Premalignant and potentially premalignant Epithelial Lesions

Actinic cheilitis

**Definition**
A common premalignant alteration of the lower lip vermilion resulting from long term or excessive exposure to UV rays from sunlight.

**Etiology**
Outdoor occupations predispose (farmer’s lip and sailor’s lip).
In addition, compromised immunity also predisposes (transplant recipients especially).

**Clinical features**
Seldom in persons < 45 years, M:F = 10:1.
Develops slowly – atrophy, smooth surface with blotchy pale areas.
Later rough scaly areas which thicken and become white.
Chronic focal ulceration (which suggests progression to squamous cell carcinoma).

**Histological features**
Atrophic stratified squamous epithelium, with marked keratin production.
Varying degrees of epithelial dysplasia.
Mild chronic inflammatory infiltrate in subjacent connective tissue.
Solar elastosis (band of amorphous basophilic change) in connective tissue.

**Treatment**
Lip balms with sunscreens.
Areas of induration, thickening, ulceration or leukoplakia should be biopsied.
Severe cases without malignancy – lip shave (vermillionectomy).
Squamous carcinoma develops in 6 – 10% of cases.

Smokeless tobacco keratosis

**Definition:**
White or gray-white plaque of the oral mucosa, associated with direct contact with snuff or chewing tobacco.

**Etiology**
Chewing tobacco or snuff.
Development of the lesion is dependent on habit duration, brand of tobacco, early onset of use, total hours of daily use, amount of tobacco used daily, and number of sites used for tobacco placement.

**Clinical features**
Young adult men, and men > 65 years.
Site is area in direct contact with tobacco.
Thin gray or gray-white plaque with a border that blends into surrounding mucosa.
Soft velvety feel; stretching of mucosa reveals a pouch.
Fissured or rippled.
Eventually becomes thickened and leathery with time.

**Histological features**
Not specific.
Hyperkeratotic, acanthotic, stratified squamous epithelium with parakeratin chevrons.
Glycogen-rich clear superficial epithelial cells.
Increased sub-epithelial vascularity and vessel engorgement.
Amorphous eosinophilic material in connective tissue.
Epithelial dysplasia uncommon; occasional severe dysplasia or carcinoma.

**Treatment**
Biopsy only for severe lesions (malignant transformation potential is low enough).
No further treatment if no evidence of dysplasia or malignancy.
Verrucous carcinoma may be associated with spit tobacco use.
Habit cessation leads to normal mucosal appearance usually in 2 to 6 weeks, in lesions that are not intensely white, or ulcerated.
Leukoplakia

Definition (leuko = white; plakia = patch)

A white patch or plaque that cannot be characterized clinically or pathologically as any other disease (WHO)

The whiteness results from a thickened surface keratin layer, or a thickened spinous layer, or both, which masks the vascularity (redness) of the underlying connective tissue

Leukoplakia is considered to be a precancerous or premalignant lesion

Dysplasia or carcinoma only in 5 – 25% of leukoplakias

1/3 oral carcinomas have leukoplakia in close proximity

Malignant transformation potential = 4%

Etiology (possible associations):

Trauma:

• Physical: Frictional (not premalignant)
• Heat: Nicotinic stomatitis
• Chemical:
  • Tobacco
  • Alcohol
  • Sanguinaria in toothpastes and mouthrinses
• UV radiation (lip)

Microorganisms

• Treponema pallidum
• Candida albicans
• HPV types 16 and 18

Clinical features

>40 years; average 60 years

Site: 70% occur on lip vermilion, buccal mucosa, gingiva; however those occurring on the tongue, lip vermilion and oral floor account for 90% of those that show dysplasia or carcinoma

Early, mild thin – gray-white, wrinkled, fissured
Thick, homogeneous – white, deeper fissures
Granular or nodular – increased surface irregularities;
Verrucous – with sharp or blunt projections

Proliferative verrucous leukoplakia is a special high-risk form
• F:M = 4:1
• Multiple keratotic plaques with roughened surface projections
• Slowly spreads to involve additional oral sites
• Persistent growth, resemble Verrucous carcinoma, then transforms into squamous carcinoma
• Rarely regresses despite therapy

Erythroleukoplakia or speckled leukoplakia – scattered patches of redness; usually displays advanced dysplasia on biopsy

**Histological spectrum of clinical leukoplakias**

Hyperorthokeratosis
• Thickening of stratum corneum by non-nucleated keratin
• Represents a benign reactive lesion analogous to irritational callus

Hyperparakeratosis
• Thickening of stratum corneum by nucleated keratin
• Represents a benign reactive lesion analogous to irritational callus

Acanthosis
• Thickening of stratum spinosum of epithelium
• Reaction to chronic irritation
• Usually occurs together with Hyperkeratosis

Epithelial atrophy
• Decrease in overall thickness of epithelium
• Occurs in association with hyperkeratosis therefore appears clinically white
• If atrophy occurs alone, area appears clinically red
• Predisposes to inflammation, ulceration and dysplasia
• Known cause is iron deficiency anemia (Plummer Vinson syndrome)

Epithelial Dysplasia
• A premalignant change in epithelium characterized by both histologic (architectural) and cytologic (cellular changes)
• Histologic changes
  • Bulbous rete pegs
  • Lack of progressive maturation toward the surface
  • Basal cell hyperplasia
  • Keratin pearls
• Lack of typical epithelial cell cohesiveness
• Cellular changes
  • Increased size of nuclei and cells
  • Altered/increased nuclear/cytoplasmic ratio
  • Nuclear and cellular pleomorphism
  • Hyperchromatic (excessively dark) nuclei
  • Increased mitotic figures
  • Atypical mitotic figures
  • Prominent large and multiple nucleoli
  • Dyskeratosis (premature keratinization)
• Dysplasia may be mild, moderate or severe
  • Mild – lower 1/3 of epithelium
  • Moderate – middle and lower 1/3 of epithelium
  • Severe – most of epithelium but not yet full thickness
• Dysplasia is often accompanied by hyperkeratosis
• Mild dysplasia can progress to moderate, then to severe dysplasia, and then to carcinoma in situ and invasive squamous cell carcinoma
• Mild dysplasia is reversible, by removing the etiological factor (e.g. smoking)

Carcinoma in Situ
• Is an epithelial dysplasia that involves the full thickness of the epithelium, but does not violate the basement membrane, or invade into the connective tissue
• May or may not be accompanied by hyperkeratosis and may therefore be clinically white (leukoplakia) or red (erythroplakia)
• Most commonly seen on lateral border of tongue, floor of mouth, ventral surface of tongue, and soft palate

Squamous carcinoma
• Is a malignant neoplasm derived from squamous epithelium
• Represents a severe epithelial change that has violated the basement membrane and invaded the connective tissue

Treatment of leukoplakia showing histological changes up to carcinoma in situ but excluding squamous carcinoma:

Surgical excision (stripping the area affected by the dysplasia or carcinoma in situ)
Prognosis

Each clinical appearance or phase of leukoplakia has a different malignant transformation potential

Clinical:

- Homogeneous thick: 1 – 7%
- Granular verruciform: 4 – 15%
- Erythroleukoplakia: 28%

Phase:

- Moderate dysplasia: 4 – 11%
- Severe dysplasia: 20 – 35%
- Cancers from dysplastic lesions develop within 3 years of the dysplasia diagnosis, but can occur much later
- 1 in 3 dysplasias recur after complete removal

Factors which increase the risk of cancers in leukoplakias

- Persistence over several years
- Occurrence in a female patient
- Occurrence in a non-smoker
- Occurrence on the oral floor or ventral tongue

Oral submucous fibrosis

Definition

A chronic progressive condition characterized by fibrosis (scarring) of the oral sub-mucosal connective tissues, chronic inflammation, epithelial atrophy, and eventually epithelial dysplasia and carcinoma

Etiology

Linked to betel quid chewing, seen primarily on the Indian subcontinent and Southeast Asia

Clinical features

- Limited ability to open the mouth (trismus)
- Oral mucosa is firm and white
- Vesicles, petechiae, melanosis, xerostomia
Mucosal burning, and pain on eating spicy foods
Mucosal rigidity caused by fibroelastic hyperplasia
Nutritional deficiency increases the risk and severity of fibrosis
Connective tissue changes: areca nut
Epithelial changes and cancer: tobacco

**Histological features**
- Dense avascular collagenous connective tissue
- Varying amounts of chronic inflammation
- Subepithelial vesicles (early)
- Hyperkeratosis
- Epithelial atrophy (older lesions)
- Epithelial dysplasia: 10 – 15% of biopsied cases
- Carcinoma: 6% of biopsied cases

**Treatment**
- Does not regress with habit cessation
- Intralesional corticosteroids
- Surgical splitting of the fibrous bands
- Follow up because malignant transformation 8% over 17 years
- 19 times more likely to develop oral carcinoma

**Erythroplakia**
Also termed “erythroplasia” – a term coined by Queyrat to describe a precancerous red lesion that develops on the penis (erythroplasia of Queyrat).

**Definition**
A red patch that cannot be clinically or pathologically diagnosed as any other condition

Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma in situ or invasive carcinoma.

**Etiology**
Presumed to be similar to squamous carcinoma
Clinical features

Point prevalence: 1 per 2500 adults; incidence unknown
Peak prevalence in older men at 65 – 74 years
Sites: floor of mouth, tongue, soft palate
Well-demarcated erythematous macule or plaque with a soft velvety texture
asymptomatic
May occur in conjunction with leukoplakia

Histological features

Epithelium:
  • Lack of keratin, atrophic
  • Underlying vasculature shows through, therefore it is red
Underlying connective tissue often shows chronic inflammation
90% show severe epithelial dysplasia, carcinoma in situ or invasive carcinoma

Treatment

View with suspicion, and BIOPSY, unless obvious source of irritation is present, in
which case observe for 2 weeks
Lesions exhibiting moderate dysplasia or worse must be removed completely
Long term follow-up
Malignant Epithelial Lesions

Squamous carcinoma

Also termed “epidermoid carcinoma”

Is the most common malignancy of the oral cavity (90%)

Oral cancer represents about 5% of human cancers

Definition

Is a malignant neoplasm derived from squamous epithelium

- Represents a severe epithelial change that has violated the basement membrane and invaded the connective tissue

Etiology

Is multifactorial:

Chemical carcinogens

- Phenols – wood products industry
- Alcohol – potentiator for tobacco
  - Dose and time dependent
- Tobacco –
  - Smokers with oral cancer are 2-3x > general population
  - Pipe and cigar smoking greater risk than cigarette
  - Relative risk for cigarette smokers is dose dependent
  - Reverse smoking – high risk
  - Smokeless tobacco also increases relative risk
- Betel quid

Radiation

- UV – lip
- X radiation (radiotherapy to head and neck area)

Deficiencies

- Iron
  - Plummer-Vinson syndrome – atrophic glossitis
- Vitamin A may be protective
Microorganisms

- Tertiary Syphilis
  - (Was associated with dorsal tongue carcinoma (rare today)
- Candida – Hyperplastic Candidiasis
- Oncogenic viruses

Oncogenic viruses

- HPV subtypes 16, 18, 31, 33

Immunosuppression

- Patients with AIDS and those who are undergoing immunosuppressive therapy for malignancy or organ transplantation are at risk

Oncogenes and tumor suppressor genes

- Proto-oncogenes have been implicated through the action of viruses, irradiation or chemical carcinogens e.g.
  - \( ras, myc, c-erbB \)
- Tumor suppressor genes allow tumor development when they become mutated or inactivated e.g.
  - \( p53, pRb, E-cadherin \)

Clinical features

More common in older men

Minimal pain in early lesions

Varied clinical presentation:

- Leukoplakia.
- Erythroplakia.
- Endophytic - invasive, burrowing, ulcerated, with raised rolled border, firm or indurated, possible destruction of underlying bone.
- Exophytic - mass-forming, fungating, verruciform, papillary, firm.

Sites:

- Lip vermilion (associated with actinic cheilitis);
- Lateral posterior and ventral tongue (most common intraoral site – 50%);
- Oral floor – 35%;
- Soft palate; gingiva; buccal mucosa; labial mucosa; hard palate
Metastasis

• Via lymphatics to ipsilateral cervical lymph nodes
• Sometimes contralateral metastasis
• 2% have distant metastasis (lungs, liver, bones)

Histological features

Arises from dysplastic epithelium
Invasive islands and cords of malignant squamous epithelial cells
Invasion is irregular extension of lesional epithelium through basement membrane into connective tissue
Individual cells, sheets and islands of cells without attachment to surface epithelium
Destruction of adipose tissue, muscle or bone
Surrounds and destroys blood vessels and lymphatics
Inflammatory response
Necrosis and hemorrhage, angiogenesis, desmoplasia
Cellular features:
• Abundant eosinophilic cytoplasm with large hyperchromatic nuclei
• Increased nuclear to cytoplasmic ratio
• Cellular and nuclear pleomorphism
• Individual cell keratinization and Keratin pearls
• Well, moderate or poorly differentiated, or anaplastic – depending on how closely it resembles the parent tissue

Treatment

Lip – surgical excision (wedge resection)
• 5 year survival 95 – 100%
• Only 8% recur
Intraoral – guided by the clinical stage of the disease and consists of
• Radical surgical excision
• Radiation therapy
• Combination of surgery and radiation therapy
• Sometimes chemotherapy used as an adjunct

Prognosis - depends on stage
• 5 yr survival:
  • 76% if no metastasis
  • 41% if cervical nodes involved
  • 9% if metastasis below the clavicle

Verrucous Carcinoma

Definition –
Is a low-grade variant of squamous carcinoma

Etiology
First reported as a spit-tobacco associated malignancy, although a regular squamous carcinoma is 25x more likely to develop

Clinical features
1 – 10% of all oral squamous carcinomas, depending on the local popularity of spit tobacco use
Males > 55 years
Usually in site of tobacco placement: mandibular vestibule, buccal mucosa, hard palate.
Usually extensive by time of diagnosis.
Diffuse, well-demarcated, painless, thick plaque with papillary or verruciform surface projections.
White, erythematous or pink – depending on amount of keratin, or inflammatory response.
Leukoplakia, or tobacco pouch keratosis may be adjacent

Histological features
Deceptively benign appearance
Abundant keratin – papillary or verruciform surface
Parakeratin plugs
Epithelial cells show apparently normal maturation sequence with no significant cellular atypia
Wide elongated rete ridges that “push” into connective tissue
Adequate sampling important, because an infiltrating squamous carcinoma may be associated

**Treatment**

Surgical excision without radical neck dissection, because metastasis is rare.
90% of patients are disease free after 5 years.
Radiotherapy is effective, but anaplastic change is feared (probably overexaggerated).
Chemotherapy may reduce size, but is not used as stand-alone treatment.

Other variants of Squamous carcinoma:

- Spindle cell carcinoma (Sarcomatoid carcinoma)
- Adenosquamous carcinoma
- Basaloid squamous carcinoma
- Maxillary sinus carcinoma
- Nasopharyngeal carcinoma
ONCOGENES, TUMOR SUPPRESSOR GENES, AND GENES WHICH REGULATE APOPTOSIS

Before looking at the details of genetic involvement in cancer, one needs to consider 7 fundamental changes in cell physiology which determine malignancy:

### Seven Hallmarks of Cancer

- **Self-sufficiency in growth signals**
- **Insensitivity to anti-growth signals**
- **Tissue invasion and metastases**
- **Sustained angiogenesis**
- **Evading apoptosis**
- **Defects in DNA repair**
- **Limitless replicative potential**

Adapted from: Robbins and Cotran, Pathologic basis of disease; 2005.

In squamous cell carcinoma or the oral cavity, some of the following have been implicated:

- **Oncogenes and tumor suppressor genes:**
  - **Proto-oncogenes** have been implicated through the action of viruses, irradiation or chemical carcinogens e.g. ras, myc, c-erbB.
  - **Tumor suppressor genes** allow tumor development when they become mutated or inactivated e.g. p53, pRb, E-cadherin.
- **Genes that regulate apoptosis (programmed cell death):**
  - e.g. p53, Bcl-2 family, death receptor, caspases.
SELF SUFFICIENCY IN GROWTH SIGNALS – ONCOGENES

- Proto-oncogenes are normal cellular genes that affect cell growth and differentiation.

- Oncogenes are genes whose products are associated with neoplastic transformation.

- Proto-oncogenes can be converted into oncogenes by:
  - Point mutations.
  - Translocations
  - Gene amplification.

- Oncogenes implicated in oral carcinogenesis:
  - C-Erb B-1
    - Located on chromosome 7.
    - C-Erb B-1 codes for the protein EGFR (Epidermal growth factor receptor).
    - Is expressed primarily in cells of epithelial origin.
    - Ligands EGF, TGF-α lead to cell proliferation, inhibition of apoptosis, and stimulation of invasion and metastasis.
    - EGFR gene amplification found in 30% of oral cancers.
    - Overexpression is also common.
    - Expression correlates with shortened patient survival.
    - Gene amplification has also been seen in pre-malignant lesions.
• Ras oncogene family
  • p21 transduces mitogenic signals from cell surface to cytoplasmic components.
  • Are activated by point mutations.
  • Approx. 15% of all human tumors carry mutated H-ras or K-ras oncogenes.
  • N-ras mutation may be early step in oral carcinogenesis.
  • 55% of lip cancers have H-ras mutation.
  • 35% of oral cancers associated with betel quid have H-ras mutations.
• C-Myc
  • C-Myc with partner protein Max regulates gene expression, and integrates cell cycle machinery with cell adhesion, cellular metabolism and the apoptotic pathways.
  • Frequently overexpressed in oral cancer as a result of gene amplification.
  • Overexpression is associated with loss of differentiation of oral squamous cell carcinomas.
• Cyclin D1
  • Cyclins are positive regulators of cell cycle progression; they drive the cell through the cell cycle.
  • CCND1 gene product regulates the Retinoblastoma gene product leading to transition from G1 to S phase.
  • 20-68% of oral cancers show expression and amplification of cyclin D1.
  • Correlates with poor survival and more frequent recurrences.
Levels at which Oncogene products work

- Growth factor e.g. TGF-α
- Growth factor receptor e.g. EGFR
- Signal transducing proteins e.g. RAS family
- Nuclear transcription factors e.g. C-myc
- Cyclins
INSENSITIVITY TO GROWTH INHIBITORY SIGNALS - TUMOR SUPPRESSOR GENES

• TSG’s are important for maintenance of cellular homeostasis, leading damaged cells to apoptosis and prevention of cancer development
  – they apply brakes to cell proliferation.

• Are inactivated by
  • Point mutations.
  • Deletions.
  • Rearrangements
    in both gene copies.

• TSG’s investigated in oral cancer:
  • p53 (TP53).
  • Retinoblastoma gene.
  • p16/p21/p27.

• p53 (TP53)
  • Normal (wild type) mediates cell cycle arrest, stimulates DNA repair after DNA damage, or induces apoptosis.
  • Derangement of p53 is one of the most common molecular aberrations in human malignancies.
  • Mutations
    • occur in 60% of oral squamous cell carcinomas
    • appear to be an early event
    • Are associated with tobacco smoking.

• Retinoblastoma (Rb) gene
  • Located on chromosome 13.
  • Gene product is a DNA binding protein.
• Involved in control of cell cycle; normal inactivates E2F responsible for cell cycle progression.
• Mutation results in uncontrolled cell proliferation.
• 6-74% of head and neck carcinomas show diminished expression.
• Loss of heterozygosity of an Rb allele in 14-37% of all tumors.
• p16, p21 and p27.
  • Act as modulators of cell cycle.
  • p16
    • Inhibits Rb, thereby releasing E2F.
    • Mutations occur in 19-58% of head and neck cancers.
    • Associated with reduced survival, increased recurrence and nodal metastasis.
  • p21
    • Expressed in 29-92% head and neck cancers, with undefined clinical relevance.
  • p27
    • 18-62% of carcinomas, correlating with improved survival.
Levels at which TSG’s act

Growth inhibitors (TP53, others)
CDK inhibitors (p16 or INK4a)
Cyclins/CDK’s
Growth factors (EGF)

Stimulate
Inactivate
Activate

Inactivated Rb
Activated Rb

E2F
E2F site
DNA

Activates transcription
Blocks transcription

Activates transcription
Blocks transcription
EVASION OF APOPTOSIS – GENES THAT REGULATE APOPTOSIS

• Accumulation of neoplastic cells may occur also as a result of mutations in genes that regulate apoptosis.

• These genes and their protein products include:
  • CD95 (also know as Fas) – the death receptor.
  • FADD - the intracellular adaptor protein.
  • Procaspase 8 and the Caspase family: Caspases 3, 8, and 9 in particular.
  • The BCL-2 family:
    • Apoptosis inhibitors: BCL-2, BCL-Xₐ (prevent cytochrome C release).
    • Apoptosis promoters: BAX (through TP53), BAD and BID (through Caspase 8).

Levels at which genes that regulate apoptosis act
Illustrative model for Oral Carcinogenesis – an accumulation of hits
Illustrative model for Oral Carcinogenesis

Adapted from: Tsantsoulis et al, Oral Oncol, 2007

NORMAL CELL  MILD DYSPLASIA  SEVERE DYSPLASIA  MALIGNANT CELL
Clonal expansion