PATHWAYS TO CANCER

- **Alcohol and Tobacco Use. Alcohol potentiates tobacco's carcinogenic actions. 15x more cancers in SMOKERS that also drink, a synergistic effect.**
- **HPV-16 (*literature also supporting 6,11,18,31,33,45, 52 & 58*): Human Papilloma Virus version 16 is responsible for 85% of all HPV related oropharyngeal cancers. Same strain responsible for 75% of all cervical cancers. *GARDASIL 9 ® Vaccine (2-3 doses depending on age) covers ALL 9 HPV types linked to cervical, Vulva/vaginal, anal, head and neck cancers and genital warts.***
  - *If an HPV+ tumor is present, THC (marijuana) in the blood activates the p38 MAPK pathway, which controls programmed cell death (apoptosis). When activated, cell death does NOT occur and allows the cancer cells to grow uncontrollably.*

  Reference: https://clincancerres.aacrjournals.org/content/26/11/2693
- **Back of mouth, throat, neck, tonsils and base of tongue.**
- Small minority of cases < 7% are idiopathic, but research is directing more study and attention that these cases are related to genetic predisposition. These cases **occur often in persons "young" (under age 40) and are AGGRESSIVE, with high morbidity and high mortality.**
- High treatment related morbidity in survivors: complications from chemotherapies, surgical interventions, loss of function and reduced quality of living in nearly all cases of oral and throat cancers regardless of what stage diagnosed.

Biopsy outcome data from the UNITED STATES

- Of all biopsied (incisional and excisional) specimens, **1.5 – 2% are cancers, ≈7.5-8.0% are severe dysplasia, which is on the borderline of becoming a cancer. Severe dysplasia really is "catching it early" and should be celebrated when discovered!**
- ≈90% of oral biopsies are a *variant of normal tissue* or non-pathogenic.
- **National average for a general practice seeing 2000 patients annually is 1 case of cancer every 3-4 years, but 5 or more cases of dysplasia (pre-cancer) a year. Nearly 1 out of 10 biopsies are cancer or severe dysplasia that is progressing toward cancer**.

Descriptors

- **Red, Pink, White, Blue-black, gray, brown and black** are words most commonly used to describe the color of oral lesions.
- ***Erythema***: Abnormal redness of the mucosa or gingiva.
- ***Erythroplakia****:* A clinical term to describe an oral mucosal lesion that appears as a smooth red path or granular red and velvety patch.

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- ***Leukoplakia*:** A clinical term for a white plaque-like lesion on the oral mucosa that cannot be rubbed off or diagnosed as a specific disease.
- ***Pallor:*** Paleness of the skin or mucosal tissues.
- ***Corrugated*:** Wrinkled
- ***Fissured*:** Clefted, grooved and showing prominent depth
- ***Papillary*:** Resembling small, nipple-shaped projections or elevations found in clusters.
- **Smooth, rough, folded.**

Be descriptive! To the pathologist it all looks like a 'chunk of meat in a little jar' by the time they receive it! Photos BEFORE biopsy are GREAT!

Interview the patient:

Personal history, Family history, Past and present medical and dental histories including medications, drug use, History of the lesion itself, how long has it presented according to the patient, Recent travel history, out of the country?

Historical data constitute a very important component in every diagnosis. Occasionally when historical data are combined with clinical observation, it is the history of the lesion that contributes more to the diagnostic process.

MICROSCOPY

- ALWAYS SUBMIT ORAL TISSUE BIOPSIES TO AN ORAL PATHOLOGIST. Do not submit to "general pathology". The oral tissues are unique, the tissue stratification is unique. Do not delay an accurate diagnosis by submitting your specimen to anyone other than an oral pathologist.
    - The microscopic examination of the biopsied specimen taken from the lesion in question contributes SIGNIFICANT information. It is often the main component in obtaining a definitive diagnosis. The SKILL of the practitioner performing the biopsy is of EQUAL importance!
- Critical to accuracy is that an adequate amount of tissue be sampled (removed) for microscopic evaluation. Scalpel removal still considered the "gold standard" for excisional microscopic examination. Laser removal becoming more prolific and when performed correctly is acceptable for biopsy as well for lesions with a low likelihood of malignancy, such as lesions with the clinical appearances of a fibroma or a mucocele. Under the microscope the biopsy margins will appear very different when a laser has been used to remove the tissue rather than a scalpel. Indicate on your script if you used a laser to remove the tissue to immediately reconcile this appearance to the oral pathologist to not cost you, your patient or the oral pathologist a moment of time in getting to the definitive diagnosis.

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When submitting your specimen(s) to pathology, include:

- The patient medical history (can lead to etiology of an oral finding, including infectious). Any history of cancers, cancer risks (tobacco, -OH).
- What is their AGE, what is their HPV status, is the patient vaccinated against HPV? are there any other STD's present or past?
- Is the patient pregnant?
- Medications, foreign travel, known disease/s or syndromes.
- If it is a bony specimen, submit the radiographs with it.
-
- Submit ANY photos of specimen prior to excision

When submitting your specimen(s) to pathology, include these details:

- DESCRIBE the lesion: Color, Size, Shape, Location, Duration, Pain, Ulcerations. Your differential diagnoses 3, 4, 5 if you have that many.
- PATIENT CONSENT SIGNED for specimen to be examined by an Oral Pathologist (*on form from Oral Pathology group or Provider that goes along with specimen*). This must be received before the oral pathologist can even begin "grossing" the specimen.

SIZE MATTERS!

- Take at least a 2mm border around all lesions. Oral Pathologists generally need at LEAST 4mm or more to adequately examine the tissue.

For small lesions, remove at least 2x the size of the lesion. Go WIDE if you are using a laser to excise.

- For lesions smaller than 1cm, excisional biopsy is recommended (take it all!). For lesions greater than 1cm, *incisional* biopsy is recommended (take a piece, with a normal border section).

Place most specimens in Formalin fluid (*NEVER ALCOHOL OF ANY KIND)*. If you suspect the lesion may be PV/MMP (pemphigus vulgaris / mucous membrane pemphigoid) use *Michel's or Zeus Solution* instead because the specimen will be examined using immunofluorescence studies for definitive diagnosis.

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AUTOFLUORESCENCE

VelScope®. ORAL ID® ViziLight Pro®

All are fluorescence *visualization tools*. There is a curve in visualization due to variances in vascularity.

- Hand-held devices that provide dentists and hygienists with an easy-to-use adjunctive mucosal examination system for the early detection of abnormal tissue.
- Emits a safe blue light into the oral cavity, which excites the tissue from the surface of the epithelium through to the basement membrane (where pre-malignant changes typically start) and into the stroma beneath, causing it to fluoresce.
- The clinician is then able to immediately view the different fluorescence responses to help differentiate between normal and abnormal tissue.
- Non-invasive, no radiation, an adjunctive device.
- Healthy tissue reflects back through the scope as a brilliant green color.
- Suspicious tissue will absorb the light and not fluoresce. It will appear extremely dark, at times almost black.

Remember, if other diagnostic information such as clinical features or history of the lesion indicate a strong possibility of malignancy and the biopsy report DOES NOT concur, perform a second biopsy.

MEDICAL HISTORY FINDINGS

Lupus Erythematosus

2 Forms

- *Discoid* (DLE): predominately affects the skin, has very few systemic manifestations and is considered relatively "benign".
- *Systemic* (SLE): affects multiple organ systems, much more severe.

Oral lesions of lips and oral mucosa are reported in up to 25% of patients with SLE. Lesions are non-specific, may be erythematous with white spots, or radiating peripheral lines, can present as painful ulcerations. Lesions often resemble Lichen Planus. Additional oral manifestations include xerostomia, dysgeusia (strange or bad taste in mouth) and glossodynia (burning mouth).

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HPV

- At least 40 types of HPV have been identified in the oral mucosa. Of both the high and low risk types, the overall prevalence of HPV in the oral cavity is 6.9%.
- Important to note: HPV+ squamous cancers have a higher 5+ year survivability than HPV- cancers.
- HPV must infect the basal cells of the epithelium. Usually this requires a break in the surface epithelium.
    - Verruca vulgaris (common wart) & Condyloma acuminatum (venereal wart)
    - VERY ubiquitous, the "common cold" of STD's. Most are eliminated from the system in 1-3 years without pathology occurring.

HSV: Herpes Simplex Virus

- Oral infections generally caused by Type 1, genital infections generally caused by Type 2.
- Oral infection occurs in an initial or *primary* form, *Primary herpetic gingivostomatitis* and a recurrent or *secondary* form *herpes labialis* (cold sores, fever blisters).

HSV 1 & 2

Recurrent infections are often produced by certain stimuli such as: Sunlight, Menstruation, Fatigue, Fever, Emotional Stress. These stimuli are thought to trigger viral replication and immunologic changes that result in clinical lesions.

HSV Treatments (not cures):

Docosanol 10% antiviral cream, brand name *Abreva (*Available OTC).

Acyclovir, antiviral drug, brand name *Zovirax, (*Rx only).

Valaciclovir, antiviral drug, brand name *Valtrex*, (Rx only).

Acyclovir 5% & Hydrocortisone 1% creme, brand name *Xerese*, (Rx only).

Famciclovir, antiviral drug, brand name *Famvir*, (Rx only)

PhotoBioModulation aka PBM (LLLT, Low level laser therapy if available in office).

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NEOPLASIA *"new growth"*

A process in which cells exhibit abnormal and uncontrolled proliferation. A *neoplasm* is a mass of such cells. The word tumor means swelling, but is commonly used as a synonym for neoplasm.

- For a neoplasia to occur, *an irreversible change* must take place in the cells, and this change *must be passed on to new cells*.

Causes of Neoplasia

Chemicals, viruses (EBV,HPV) and ionizing radiation have all been shown to cause neoplastic transformation of cells in the laboratory. Neoplastic transformation may also occur spontaneously secondary to a genetic mutation.

Names of Tumors

The prefix of the name of a benign tumor is determined by the cell or the tissue of origin.

The suffix *–oma* is used to indicate a tumor. i.e. Lipoma: benign tumor of FAT, Osteoma: benign tumor of BONE

Malignant

- Within epithelium: *carcinoma, Carcinomas are about 10 times more common than sarcomas*
- Within connective tissue: sarcoma

Treatment

- Benign tumors are generally treated by surgical excision. Enucleation or wide surgical excision local to the tumor.
- Malignant tumors are treated by surgical excision, chemotherapy or radiation; a combination of two or three of these is often used.

PREMALIGNANT LESIONS OF THE MOUTH

- Leukoplakia. This is a clinical term, not a microscopic appearance. A white plaque-like lesion visibly seen that cannot be rubbed off and cannot be diagnosed clinically as a specific disease.
- Often referred to as *idiopathic leukoplakia*, emphasizing that the specific cause of the lesion is unknown. Microscopically leukoplakia appearance does vary; therefore, a biopsy is essential to establish a definitive diagnosis. When examined microscopically, leukoplakia may show epithelial dysplasia, which is a pre-malignant condition, OR squamous cell carcinoma, a malignant condition.

PROTOCOL FOR LEUKOPLAKIA

When a white lesion is identified, the first goal is to identify the cause. Any associated irritation should be removed and 10-14 days is a reasonable period of time to allow for resolution.

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If the lesion is not resolved, a biopsy and microscopic examination must be performed. If the lesion is diagnosed as epithelial dysplasia or cannot be diagnosed as a specific disease, it should be removed completely.

If discovered on the floor of mouth, ventrolateral tongue, soft palate or lip, the lesion should be removed regardless of the microscopic appearance because of the increased risk of squamous cell carcinoma development in these areas.

PREMALIGNANT LESIONS

- *Erythroplakia*: Clinical term, describes a mucosal lesion that appears as a smooth red patch, or a granular red and velvety patch. Red lesions are closer to blood supply. No longer producing keratin, epithelial cells are immature, atrophic, proliferating rapidly.
- Most cases occur on floor of the mouth, tongue and soft palate and is MUCH less common than leukoplakia, roughly 1 in 60 of red vs. white. 90% of erythroplakia cases demonstrate epithelial dysplasia OR squamous cell carcinoma when examined microscopically. **Because of this, erythroplakias are considered a far more serious clinical finding than leukoplakias.**

PROTOCOL FOR ERYTHROPLAKIA

- Treatment depends on the microscopic diagnosis, but *always includes* surgical removal of the entire lesion.
- Close, long-term follow up examinations are indicated because of the potential for recurrence. An oral cancer screening should be performed at every office visit.

EPITHELIAL DYSPLASIA

- MICROSCOPIC diagnosis that indicates a disordered growth. **It is considered a premalignant condition. ED lesions frequently precede squamous cell carcinoma.**
- Unlike SCC though, ED can revert back to normal if the stimulus (like smoking or smokeless tobacco use) is removed.
- Abnormal maturation of epithelial cells
- Disorganized epithelial layers
- Hyperplasia of the basal cells
- Epithelial cells with enlarged and hyperchromatic nuclei, increased nuclear-to-cytoplasmic ratios, *abnormal keratinization*, and *increased numbers of normal and abnormal mitotic figures.*

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MALIGNANT LESIONS

SQUAMOUS CELL CARCINOMA

- MOST COMMON primary malignancy of the mouth. Just like other malignancies, can infiltrate adjacent tissues and metastasize to distant sites. From the mouth, SCC usually metastasizes to lymph nodes of the neck and then to more distant sites such as the lungs and liver.

WHERE IS THE LINE BETWEEN A POTENTIALLY REVERSIBLE DYSPLASIA AND AN IRREVERSIBLE CARCINOMA?

- Dysplasia becomes carcinoma is when the tumor cells INVADE *through the basement membrane* of the epithelium into the underlying connective tissue.
- **SCC may occur anywhere in the mouth, but MOST are seen once again on the *floor of the mouth, ventrolateral tongue and soft palate (including tonsillar area).***
- SCC also are found on vermillion border of lips and skin of the face. These locations are associated with sun exposure. The prognosis of SCC in these areas is far better than that of the oral mucosa.

RISK FACTORS FOR SCC

- AGE. The majority of SCC occur in patients over 40 years of age. Overall no gender predilection.
- HPV, high-risk strains have been identified in SCC of the oropharynx.
- TOBACCO. Cigars, pipe, cigarettes, snuff and smokeless tobacco use.
- ALCOHOL. Slightly adds risk, but **more significantly to those who also use tobacco**.
- PREVIOUS CANCER HISTORY

TREATMENT AND PROGNOSIS OF SCC

- Generally treated by surgical excision. Radiation and chemotherapy or one or the other may be used in combination with surgery.
- The smaller the better. In oral tumors, determining the presence or absence of cervical lymph node involvement and distant metastasis are important to predicting prognosis.

BASAL CELL CARCINOMA

A malignant skin tumor associated with sun exposure. It does NOT occur in the oral cavity, but does frequently arise on the skin of the face and appears as a non-healing nodule or "bump", sometimes ulcerated (non-healing), with rolled borders.

More frequent in white adults, with no sex predilection. Tumor is usually well differentiated and rarely metastasizes. Treatment is by surgical excision.

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TUMORS OF MELANIN-PRODUCING CELLS

- Melanocytic nevus/nevi: a *benign* tumor of melanocytes (melanin-producing cells): a mole.
- Can be born with it, or may develop during lifetime. Occur on the skin and oral mucosa, hard palate and buccal mucosa most frequently, and nearly twice as often in women than men.
- Usually first identified between the ages of 20-50 years of age.

MALIGNANT MELANOMA

Know the ABCDEs when assessing pigmented lesions: Asymmetry, Border, Color, Diameter, Evolving

- Asymmetric: Is one half different from the other?
- Borders: Is the border of the lesion irregular?
- Color: Does the color of the lesion vary from tan to black? From red to blue?
- Diameter: Is the lesion larger than 6mm?
- Evolving: Is the lesion changing in size, shape or color?
- Most arise on the skin as a result of prolonged sun exposure. A primary lesion in the mouth is rare, but possible. More common is a secondary lesion that is a metastasis into the mouth from another location.
- Usually presents as a **rapidly enlarging** blue-to-black mass. It is a very aggressive tumor with unpredictable behavior and early metastasis.
- ***Most common intraoral lesions are the hard palate and maxillary gingiva***. Most commonly seen in persons 40 years of age and older, with no sex predilection. Treated with surgical excision, and often chemotherapy.
- **Prognosis for oral malignant melanoma is POOR.**

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METASTATIC CANCERS IN THE MOUTH

"BLT with KP": BREAST, LUNG, THYROID, KIDNEY, PROSTATE

THYROID CX

- **PAPILLARY (LOW MET)**
- **FOLLICULAR (LOW MET)**
- ***MEDULLARY (HIGH MET)***
- ***ANAPLASTIC (HIGH MET)***

ASK QUESTIONS- WHAT TYPE OF THYROID CANCER? HOW LONG AGO?

METASTATIC CANCERS CAN SPREAD TO THE ORAL TISSUES

- **Posterior mandible common for metastatic lesions due to LOTS OF MARROW AND BLOOD SUPPLY.**

FOR THE DENTAL PATIENT WITH ORAL CANCER:

Oncology Pocket Guide to Oral Health. Free Download from US Department of Health and Human Services National Institutes of Health Department of Oral and Craniofacial Research.

https://www.nidcr.nih.gov/sites/default/files/2017-09/oncology-guide-oral-health.pdf

FOR THE DENTAL PROVIDER AND CLINICAL DENTAL CARE TEAM:

Dental Providers Oncology Pocket Guide. Free Download from US Department of Health and Human Services National Institutes of Health Department of Oral and Craniofacial Research.

https://www.nidcr.nih.gov/sites/default/files/2017-09/oncology-guide-dental-provider_0.pdf

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