

# Upper Aerodigestive Tract

## Squamous Lesions

### General

Both benign and malignant conditions can sometimes have similar clinical appearances.

**"Leukoplakia"**—clinical term for a **white** plaque on a mucous membrane

**"Erythroplakia"**—clinical term for a **red** plaque. Higher risk of dysplasia.

**"Speckled Erythroplakia"**—clinical term for a mixed red and white lesion.

May represent a wide spectrum of histologic changes often falling within the general category of keratosis (abnormal presence and/or excessive keratin) with or without dysplasia.

Any type of lesion may be biopsied to evaluate for malignancy/dysplasia.

### Non-neoplastic Lesions

May mimic cancer clinically, often with leukoplakia or ulceration

### Candidiasis

Most common oral fungal infection.

Often occurs in **immunocompromised** patients, but can occur in healthy individuals.

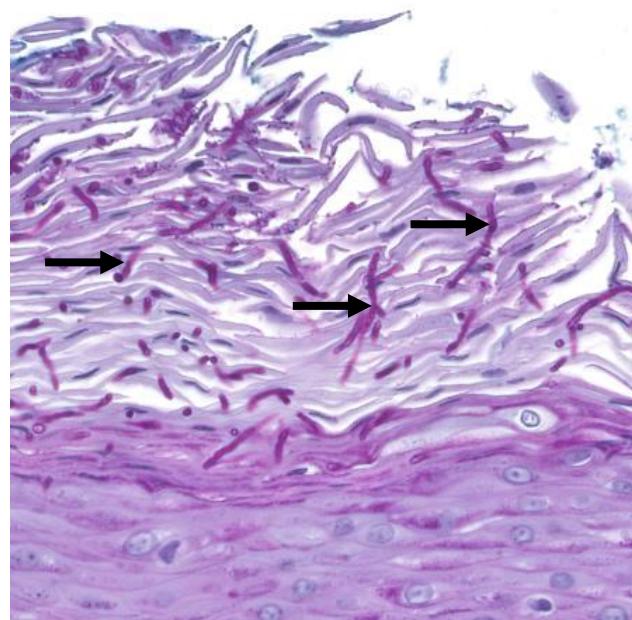
Often appears clinically like a **white plaque**.

Dimorphic fungi with yeast forms and hyphae/pseudohyphae → **hyphal form causes tissue invasion/symptoms** so look for hyphae to make Dx (yeast only is not good enough!)

Often seen with **parakeratosis and acute inflammation** (so consider this Dx and do stains whenever you see this).

Can **highlight with PASd or GMS**

May see accompanying reactive epithelial changes like hyperplasia.



### Herpes Simplex Virus

Virus **infects epithelial cells** and ganglion cells.

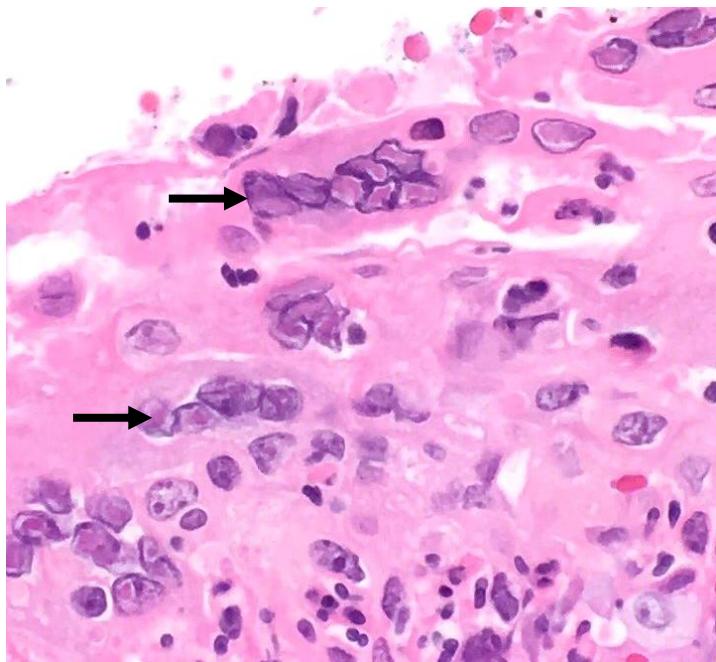
Two types classically infecting different sites:

Type 1= Oral, Type 2=Genital, but not always true.

Infected cells show classic **ground glass intranuclear inclusions** with "**3 M's**": **Molding**, **Margination**, **Multinucleation**.

Often associated **ulceration** with acute and chronic inflammation.

CMV can cause similar ulcers, but is much rarer, usually only seen in the immunocompromised, and the eosinophilic intranuclear inclusions are seen in mesenchymal cells.



## Lichen Planus

Same as on the skin (often also involves mucous membranes).

**Chronic, self-limited inflammatory reaction.**

**Multifocal** (if focal → consider *Lichenoid keratosis*)

“Band-like” T-cell infiltrate below epithelium



“Saw-tooth” rete ridges

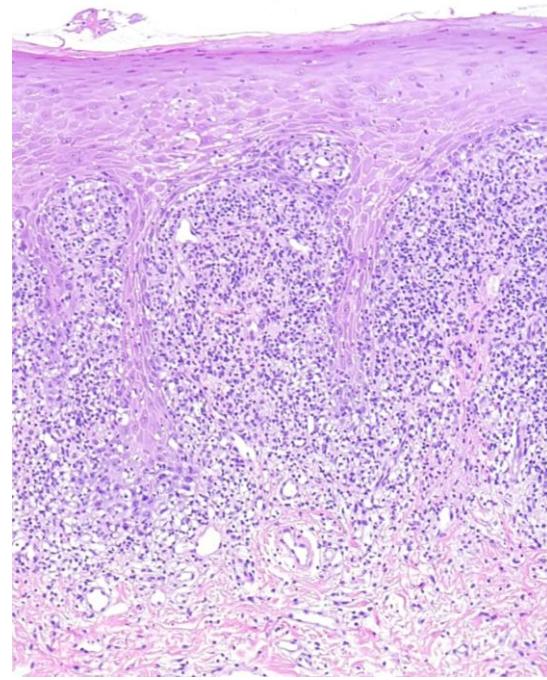
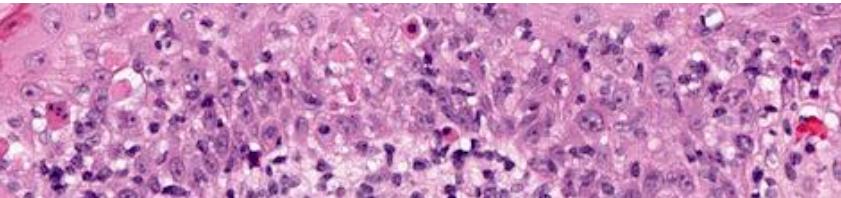
Often hydropic degeneration and/or degenerating keratinocytes

**NO significant atypia** (otherwise consider dysplasia)

Variable thickness and keratinization

Unknown etiology. Associated with many medications and Hep C.

Clinical 5P's: **Purple, Pruritic, Polygonal, Planar, Papules.**



## Hairy Leukoplakia

Epithelial hyperplasia induced by Epstein-Barr virus (**EBV**).

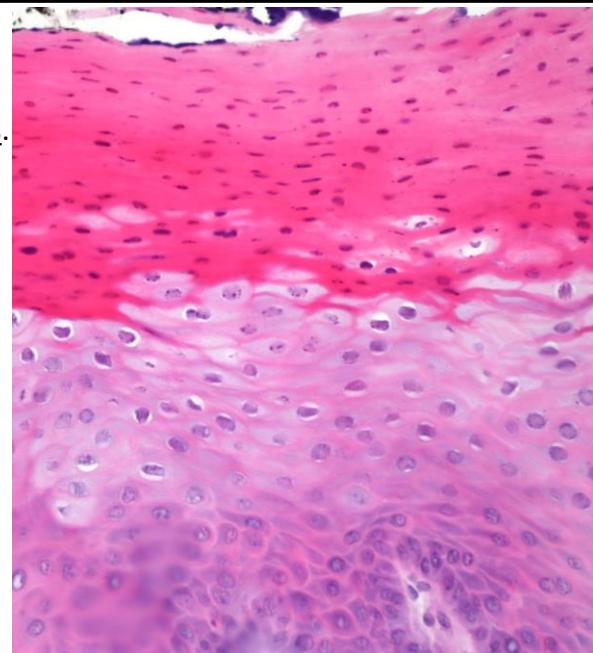
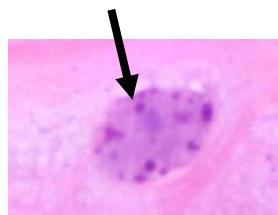
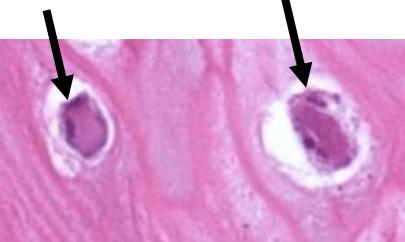
Often on the lateral tongue of immunocompromised patients.

**Acanthosis and parakeratosis**

“Balloon” cells in spinous layer with viral cytopathic effect including eosinophilic nuclear inclusions and ballooning degeneration → highlighted by EBER in situ hybridization

Often cointfected with candida.

Little inflammation. No dysplasia.



## Geographic Tongue

aka “*Benign migratory glossitis*”

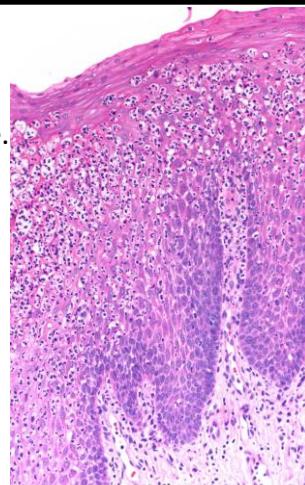
Idiopathic inflammatory condition, primarily on **tongue**.

Often asymptomatic → self-resolves

**Multiple, well-defined erythematous islands with raised whitish yellow borders that rapidly appear → migrate** around tongue.

Epithelium with hyperparakeratosis, acanthosis, spongiosis, elongated rete ridges, and collections of neutrophils (Monro abscesses).

Lamina propria acute and chronic inflammation



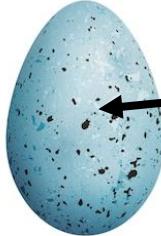
## Reactive vs Dysplastic Changes

### Benign/Reactive

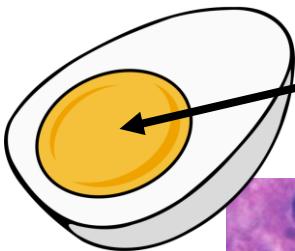
*“Think Eggs”*

**Cytology:** Although they may enlarge, nuclei are still rounded with smooth nuclear contours.

Low N:C ratios (More cytoplasm)



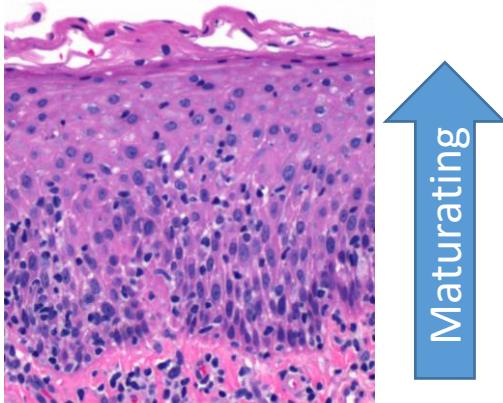
Nuclei are smooth  
Round/oval, often with  
speckled chromatin



Sometimes have a  
prominent nucleolus  
(think Yolk)



Lots of inflammation? If so, raise your threshold to account for reactive changes!



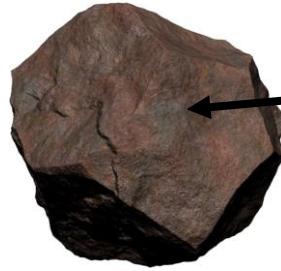
**Architecture:** Often matures towards surface, with highest N:C ratio cells confined to the base  
Cells seem to “Know which way is up”

### *“Think Boulders”*

### Dysplastic

**Cytology:** Nuclei are big, irregular, jagged, rough, and dark.

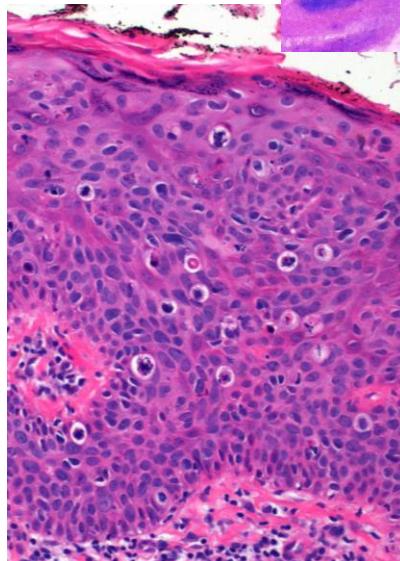
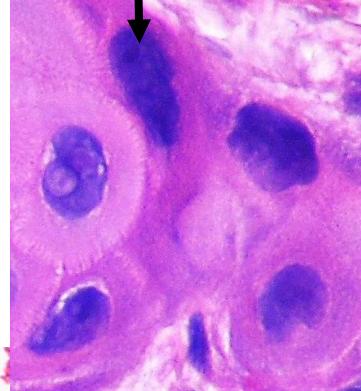
High N:C ratios (mostly nucleus!)



Nuclei are Dark with Irregular crinkled contours

Dyskeratotic cells

Usually no nucleoli  
(unless perhaps invasive)



**Architecture:** No maturation in traditional High-grade dysplasia. Many cells don't know which way is up.

However, can see maturation in low-grade dysplasia and keratinizing dysplasia.

# Squamous Neoplasms, Non-HPV related

Majority of oral cavity, larynx, and pharynx cancers are squamous cell carcinoma.

**Major risk factors:** smoking (most important cause), alcohol, and betel-quid chewing.  
→ synergistically increase risk together exponentially (not just additive)

Often **clinically appear white to erythematous**. Erythematous lesions are more frequently dysplastic.

Genomically unstable with chromosome gains/losses. Frequent mutations in TP53.

## Squamous Dysplasia

Epithelium with accumulated genetic changes → **risk of progression to squamous cell carcinoma**.

Non-obligate precursor → most cases of dysplasia do not progress to SCC (higher grade = higher risk)

**Features of nuclear/cellular “atypia”:** marked variation in size/shape, marked hyperchromasia, prominent nucleoli

Epithelium may be atrophic or acanthotic, **keratinizing** or non-keratinizing.

**Grade using scheme below based on maturation, but if there is severe atypia it is acceptable to upgrade to high-grade dysplasia even if it matures at the surface.**

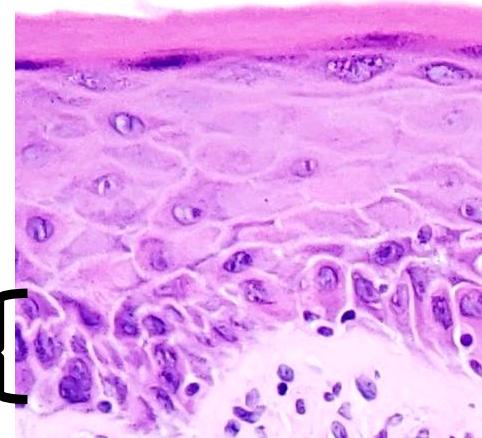
Not always reproducible! (So consider showing another person if it's important)

### Low-Grade Dysplasia (previously mild dysplasia)

Low Malignant Potential (may regress or not advance)  
Limited to LOWER half of epithelium, with surface maturation

Architectural criteria      Stratification preserved with retained orientation  
(vertical cells at bottom, horizontal cells at top)

Cytologic Criteria      At most minimal cellular atypia  
Rare mitoses, in or near basal layer.  
Few dyskeratotic cells

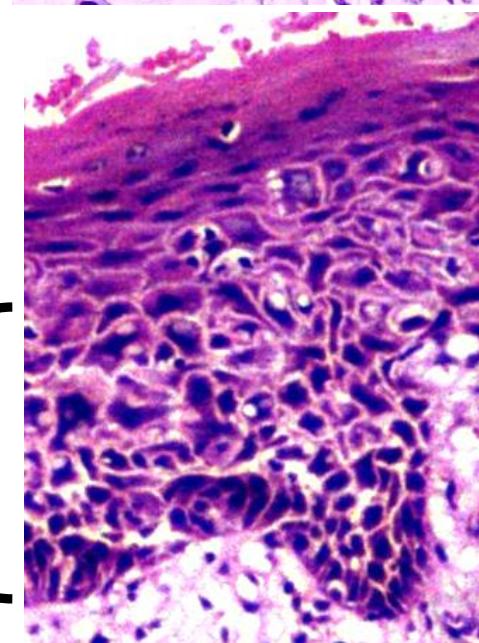


### High-Grade Dysplasia (previously moderate to severe dysplasia or CIS)

Pre-malignant lesion  
Involves at least half of the epithelium, and may be full thickness

Architectural criteria      Abnormal maturation  
Altered cells involve ≥1/2 of thickness  
Disordered stratification  
Can be keratinizing or non-keratinizing  
Intact basement membrane  
No stromal alterations

Cytologic Criteria      Conspicuous cellular atypia  
Increased N:C ratio  
Increased mitoses at or above basal layer  
Dyskeratotic or apoptotic cells throughout



## Proliferative Verrucous Leukoplakia

Multifocal, progressive disorder → very high rate of recurrence and transformation to SCC. Often older females. Unknown etiology.

Oral cavity: often involves gingival, alveolar mucosa, and palate.

Appearance changes with time:  
Starts with **localized** flat or verrucous **hyperorthokeratosis**  
Often lichenoid interface mucositis.

Eventually becomes **multifocal** and develops **dysplasia**.

Dx often requires **clinical and pathologic correlation** as findings on one biopsy are not diagnostic (must know multifocal, progressive).

May progress to traditional or verrucous SCC.



## Conventional Squamous Cell Carcinoma

Malignant epithelial tumor with squamous differentiation.

→ **Keratinization** (±keratin pearls) and/or **intercellular bridges**

**Features of invasion:** downward growth of islands, cords and isolated tumor cells, irregular interface, desmoplastic response, lymphovascular invasion, perineural invasion.

Grading is irrespective of keratinization.

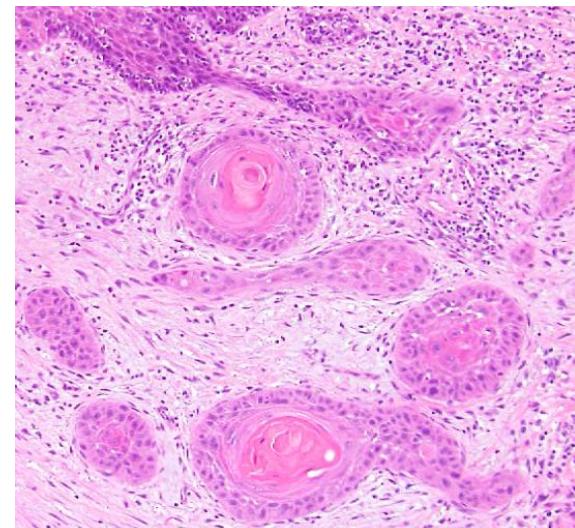
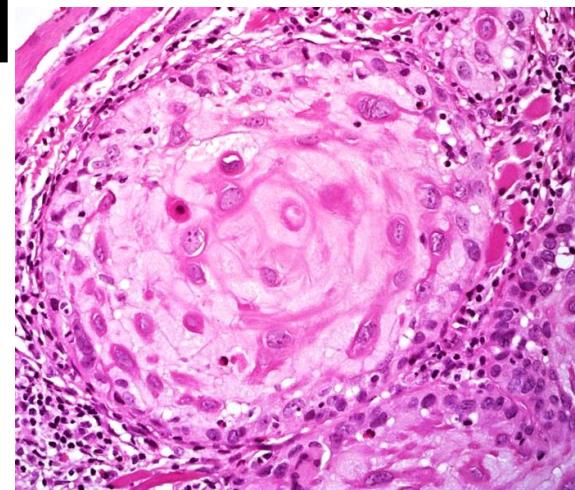
Well-differentiated: closely resemble normal squamous mucosa (matures somewhat normally), few mitoses.

Moderately-differentiated: more pleomorphism and mitoses.

Poorly-differentiated: basal-type cells predominate with lots of mitoses. Often lose expression of HMWCKs.

Depending on location, can present with mass (oral cavity), hoarseness (supraglottic larynx) or dyspnea/stridor (subglottic larynx), etc..

**Frequently metastasizes to cervical lymph nodes** → lymph node mets is the single most adverse prognostic factor.  
Extracapsular extension is a particularly associated with regional recurrence and worse survival.



## Verrucous Squamous Cell Carcinoma

Variant of Well-differentiated Squamous Cell Carcinoma

Dramatic **acanthosis** with club-shaped projections and invaginations. Marked “church-spire” keratinization.

**No** significant cytologic atypia

Proliferative basal cell layer only 1-2 cells thick.

Only very rare mitoses in basal layer.

**Well-defined “Pushing” invasion**, often with

associated **lymphocytic inflammation**.

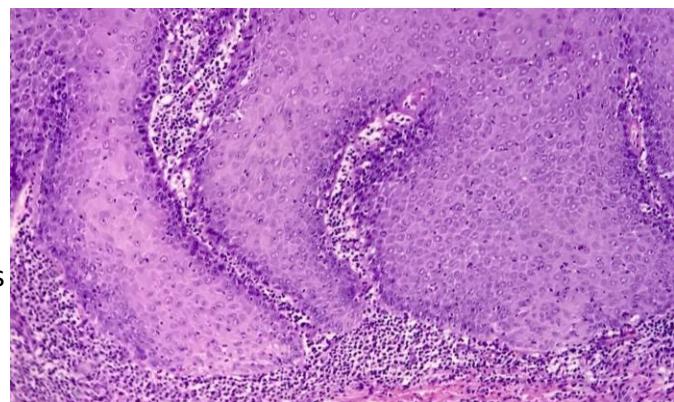
**NO** infiltrative growth.

Often need to see nearby epithelium to show *relative* invasion beneath basal layer of nearby epithelium.

**Locally destructive/invasive, but does not metastasize**

May be very hard to Dx on small biopsies, requiring clinical correlation. If clinically concerned for malignancy, but biopsy looks like benign → consider this Dx!

If infiltrative growth → conventional SCC



## Spindle Cell Squamous Cell Carcinoma

aka “Sarcomatoid carcinoma” or “Carcinosarcoma”

Squamous cell carcinoma variant with predominantly **malignant spindle and/or pleomorphic cells**.

Often an **ulcerated polypoid mass**.

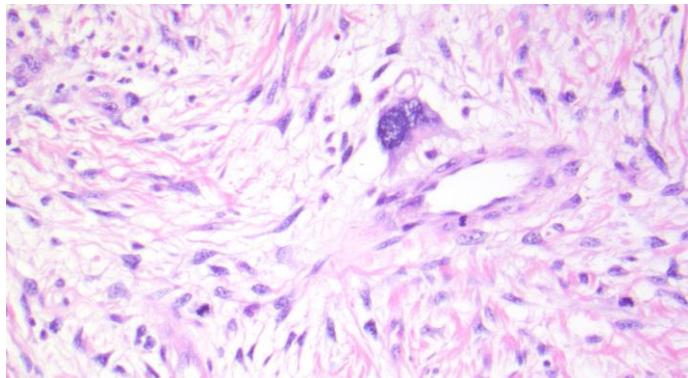
**Epithelial→mesenchymal transition**

Can have heterologous differentiation.

**Must have evidence of epithelial differentiation**,

either by morphology (e.g., adjacent conventional SCC or dysplasia) or by IHC (e.g., CK, p40, etc..)

Similar prognosis to conventional SCC.



**Basaloid Squamous Cell Carcinoma:** Basaloid, hyperchromatic appearance (high N:C ratio) often with a conventional component. HPV-negative. Rounded nests with peripheral palisading and admixed hyalinized stroma. Frequent mitoses and comedonecrosis. May mimic a salivary gland neoplasm and be SOX10 positive, but diffuse p63/p40 (which is often patchy in adenoid cystic carcinoma). More aggressive.

**Papillary Squamous Cell Carcinoma:** Exophytic papillary growth pattern with thin fibrovascular cores covered by severely dysplastic basaloid cells. Uncommon. May be HPV-related in oropharynx, but not elsewhere. Better prognosis.

**Adenosquamous Carcinoma:** Arises from squamous epithelium but shows both squamous and glandular differentiation.

**Lymphoepithelial Carcinoma:** Sheets of pleomorphic cells with a prominent intratumor chronic inflammatory infiltrate. Like nasopharyngeal carcinoma, but not often associated with EBV.

# HPV-related Squamous Lesions

## Verruca Vulgaris

Benign squamous proliferation in oral cavity

Caused by **low-risk HPV** (e.g., Type 2 and 4)

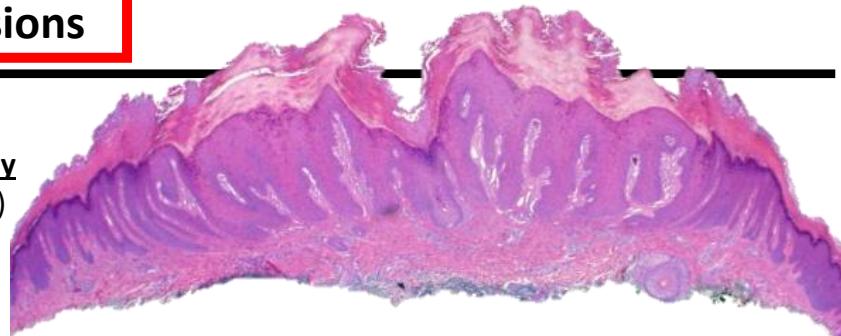
Identical to on the skin.

**Exophytic and papillomatous.**

**Hyperkeratosis and acanthosis.**

Elongated and “cup-like” rete ridges.

Cytologically bland with prominent granular layer and occasional koilocytes.



**Condyloma Acuminatum:** Oral equivalent of anogenital condyloma. HPV types 6 or 11. Often sexually transmitted. Often larger than verruca vulgaris.

## Multifocal Epithelial Hyperplasia *aka “Heck’s Disease”*

Multifocal benign squamous proliferation in oral cavity caused by HPV.

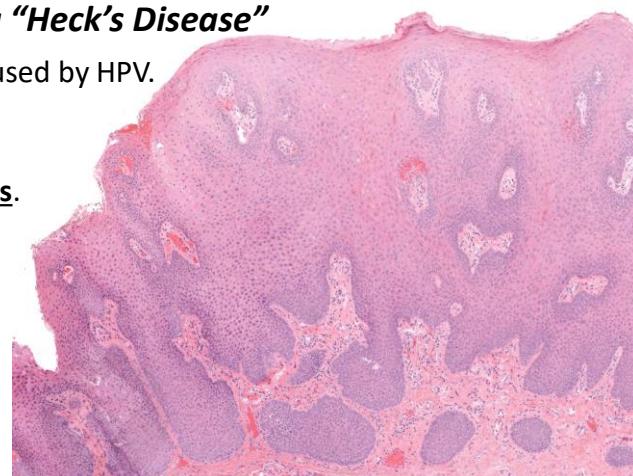
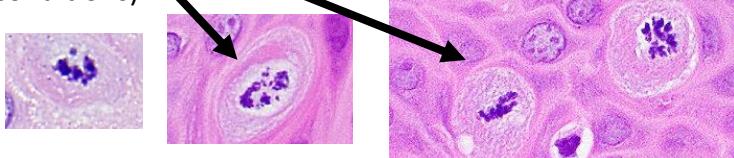
Most common in **children/adolescent girls**.

**HPV types 13 or 32 often.**

Often located on **lips or buccal mucosa** → multiple papules.

Mild **hyperkeratosis**, prominent acanthosis, normal cell maturation. Occasional koilocytes.

“Mitosoid” figures are hallmark (not often seen in other conditions)



## Squamous Papilloma

Benign exophytic squamous proliferations with branching fibrovascular cores.

Usually associated with HPV types 6 or 11.

Can get through sexual or non-sexual contact.

Variable koilocytes (may be obvious or subtle)

Often solitary.

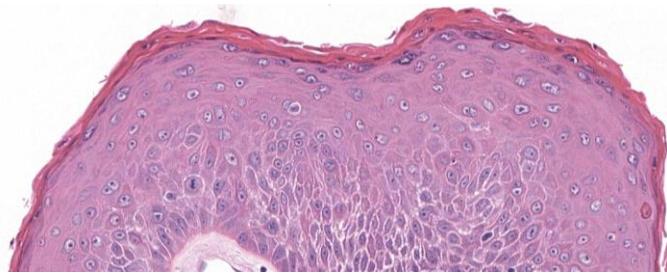
Malignant transformation is very rare.



*If multiple, especially if young, consider:*

**Recurrent Respiratory Papillomatosis (RPR)—**

multiple, recurrent papillomas in the respiratory tract of children and young adults → high morbidity as can obstruct breathing, swallowing, etc...



# Squamous Cell Carcinoma, HPV-Positive

**Squamous cell carcinoma associated with High-risk HPV'**

>90% caused by **HPV type 16** → associated with **oral sex**

Incidence rising: Frequently white men in 50's

Strong predilection to **oropharynx**: **Base of Tongue (BOT)** and **Tonsils**

Often presents at high clinical stage with a small/occult oropharyngeal primary and cervical lymph node metastases, which are often large and cystic.

Distinct morphology:

**Non-keratinizing, high N:C ratios** → basaloid appearance.

**Frequent mitoses and/or apoptotic figures.**

Frequent associated lymphocytes/lymphoid stroma.

Some morphologic spectrum as can be papillary, etc...

Arises in crypts of tonsils → grows/invasions as nests/lobules.

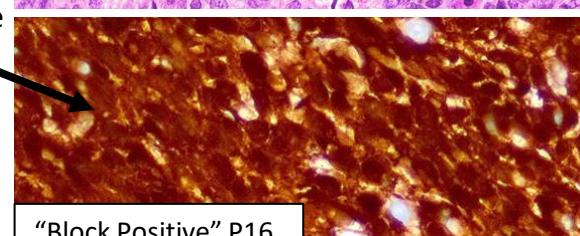
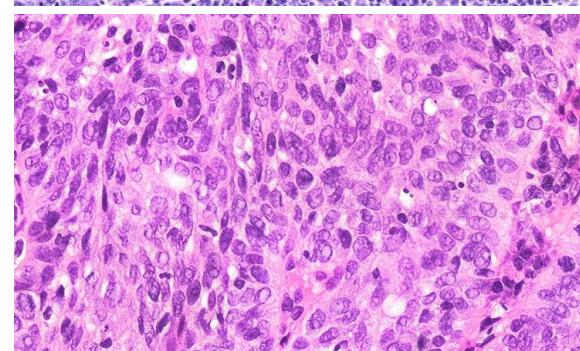
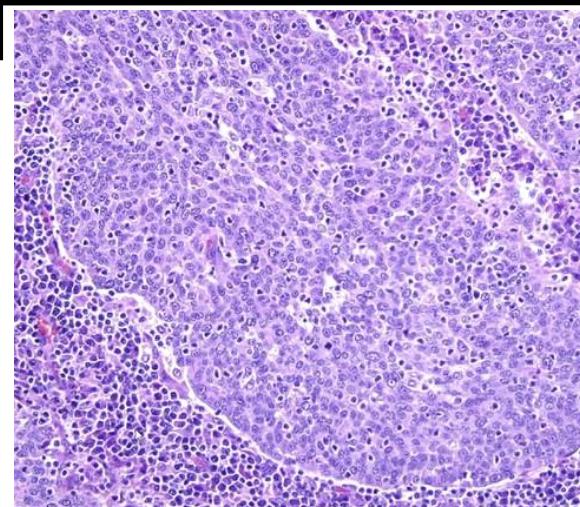
No recognizable *in situ* component/background dysplasia.

Grading is NOT applicable!!

HPV can be detected by: *In situ hybridization* or PCR.

**Diffuse “block positive” staining with p16** is used as a reliable surrogate marker for the presence of high-risk HPV in oropharyngeal carcinomas (if appropriate morphology).

Significantly better prognosis than conventional SCC



"Block Positive" P16

Characteristic	HPV-Positive SCC	HPV-Negative SCC
Median Age	~50 yrs	~65 yrs
Risk Factors	Sexual behavior	Smoking and Alcohol
Background Dysplasia	Rare	Frequent
Morphology	Commonly non-keratinizing with high N:C ratio	Conventional, often keratinizing
Grading	Not Applicable	Applicable
P16 IHC	Positive ("Block")	Negative
Lymph node metastases	Frequently cystic	Uncommonly cystic
Postulated origin	Reticulated epithelium of invaginated crypts	Surface epithelium
3-year survival	~80%	~60%

## Important Staging Details:

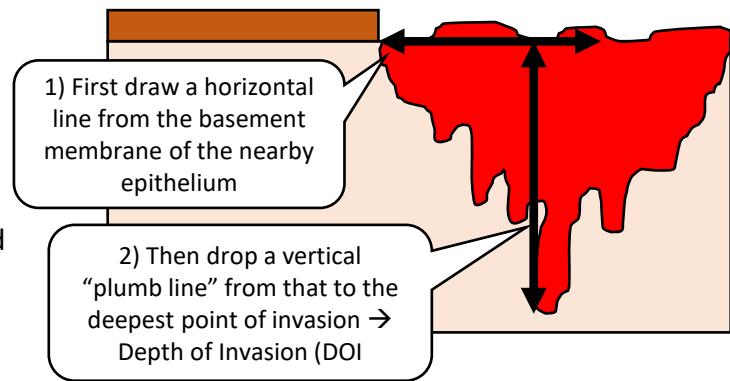
### Use the right Checklist!

There are separate checklists and staging criteria for the Oral Cavity & Lip, Pharynx, and Larynx. Make sure you use the right one as they are very different!

### Depth of invasion:

Particularly in oral cavity, predictive of regional lymph node metastasis.

Measure by drawing a horizontal line from the basement membrane of adjacent epithelium and then dropping a “plumb line” from this (see →)

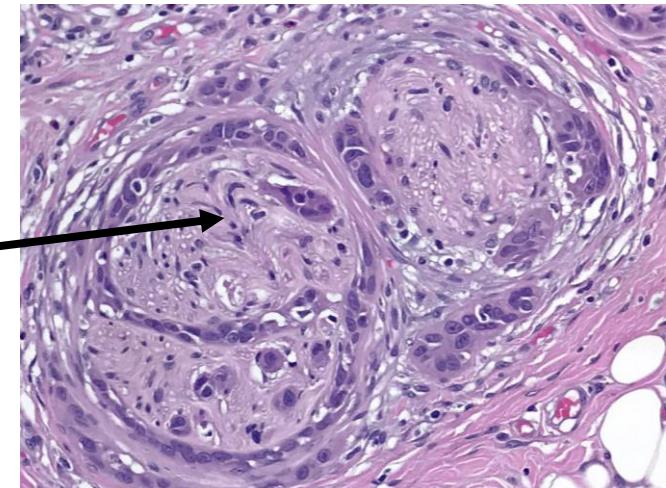


### Perineural invasion (PNI):

Poor prognosis at all sites (associated with recurrence and metastasis), so concurrent chemoradiation is often considered.

Any size nerve counts.

Tumor should “have a relationship” with the nerve  
(not just be near the nerve or passing by the nerve)



### Extranodal extension (ENE):

Nodal status is the most important prognostic factor in upper aerodigestive tract SCC. All macroscopically negative or equivocal lymph nodes should be entirely submitted.

ENE is defined as of extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction.

Soft tissue deposits appear to be the equivalent of a positive lymph node with ENE and should be recorded as such

