1 **Bumps & Lumps….**
What's HPV Got To Do With It?

2 hour Oral & Pharyngeal Pathology Review

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2 **Bumps & Lumps…**
What's HPV Got To Do With It?

Patient Assessment
- Clinical
- Diagnostic tools

Human Papilloma Virus Infection
- Low risk
- High risk

Squamous cell carcinoma
- Oral Cancer
- Pharyngeal (tonsillar) Cancer

3 **Early Detection is Essential**
- Oral CA = 3 X more common than cervical CA, with 2 x the # of deaths
- Oral cancer is more prevalent than melanoma & Hodgkin lymphoma

4 **2018 Statistics: <u>Oral & Oropharyngeal (OP)</u>**
<u>Ca Estimates</u>
- ~51,540 oral or OP Ca cases (2.9% of all new Ca)
- ~10,030 related deaths (1.6% of all Ca deaths)
- 64.5% 5 yr. Survival rate (2007 – 2013)
- Distribution:
  - –males 2X > female
  - –Blacks = whites
- Recent years for both men & women:
  - –Decrease in new HPV (-) oral & OP Ca
  - –Rise in HPV (+) oral & OP
-

5 **2018 Statistics: Oral & Oropharyngeal Ca**
- Average age of diagnosis = 62
- > 25% are under 55 yrs.
- Incidence varies geographically
  - –Much more prevalent in Hungary, France than U.S.
  - –Less in Mexico & Japan than U.S.
- Death rates decreasing over last 30 yrs.
- Oral & OP Ca pts have increased risk of other related lesions (primary or secondary neoplasms)
  - –Lifelong regular screening

•

6 **What are some Oral CA Risk Factors?**

- Smoking & nicotine
- Alcohol
- HPV
- Chemical /physical trauma
- Immunodeficiency
- Inherited disorders
  –Addison's
- Iron deficiency anemia
-

7 **Nicotine Stomatitis**
Moderate risk until changes

8 **Oral Submucous Fibrosis**

1 • Chronic betel quid use
- Firm, banding, may be painful
- Loss of elasticity
- May progress to SCC

9

Oral Submucous Fibrosis

Areca nut or betel quid chewing

So. E. Asia, India

1% Ca. risk

10 **Vaping**

11 **Burns, Explosions, lung damage: bronchiolitis obliterans**

12 **E-Cig Research (70 K people) showed:**

- Super-heated nicotine vapor = addictive
- "E-juice" = flavorings, propylene glycol, glycerin, often nicotine (kid-friendly)
- 5 carcinogens (toxins) in urine of 16 y-o's who vape
- E-cigs encourage transition to cigs
- E-cigs double risk of heart attacks
- E-cigs + cigs leads to 5x risk of heart attacks
- Promoted as smoking cessation tools, but most (afraid to stop): become dual users
- Cheaper than cigs
-
-
-

13 **Oral Cancer Risk Factors**

- Tobacco & alcohol involved in 80% of cases
- Synergistic effect:
  - –Alcohol alone inc. risk 0-2 X
  - –Smoking (2 ppd) inc. risk 5 X
  - –Smoking & heavy drinking inc. risk 15 X
- Low socioeconomic status increases risk:
  - –Poor access to care
  - –Nutrient-poor diet

14 **Online Cancer Risk Assessment Tool**

Why do a risk assessment?

Set OP screening exam recall

Justify screening cost & need

Patient education

Legal liability

"Why wasn't this caught by the dentist earlier???"

15 **Select an assessment**

1 DENTAL CARIES
PERIODONTAL DISEASES
ORAL PATHOLOGY ✓

Risk assessment supports diagnostic steps, tx. & payment?

16 **Philips Questionnaire (23?'s)**

1
- CA history
- Radiation therapy
- Leukoplakia
- Erythroplakia
- Non-healing ulcer
- Swelling, numbness, tingling
- Difficulty swallowing, chewing
- Sore throat, hoarseness
- Non-painful enlargement
-
-
-

•

2 • Lichen planus
• Tobacco
• Alcohol
• Betel nut, quid, areca nut
• Immune suppression
• Sunburns
• Poor nutrition
• HPV
• ≥ 50

17 **What assessments do you do?**

A. Visual exam
B. Palpation
C. Interview
D. Visualization technology (light)
E. Biopsy / referral

18 **The Possibilities….**

• Variant of normal
• Injury
• Inherited condition
• Reactive lesion
• Infectious condition
• Feature of systemic condition
• Neoplasm
•
• A moment in time. Pathogenesis

•

19 **Early Signs of Oral Cancer**

Clinical:
• Small white lesions
• Small red velvety lesions
• Combination red and white lesions

20 **Early Signs of Oral Cancer**

Clinical:
• Indurated nodules or masses
• Ulcers that do not heal or that persist for longer than 2 weeks
• Extraction site that doesn't heal

21 **Early Signs of Oral Pharyngeal (OP) Cancer**

1 • Sore, irritation, lump or thickening
• White or red patch
• Difficulty in chewing or swallowing

- Ear pain
- Difficulty moving the tongue or jaw

22 **Early Signs of OP Cancer**

1
- Hoarseness, sore throat
- Feeling that something is caught in the throat
- Numbness (tongue or other areas)
- Swelling of the jaw that causes dentures to fit poorly or become uncomfortable

23 **Differential Diagnosis**

- List of most likely pathologies
- Clinician decides diagnostic method to reach definitive diagnosis

24 **Definitive Diagnosis**

1 How?

2
- Clinical
- Historical
- Therapeutic
- Laboratory
- Surgical
- Microscopic
- Molecular

25 **TNM staging: T = tumor size, N = palpable nodes M = metastasis**

1
- T_1: < 2 cm diameter
- T_2: 2-4 cm diameter
- T_3: > 4 cm diameter
- T_4: invading adjacent tissue

2
- N_0: 0 nodes
- N_1: Ipsilateral nodes
- N_2: Contralateral or bilateral nodes
- N_3: Fixed nodes

26 **Tumor Stages**

1
- I: $T_1 N_0 M_0$
- II: $T_2 N_0 M_0$
- III: $T_3 N_0 M_0$
- III: $T_{1-3} N_{0-1} M_0$
- IV: $T_{1-4} N_{2-3} M_{0-1}$

27 **Tumor Advancement Terms**

1
- Local: Stage I, II, some III Ca – not outside of primary site, no lymph nodes
- Regional: Stage III, some IV if not metastasized - spread to nearby area &/or lymph nodes

• Distant: metastasized

28 **Neoplasia –**
"new growth"

Uncontrolled and unlimited proliferation of cells

Irreversible

29 **Neoplasms**

• SCC = most common oral cancer
• Skin reacts normally to use & trauma with:
  –Hyperplasia
  –Keratinization
  –Melanin
• Neoplastic cells are permanently altered

30 **Cells of Malignant Tumors**

• Pleomorphic
• Hyperchromatic
• Mitotic figures
• Keratin pearls

31 **Fluorescence and reflectance spectroscopy**

• Technology successfully used for diagnosis of cancer in:
  –Lung
  –GI Tract
    • Esophagus
    • Colon
  –Skin
  –Cervix
  –Oral cavity
•

32 **What shows up dark?**
Heavy molecules absorb light

• Dysplasia, malignancy (chromatin)
• Moles, freckles, pigmentation, melanoma (melanin)
• Blood (hemoglobin)
  –Vessels
  –Inflammation
  –
• Blanching reveals vascularization

33 **In addition to Dysplasia and Oral Cancer**
We can also discover these conditions:

- Lichen Planus
- Lichenoid mucositis
- Squamous Papillomas
- Candidiasis
- Viral and bacterial infections
- Inflammation from a variety of causes (e.g trauma)
- Salivary gland tumors
-

34 **The Identafi Exam Directions**

- Conduct tactile exam per ADA guidelines
- Conduct conventional oral examination with white light
- Conduct thorough exam with violet light
- Conduct site specific exam with green-amber light if lesion found
- Document all areas of concern
- Follow-up or refer if necessary

35

36

37 **The Exam**

Violet light enhances normal tissue's natural fluorescence.
Suspect tissue appears dark

38 **The Exam**

39 **What an Abnormal Lesions Looks Like**

40 **Red & White Lesions**
Lights = most useful for red

41 **The Value of Fluorescence and Reflectance Spectroscopy**

- Early ID of dysplasia & carcinoma-in-situ (sub-surface alterations)
- Determining location for biopsy
- Assessing change, healing, resolution or progression of suspicious lesions
- Confirming symmetry, normal vasculature
- Recording & communicating oral findings

42 **Microscopic Differences**

- Epithelial dysplasia – premalignant histological diagnosis (abnormal cells have not gone through the basement membrane); may be a white, red, or mixed in color lesion; frequently precedes squamous cell carcinoma
- Carcinoma in situ – severe dysplasia of the entire epithelium
- Squamous cell Carcinoma (SCC) - malignant

43 **Squamous Cell Ca: Most common Oral & OP Ca**

All asymptomatic, long standing lesions

44 **Verrucous Carcinoma**

1 • A form of squamous cell carcinoma; slow growing exophytic tumor with a pebbly white and red surface
• Better prognosis because basement membrane is intact; no invasion (metastasis)
• Tx ~ excision

45 **What's HPV Got To Do With It?**

• HPV causes benign papillary oral "warts"
• HPV is linked to oral, OP cancer
• Detection is important
• Professional knowledge
• Public awareness

46 **Human Papillomavirus (HPV)**

• >150 types (> 40 found orally)
• Infects epithelium
• Species-specific (infects rabbits, cattle)
• 20 mil infected in U.S., 6 mil / yr
• May be associated w/ CA of mouth, base of tongue, tonsils, throat
• HPV = separate CA risk from tobacco, alcohol
•

47 **HPV- Related Lesions**

• Oral prevalence = 6.9%
• ~50% of males tested = HPV (+)
• Most infections = cleared fm body ~ 1 yr w/t causing cell changes
• Some remain ~ 20 mos (no clinical signs)
• Some appear cleared but return
• May progress, alter cells DNA, cause dysplasia / CA

48 **Oral & pharyngeal Cancer Rates**

• In 2018: 51,540 new cases - oral + pharyngeal Ca
  –(10,030 deaths)
• From 1973 to 2001 overall incidence of Oral Ca decreased
  –Incidence of tongue base, tonsil & oropharynx Ca increased
• Overall 5-yr survival = 60% (increased steadily since 1975)
  –62% 5-yr survival for white men
  –35% for black men (later diagnosis)
  –

49 **Transmission / Pathogenesis**

• Direct contact
• HPV must infect basal epi cells
• Usually requires break in skin
• Proliferation of basal cells = common
• HPV inserts into nuclear material of epi cells

- Alters cells: visible microscopically

50 **Koilocytes: HPV infected cells**

51 **HPV-related Oral Epithelial Dysplasia**

Previously: "koilocytic dysplasia" (1998)

Proposed new name: "HPV-associated oral intraepithelial neoplasia"

52 **Different HPV Types**

1 • Specific HPV types cause different lesions & have varied CA potential
- Low Risk:
  - –Type 6 & 11: assoc. w/ benign warts:
    - Papilloma
    - Verruca vulgaris
    - Condyloma acuminatum
    - Multifocal epi. Hyperplasia (Heck)
  - –

53 **High Risk**

1 • HPV 16, 18, 31, 45 = cause flat, non or hardly visible dysplastic lesions
- 16 & 18 = cause ~95% of cervical CA, now assoc. with oral / pharyngeal CA
- Viral particles ID'd by immunologic staining
-
-

54 **High-risk HPV**

1 • Chronic high-risk HPV increases OP Ca 6-50X
- HPV-16 & 18 causes > 90% of tonsillar Ca
- **Other high-risk subtypes: HPV- 31, 33, 45, 52, 58

55 **HPV (+) Oropharyngeal (Tonsillar) Ca Risk Factors**

- 90% of OP cases = HPV (+), incidence = increasing
- Males 5 X > females
- Smoking related to 50-65% cases
- Strongly related to sexual history
- Marijuana increases risk
- Alcohol not significant factor
- Lymph node metastasis at presentation: 80-85%

56 **HPV (-) Oropharyngeal (Tonsillar) Ca**

- Only 10% of OP Ca = HPV (-), incidence = decreasing
- Males 5X > Females
- Smoking related in 80-90% cases
- ETOH has synergistic effect
- Sexual history = unrelated
- 3-5 X higher mortality than HPV(+) OP Ca

57 **Oral & Pharyngeal Cancer**

1 HPV (-)
- Decreasing
- Older patients
- Low socioeconomic status
- Risk = tobacco & alcohol
- Poor survival prognosis (40% 3 yr survival)

2 HPV (+)
- Increasing
- Younger patients
- Higher socioeconomic status
- Risk sexual history
- Better prognosis (80% 3 yr survival)
  - –Smoking, tobacco negates benefit

58 **Oral and oropharyngeal HPV Transmission**
- Sexual (oral-genital) contact
  - –Includes deep kissing
- Rare: vertical transmission at birth
- Parents to child – saliva?

59 **Types of HPV Infection (duration)**
- Transient carrier: no lesions, infection clears (+ serum antibody)
- Chronic carrier: commonly associated with high-risk HPV & immunosuppression

60 **Types of HPV Infection (Viral Type)**

1 Low-risk types
- Benign lesions; papilloma, verruca (common dermal warts), condyloma (genital warts)
-

2 High-risk types
- Precancerous lesions: HPV-associated dysplasia
- Malignancies: HPV-associated squamous cell Ca
-

61 **HPV Diagnosis**
- Cytology & histology = PAP smear, less predictive of HPV-related Ca than molecular HPV testing
- Oral exfoliative cytology or rinse - miss HPV infected cells
  - Within folds of tonsils
  - Deep in throat
- Molecular testing detects persistence of high-risk HPV
- HPV DNA expression & proteins indicate pathogenesis

62 **HPV Infection Mechanisms and Detection**
- HPV enters tissue, infects basal layer of epithelium
  - –Broken tissue
- HPV DNA integrates into host cell DNA through oncoproteins E6 & E7

63 **HPV Infection Mechanisms and Detection**

- Cells proliferate unchecked, over-express p16: a detectable protein
- Infected epithelial cells can be tested by immunohistochemistry (IHC) to show p16

64 **Molecular HPV Testing**

- Early (+) tests may be false alarms! HPV may clear
- Secondary markers show progression
- HPV genes (2 viral oncoproteins E6, E7)
- Host biomarkers (nucleoproteins in dysplastic cells)
- Viral load may predict HPV progression, but varies
-

65 **HPV Diagnosis**

- Transient carrier (most common)
  - –Virus usually clears in 1-3 years
  - –Detect presence in mucosa by:
    - In-situ hybridization
    - Polymerase chain reaction (PCR)
    - Antibody status
- Chronic carrier (uncommon)
  - –High risk HPV type persists, more likely to progress
  - –Detect HPV by:
  - –Antibody status + molecular testing, repeated

66 **Molecular HPV Testing Methods**

- Hybridization – limited specificity
- PCR – highly specific, must repeat for each subtype
- Combined (multiplexing) broad spectrum molecular testing "cocktails" must address different ethnic variants
- Tests: detect infection, "cure / clearance", sequential / re-infection, persistence
- Automated massive sequencing = most efficient, promising
- Need secondary marker tests to ID progression
-

67 **How Do You ID HPV-related Lesions?**

- DNA probe may include transitory HPV infections
- P16+ may be non-specific alone
- Need both:
  - –Evidence of HPV DNA
  - –Evidence of viral DNA integration into host cells: (p16+)

68 **HPV-16 Diversity**

- HPV subtype variants categorized by geographical regions & ethnic groups:
  - –European & Asian
  - –Asian American
  - –African
  - –North American

- Subtypes vary:
  - –Pathogenicity, immunogenicity, tumorigenicity

69 **HPV Salivary Diagnostic Tests**

1. OraRisk HPV
2. OraGenomics
3. MOP Oral Cancer Genetic Test

- FDA cleared (substantially equivalent)
- But….. Do they help your tx plan?
- Does HPV (+) test = real risk for Ca?
-

70 **OraRisk sm HPV® (OralDNA Labs & Quest Labs (2010)**

- Indications:
  - –Traditional oral Ca risk factors; sexually active, family hx of oral Ca, signs & symptoms of oral Ca, suspicious oral lesion, smoker & drinker
- Non-invasive, easy-to-use
  - –Gargle/swish w/ sterile saline – 30 sec., expectorate into funnel-top tube, ship, report
- PCR shows HPV type
  - –(+) test w/no lesion: repeat in 6 mos. If (+) again, refer to specialist

71 **OraRisk sm HPV® Test Value**

1 (-)

- Most HPV infections cleared spontaneously (may take 3 years, esp. in males.
- Tests do not distinguish episodal (transient) from integrated (established) HPV (need p16)
- Hard to get sample from tonsils, oropharynx (High HPV risk area)
- Unestablished referral protocol

2 (+)

- Easy
- Educates patients
- Focuses assessment
- Can be combined with other tests

72 **HPV Vaccine**

1
- Some subtypes not included
- Long term immunity = unknown
- Shown to prevent cervical Ca
- May prevent oropharyngeal (tonsillar) Ca
-

73 **HPV Vaccines**

- Gardasil (Merck, 2006) = quadrivalent recombinant vac.
  - –HPV 6, 11, 16, 18
- Gardasil 9 (Merck, 2014) = Gardasil + 5 additional subtypes (31, 33, 45, 52, 58)
  - –9-14 yrs: 2 doses
  - –15 – 26 yrs: 3 doses

–Vaccine risks: Guillian-Barré syndrome: similar to other vaccines, 2 / 100,000 girls vaccinated

74 **Verruca Vulgaris (wart)**

- Common skin lesion; less common in oral mucosa
- Etiology ~ human papillomavirus
- Autoinoculation from hands or fingers to lips (most common location) or mouth
- Lesion appears as a white, papillary, exophytic lesion
-
-

75 **Verruca Vulgaris (wart)**

- Diagnosis ~ microscopic & molecular
  (finger-like projections of keratotic squamous epithelium with vascular CT)

- Treatment ~ surgical excision, may recur

76 **Squamous Papilloma**

Most common epi papillary lesion
Assoc. w/ HPV 6,11,16
Often solitary
Asymptomatic

77 **Papilloma**

1 • Cauliflower-like
- White (increased keratin) or pink
- Differential diagnosis ~ verruca vulgaris or condyloma acuminatum
- Tx ~ surgical excision with base; usually does not recur
-

78 **Condyloma Acuminatum**

- Benign, papillary lesion
- Transmitted by sexual contact; oral-genital contact or self-inoculation
- More diffuse: multiple lesions
- Oral lesions are pink, papillary, bulbous masses; less keratinized than the verruca vulgaris
- Diagnosis ~ microscopic, molecular
- Treatment ~ surgical excision, may recur

79

80 **Multifocal Epithelial Hyperplasia *Heck disease***

1 • Multiple white to pale-pink nodules throughout the oral cavity
- HPV
- Most common in children
- Diagnosis ~ clinical and microscopic
- Treatment; may resolve spontaneously, or excision

•

81 ☐ **Extra-Oral & Intra-Oral Exam: The Face**

- Lymph nodes
- Salivary glands
- Cysts
- Infections
- Dysplasia / Neoplasms
- Symmetry!
- Function
- Patient sensations
- History

•

82 ☐ **Neck (+ pre & post-auricular nodes)**

83 ☐ **The Lips**

1 • Trauma / scars
- Infections
- Blocked ducts
- Cysts
- Sub-surface tumors
  - –Epithelial
  - –Salivary gland
- Dysplasia / CA
- Loss of vermillion border

84 ☐ **Angular Cheilitis**

85 ☐ **Solar Cheilitis**

86 ☐ **Oral & OP Lesion Descriptions**

- Papillary lesions
- Red & white lesions
- Masses

- Appearance / presentation
- Differential diagnosis
- Definitive diagnosis

87 ☐ **Basic Description**

- Tissue loss
  - –Atrophy
  - –Wear / trauma
  - –Is epithelium intact?
- Tissue expansion
  - –Swelling, edema

–Hyperplasia
–Hypertrophy
• Tissue change (alteration)
•

88 **Descriptions**
• Clinical appearance, exact location
–Shape, borders, attachment
• Color
• Size
• Soft tissue consistency
• Surface texture & integrity
• Radiographic appearance
• History (ask!)
• Symptoms

89 **Terms**
Macules, Plaques, Patches

90 **Macule**
• Color different from surrounding tissue
• Flat

91 **Patch / Plaque: Surface Alteration**
• Depth & attachment: firmly / loosely adherent?
• Size, shape & borders, location, color, surface texture, density / consistency, integrity
• History? Clinical impression?
•
•

92 **Color: erythematous, speckled, pink, blue, brown, black, white**

93 **Surface Texture**
Corrugated Fissured

94

Denuded, circumscribed

Geographic tongue

Multiple confluent patches of smooth denuded mucosa on dorsal and lateral tongue, with distinct (well circumscribed) red borders surrounded with white raised, thickened tissue. Denuded areas are sensitive to PH, spices.

95

Denuded, circumscribed

Geographic stomatitis

96 **Tissue mass: Feel it –**

Is it indurated (hardened), soft, firm?

- Fixed
- Movable
- Does it have…
  - –Distinct borders?
  - –Diffuse borders?
- On the tissue?
- In the tissue?
- Which tissue?
- Painful?

97 **Nodule: Exophytic, Endodphytic**

98 **Lobule: Clinical Appearance**

- Lobule: gross clinical description
  - –Adj: lobulated
- A segment or lobe that is a part of the whole
- Lobes sometimes appear fused together.

99 **Unilocular: radiological or gross surgical description**

100 **Pedunculated**

- Attached by a stem-like or stalk base

101

1 • Fixed vs. Movable
2 • Firmly vs. Loosely attached

102 **Is it solid or fluid filled?**

103 **Describe Density**

-
- Solid
- Firm
- Thickened
- Hard
- Soft
- Fluctuant

104 **Vesicles / Ulcerations**

105 **Leukoplakia**

106 **Erythroplakia**

107 **Speckled Leukoplakia**

108 **Bumps & Lumps…**

What's HPV Got To Do With It?

Patient Assessment
- Clinical
- Diagnostic tools

Human Papilloma Virus Infection
- Low risk
- High risk

Squamous cell carcinoma
- Oral Cancer
- Pharyngeal (tonsillar) Cancer