TOPICS IN ORAL PATHOLOGY

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HPV ORAL LESIONS

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HPV lesions you may encounter in clinic:

**Low-risk**
- Verruca vulgaris
- Squamous papilloma
- Heck’s disease
- Condyloma acuminatum

**High risk**
- Oropharynx lesions with induration / ulceration

What is the significance of HPV in the oral mucosa?

- Not all HPVs are the same
- Low risk vs. High risk
- Not all infections result in disease
- Episomal vs. integrated
- Not all infections result in carcinogenesis
- Do we test all HPV lesions?
- Oral cavity cancer has 6% association with HR HPV (mostly 16)
- Many cases of OCSCC could be prevented by HPV vaccination
- Oropharyngeal SCC is biologically different that OCSCC
HPV evolution

- Between 1984 and 2004, the HPV-associated OPSCC increased from 16% to 72%
  - Surveillance, epidemiology, and end results (SEERS)
- HPV DNA detected in 24% of OCSCC, but not E6/E7 oncogenes tested
  - Kreimer 2005

One cancer, two diseases

<table>
<thead>
<tr>
<th>Non-HPV-associated SCC</th>
<th>HPV-associated SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity proper except Waldayer’s ring</td>
<td>Waldayer’s ring and “pharynx”, tonsils, BOT</td>
</tr>
<tr>
<td>Tobacco and alcohol main risk factors</td>
<td>HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82</td>
</tr>
<tr>
<td>Better differentiated</td>
<td>Sexual behavior</td>
</tr>
<tr>
<td>OCSCC</td>
<td>Basaloid histology</td>
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<tr>
<td></td>
<td>OFSCC</td>
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</table>
What is the link between HPV and SCC?

- HPV DNA in 9.8% of OCSCC, and high-risk E6/E7 oncogenes in 5.9%
  - Lingen 2013
- FOM / Tongue
- Similar age
- Men
- Early stage
HPV etiologic fraction of SCC

- OCSCC: 6%
- OFSCC: 70%

PERIODONTAL LESIONS

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### Some Common suspects

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Masses</strong></td>
<td>• PPPF, oral focal mucinosis, giant cell fibroma</td>
</tr>
<tr>
<td><strong>Cysts</strong></td>
<td>• Gingival, LPC</td>
</tr>
<tr>
<td><strong>Bone lesions</strong></td>
<td>• Osteoma, exostosis, parosteal osteosarcoma, central lesions</td>
</tr>
<tr>
<td><strong>Macules/patches</strong></td>
<td>• OMM, AT, Nevus</td>
</tr>
<tr>
<td><strong>Ulcers</strong></td>
<td>• ELP, PV</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>• HPK, Dyspl, VX</td>
</tr>
<tr>
<td><strong>Red</strong></td>
<td>• LP, MMP</td>
</tr>
<tr>
<td><strong>Blisters/bulla</strong></td>
<td>• MMP, HSV</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>• Leukemia, SCC, sarcomas</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>• Breast, prostate</td>
</tr>
</tbody>
</table>

### Attached gingiva

#### Frequently encountered:
- HSV
- Fistula/abscess
- Pyogenic granuloma
- Peripheral ossifying fibroma
- Peripheral giant cell granuloma
- Fibroma / giant cell fibroma
- Gingival cyst / LPC
- Loc. juv. spongiotic gingival hyperplasia
- Oral focal mucinosis
- Immune-mediated disorders
- Malignancies or metastases
- Peripheral odontogenic tumors

#### “Never” encountered:
- Lipoma
- Mucocele
Basic Workup for gingival lesions

- History and evolution (frequency, locations)
- Symptoms
- Phases of the lesion
- Define the lesion(s)
- Palpation
- Signs of inflammation or infection
- Signs of trauma
- Measurements
- Expansion of cortex
- Probing depths
- Tooth vitality
- Photographs
- Radiographic evaluation
- Manage based on DX
- DDX
- Additional tests

Components of the periodontal apparatus

- Epithelial
- Fibroblast
- Osteoclast
- Osteoblast
- Inflammatory
- Endothelial
All these lesions are reactive…so…remove the etiology and the lesion…or it will be back!

Hyperkeratosis

Fibroma

Fistula

PG

POF

PGCG

Periodontal lesions

XEROSTOMIA

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Who gets it?

• Anyone can get it! However, it is most frequent in:
  • Polypharmacy (xerogenic drugs)
  • SS
  • Adults
  • Females
  • Postmenopausal
  • Many diseases

Subjective vs. Objective assessment of salivary function:

Subjective:
  • Does the amount of saliva in your mouth seem too little?
  • Does your mouth feel dry when eating a meal?
  • Do you have difficulty swallowing any food?
  • Do you sip liquids to aid in swallowing dry food?

Objective:
  • Stimulated
  • Unstimulated
Sialometry

- Mostly when compared it to the same person over time.
  - Measurement
    - NPO for one hour before test
      - Unstimulated \( > 0.25 \text{ ml/min} \) is “normal”
      - Stimulated \( > 1.00 \text{ ml/min} \) is “normal”
        - Stimulated (usually with a piece of paraffin or periodic mechanical friction to lateral tongue)
    - May measure variable number of minutes, but usually between 1 and 5 minutes. Always report as ml/min.

Treatment/management of xerostomia

- 1 - Determine the cause and if possible eliminate it.
- 2 – Protect tissues from further damage (fluoride, enamelectomy/polishing, etc.)
- 3 - Stimulate salivary flow if possible
  - Physical stimulation (foreign bodies, salivary production stimulators -flavors, massage, muscle function, etc.)
- Drugs – check pharmacology and medical history for each case!!!
  - Pilocarpine hydrochloride (Salagen™)
  - Cevimeline hydrochloride (Evoxac™)
- 4 – Coat the surfaces
  - Oil-based products are longer lasting
  - Commercially available products are better accepted
JAW LESIONS

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Benign Fibro-osseous Lesions

- Cemento-osseous dysplasia
  - Periapical (common cementoma)
  - Focal
  - Florid
  - Gigantiform cementoma

- Fibrous dysplasia
  - Monostotic
  - Craniofacial
  - Polyostotic
    - AMAS & Jaffe

- Cemento-ossifying fibroma
  - Conventional
  - Aggressive / Active
    - Psammomatoid & Trabecular

- "Others" (not really BFOLs)
  - Osteoma
  - Osteoid osteoma
  - Osteoblastoma
  - Osteochondroma
  - Cementoblastoma
  - ??? TBC, CGCLs, Cherubism, ABC

4/17/2014
- Do we really know the etiology of BFOLs?
Are They all the same family of disease?
Is cementum a type of bone?
Is the terminology correct?

Dysplastic / neoplastic?
Reactive
Neoplastic

Fibrous dysplasia
Cemento-osseous dysplasia
Ossifying fibroma

Fibrous dysplasia

• Currently is considered to be a developmental, tumorlike (hamartomatous), fibro-osseous disease of unknown etiology
• However:
  • Theory that somatic mutations in the GNAS1 gene cause it
  • 1 case with clonal structural chromosomal aberrations in a case of monostotic FD suggesting a neoplastic process
• Onset during 1st and 2nd decades, painless swelling of involved bone
• Typically contiguous involvement of maxillofacial and cranial bones
• Radiographic appearance reflects histologic features, ground-glass opacity without defined borders
Periapical Osseous dysplasia
(periapical cemento-osseous dysplasia)

- Predilection for middle-aged black females
- One or more (0.5cm or less) circumscribed lesions in periapical areas of vital teeth
- Painless, nonexpansile, usual location in anterior mandible
- Radiographic features can be radiolucent, mixed density, or opaque with lucent rim
- Cellular fibrous stroma with woven and/or lamellar bone and/or oval calcifications

Focal osseous dysplasia
(focal cemento-osseous dysplasia)

- Predilection for middle-aged black females
- Painless, nonexpansile, usual location in mandibular molar region, often in edentulous area
- Most often demonstrates circumscribed radiolucency with opacities
- Surgical findings reflect gross features: difficult to remove resulting in small hemorrhagic gritty fragments
Florid osseous dysplasia
(florid cemento-osseous dysplasia)

- Predilection for middle-aged black females
- Painless, nonexpansile; involvement of two or more jaw quadrants
- Radiographic features are multiple confluent lobular sclerotic masses in tooth-bearing areas
- Initially unencapsulated proliferation of cellular fibrous tissue with trabeculae of woven bone and/or oval calcifications without inflammation
- Late-stage lesions show acellular, avascular, coalesced sclerotic bony masses
- May be associated with superimposed infection and osteomyelitis
- Sometimes associated with simple bone cysts (idiopathic bone cavities)

Familial gigantiform cementoma
(familial florid osseous dysplasia)

- Autosomal dominant inheritance with variable expressivity
- Multiple quadrant involvement of radiopaque lesions similar to florid OD
- Variable presence of rapidly expansile lesions, especially in anterior mandible
- Onset at young age
- No racial predilection
Ossifying fibroma
(cemento-ossifying fibroma)

- Well demarcated radiographically with smooth, often sclerotic borders
- Usually a solitary lesion; majority in mandible
- Centrifugal growth pattern (maintains round/oval shape with enlargement)
- "Shells out" from surrounding bone intact or in large pieces

JAOF

- Not all JAOFs are diagnosed in children and adolescents,
- Not all JAOFs exhibit locally aggressive behavior,
- Not all lesions reported as JAOF have the same histopathologic features.
  - JAOF, trabecular variant, are those that correspond to the WHO definition
  - JAOF, psammomatoid variant, are those that correspond to the 1991 definition of Johnson et al. and contain spherical ossicles.
AUTOIMMUNE DISEASES

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Pemphigoid

Autoimmune – defect is with hemi-desmosome connecting basal layer with connective tissue

Associated with ocular problems, must have ophthalmology evaluation if suspected
Pemphigoid

Histology

Sub-basilar split of epithelium from underlying connective tissue

DIF – positive for a line of IgG, C3 at BMZ

Pemphigoid

- IgG autoantibodies specific for the hemidesmosomal antigens:
  - BP230 (BPAg1)
    - intracellular component of the hemidesmosome;
  - BP180 (BPAg2)
    - (type XVII collagen) is a transmembranous protein with a collagenous extracellular domain.
Pemphigus

Autoimmune

Can be associated with underlying malignancy elsewhere in body (paraneoplastic pemphigus)

Pemphigus

- Histology
  - Acantholysis of epithelium, tombstone appearance
  - DIF – intraepithelial chicken wire pattern of IgG and C3
Erythema multiforme

- Acute, recurrent type IV reaction
- Young adult males
- EM
  - 60-70% of EM pts have oral lesions
  - 40 of all EM pts have oral lesions only
- Many times a self limiting reaction
- Trigger factor??
  - Drugs
  - Viruses
  - Bacteria
  - Etc
- Treat with steroids and watch the airway
  - Steven Johnson syndrome

Sjögren's Syndrome

**Definition**

- A systemic autoimmune - rheumatic exocrinopathy that affects mainly the salivary and lacrimal glands producing sicca symptoms due to lymphocytic infiltration.
Sjögren's Syndrome

Classification
- Primary
  - Not associated with any other rheumatic / autoimmune disease
- Secondary
  - Associated with another rheumatic / autoimmune disease
    - RA, SLE, scleroderma, polymyositis, dermatomyositis, or systemic vasculitis

Pathogenesis
- Lymphocytic infiltration of gland
- Acinar areas
- Does not account for total of symptoms
- Variable volumes do not correlate well with complaints
- Lubricant and protective features of secretions are altered

Multifactorial
- Immunologic, neurological, and endocrine factors, viruses (EBV, Coxackie, HepC, HIV)
Sjögren’s Syndrome

- Clinical manifestations
  - Glandular (Sicca)
    - Xerostomia
    - Xerophthalmia
    - Vaginal dryness
    - Glandular enlargement
  - Skin
    - Xeroderma
    - Vasculitis
  - Extra-glandular
    - Arthralgia, myalgia, miositis
    - Vasculitis / vasculopathy
    - Interstitial lung disease
    - Lymphadenopathy
    - Interstitial nephritis
    - Autoimmune hepatitis
    - Biliary cirrhosis
    - Cognitive dysfunction

Sjögren’s Syndrome

- Oral findings
  - Xerostomia
  - Frothy saliva
  - Decreased pooling in FOM
  - Difficulty swallowing and wearing dentures
  - Altered taste
  - Fissured and “bald” tongue
  - Candidiasis (angular cheilitis and erythematous)
  - Cervical caries
  - Retrograde bacterial sialadenitis
  - Salivary gland enlargement
Sjögren's Syndrome

- **Treatment**
  - **Topical**
    - Eyes, mouth, other mucosas
  - **Systemic**
    - Vasculitis, fatigue, pain, sleep

- **Prognosis**
  - Secondary to sicca
  - Lymphoma (approx. 6-10% of SS patients)

Oral Lichen Planus

- Common dermatologic disease that may involve mucosal sites
  - Immunologically mediated mucocutaneous disorder
  - Medication or substance-induced (?LP)
  - Foreign bodies (LP?)
  - Stress
  - 1% of pop. Skin LP
  - 0.1-2.2% of pop. OLP
Oral Lichen Planus

Clinical Features:
- Middle-aged adults
- Women 3:2
- Skin: purple, pruritic papules at the flexor surfaces of the extremities with *Wickham’s striae*
- Oral: reticular and erosive

Diagnosis
- always rule out “reactions”
  - Reticular – usually clinical
  - Erosive – Biopsy
    - H & E routine stain – use formalin as fixative
    - Direct Immunofluorescence – use Michel’s solution as transport media
    - The purpose is to rule out other diseases; LP has no specific pattern in DIF
Oral Lichen Planus

• Treatment (management)

  • Reticular:
    • No treatment necessary for asymptomatic cases
    • Avoid anything that produces oral discomfort or trauma
    • If symptoms occur, treat like erosive variant after ruling out Candidiasis
    • Yearly follow-up

Oral Lichen Planus

• Treatment (management)

  • Based on symptoms
  
  • Erosive:
    • Corticosteroids
      • Topical
      • Systemic
    • Tacrolimus (Protopic)
    • Bi-annual follow-up
Oral Lichen Planus

- Is it pre-malignant?
  - Erosive variant is more suspicious (1-5%)
  - Follow-up and excise atypical areas

Topical and systemic Medicines

**Topical steroids**
- Fluocinonide
- Clobetasol
- Dexamethasone
- Dex and others
- Tacrolimus

**Systemic**
- Prednisone
- Medrol Dosepak
- Trental
- Tetracycline and nicotinamide
- Other immunomodulating drugs
Steroids side effects

- Sodium and water retention
- Hypertension
- Hypernatremia/Hypokalemia
- Hyperglycemia
- Candida infection
- Mood changes
- Peptic ulcer disease

Long term side effects
- Muscle wasting/fat deposits
- Delayed wound healing
- Osteoporosis
- Cataracts

How do we decide?

- Physician consultations
- Dexterity of patient
- Compliance factor
- Third party involvement
- Other medical conditions
- Extent of the lesions
- Patient’s wishes and expectations

How to choose?
### Our favorite steroids:

- **Dexamethasone elixir (Decadron)**
- **Fluocinonide gel (Lidex)**
- **Clobetasol gel (Temovate)**
- **Medrol dosepack**

### How do we choose?
- Extent of the lesions
- Other medical conditions
- Medication interactions
- Physician consultations
- Dexterity of patient
- Compliance factor
- Third party involvement
- Patient’s wishes and expectations

### Dexamethasone elixir 0.05mg/5cc (Decadron)

**Disp:** One pint

**Sig:** Use one tablespoonful as mouthwash for 2 minutes and expectorate. NPO 15 min after use. Repeat QID.

**Refills:** 6 months

### Our way:
- Use 5 min after oral hygiene
- Use a timer
- Longer exposure is even better
- Make sure to spit it out
- Sometimes I calculate a dose and have the patient swallow it in the AM qd
- If it gets too frothy or diluted, spit out after one minute and use a fresh Tb for second minute
- Do not rinse after use
- NPO 15-20 min after use
- Last dose before bedtime
- Watch for Candida!
### Fluocinonide 0.05% gel

**Disp.** 30 g tube  

**Sig:** Apply a thin coat to dry oral lesions. Repeat QID. NPO 20 min after use.  

**Refill:** 6 months

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**Our way:**

- Apply to dry lesions – use Q-tips  
- Dry, apply, hold 2 minutes  
- Use 10 min after oral hygiene  
- Last dose before bedtime  
- Do not rinse after use  
- OK to use in mouth (external use only)  
- OK to use in gauze or dress with gauze  
- A thin coat does the trick  
- NPO 20 minutes after use  
- Medicine only acts on contact!

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### Clobetasol 0.05% gel (Temovate)

**Disp.** 15 gram tube  

**Sig:** Apply a thin coat to dry oral lesion. Repeat QID. Discontinue after 2 weeks of use.  

**Refill:** None

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**Our way:**

- Same application method that fluocinonide  
- Much more potent than fluocinonide  
- After 2 weeks of use may induce mucosal atrophy  
- Higher incidence of Candidiasis  
- OK for skin conditions also
FDA Black Box Warning:

- Tacrolimus 0.1% (Protopic)
  - Disp: 30 g tube
  - Apply a thin coat to oral lesions BID. Do not exceed 2 weeks of use. Taper as needed.

Systemic steroids

- Prednisone
  - Medrol dosepack
  - Other tapered regimens
  - Continuous dosage of prednisone (must calculate dose, check pharmacology, and monitor often)
Medrol dosepack

Disp: One dosepack

Sig: Take as directed on package starting in the AM of day 1.

Refill: None.

Our way:

- Make sure it is OK based on medical history and other drugs
- If questions, call PCP MD and request written OK
- Use only when clear of Candidiasis
- Request patient’s feedback q3d and at end of pack
- Usually followed by a topical steroid
- Good for “special occasions”
- Be vigilant about side effects