases that resemble lp, these patients must be followed closely with re-biopsy to detect malignant transformation
- Tobacco NOT typically involved
- Erosive and atrophic forms most often associated with this

Red and white lesion on the left lateral tongue
Red and white lesion on the left floor of mouth

Lichenoid mucositis on buccal mucosa  Squamous cell carcinomas on the left lateral and dorsal tongue
DENTAL MANAGEMENT CONSIDERATIONS IN PEMPHIGUS and PEMPHIGOID

- Imunosuppressants; increased risk of infections
- More frequent appointments
- Be gentle during maintenance appointments; avoid harsh abrasives
- Use simple hand scaling instruments
- Provide a list of rinses not containing irritating ingredients

REFERRALS

- Dentist or dental specialist experienced in performing biopsies of vesiculobullous lesions
- Oral medicine; oral and maxillofacial pathology
- Dermatologist
- Ophthalmologist
- Rheumatologist
- Other specialties
TREATMENT

Treatment of blistering diseases consists of three phases:
• Control
• Consolidation
• Maintenance

Relapse may occur at any time, resulting in renewed disease control effort.

Common Therapies:
• Topical steroids
• Systemic Corticosteroids
• Immunosuppressants
• Biologics
• IVIG

Key Concepts
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• Treatment of oral lesions may include topical corticosteroids initially or to treat breakthrough lesions; systemic therapy is almost always needed for disease control
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• Consult with Oral Medicine or Oral Pathology, Dermatology, Oral Surgery
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