Oral Epithelial Tumors, Melanocytic Nevi, and Melanoma (I)

**Introduction:**
- Oral Epithelial Tumors may be:
  - Benign tumors → Sequamous cell Papilloma
  - Malignant tumors → Sequamous cell carcinoma, Basal cell carcinoma & melanoma
- The main tumors derived from oral epithelium are the **Sequamous cell Papilloma** (benign neoplasm) and **Sequamous cell carcinoma** (malignant neoplasm)
- Basal cell carcinoma doesn't occur in the oral cavity but may present on the lip and involve the vermillion border
- Melanocytic nevi (hamartoma) and melanoma (malignant neoplasm) are derived from Melanocytes and/or their precursors

**Human Papilloma virus (HPV) and associated lesions:**
- HPV is a DNA virus with more than 75 types, of which at least 16 types have been isolated from oral lesions
- The majority of HPV are low risk types and associated with benign lesions of skin and oral mucosa
  - Certain types of HPV may be present in clinically healthy oral mucosa (normal epithelium) and so the identification of HPV in a lesion doesn't necessarily imply a causal relationship
- HPV may be associated with abnormal epithelial proliferation:
  - Hyperplasia → warts
  - Benign neoplasia → Papilloma
  - Oral premalignant lesions → leukoplakia
  - Malignant neoplasia → Sequamous cell carcinoma

**Koilocytes**
- Koilocytes are virally infected epithelial cells with HPV and have many cellular changes (koilocytic changes), such as: shrinkage of the nucleus "pyknotic nucleus", vacuolation around the nucleus "peri-nuclear vacuolization", irregular borders
- We are going to discuss the following HPV-associated lesions:
  - **Sequamous cell Papilloma** → neoplasm
  - **Verruca vulgaris (common wart)** → viral infection
  - **Condyloma accuminatum (venereal wart)** → viral infection
  - **Focal epithelial hyperplasia** → viral infection

**All of these lesions appear clinically as elevated lesions**

1. **Sequamous cell Papilloma**:
   - It is a common benign tumor of oral mucosa
   - Benign tumor = true tumor (NOT reactive)

**Clinical presentation:**
- Usually a solitary lesion (single)
Dr. Tahani Abualteen

- Can occur anywhere on the oral mucosa
- Most occur in adults (most often) but may also be seen in children
- Vary in size (mostly small)
- May be Pedunculated (most often) or sessile
- Presents as a warty or cauliflower-like growth with a white or pink surface (most often) depending on the amount of keratin present

- **Histopathological presentation:**
  - Papillary finger-like epithelial proliferation supported by thin fibrovascular cores
  - The epithelium shows variable keratosis
  - Mitotic figures are often seen in the basal layer of the epithelium
  - Features of epithelial dysplasia aren’t present
- No reports of malignant transformation (NOT a premalignant lesion)
- Treatment: conservative excision

2. Verruca Vulgaris (Common Wart):
   - **Clinical presentation:**
     - Oral lesions clinically present as Sequamous cell Papillomas (differentiation is only made through biopsy & then microscopic examination)
Dr. Tahani Abualteen

- May be **Pedunculated** (most often) or **sessile**
- May be **single or multiple**
- Appear **white** (most often) because of **hyperkeratosis**
- Seen most often on **fingers in children** when oral lesions may be associated with autoinoculation from warts on the fingers and lips
- **Common warts on the skin** are usually associated with HPV types 2 or 4 infections

- **Histopathological presentation:**
  - Papillary finger-like epithelial proliferation supported by **thin fibrovascular cores** (papillae may be **less pronounced** compared to Sequamous cell Papilloma)
  - **Hyperkeratosis**
    - **Excessive keratinization** (Orthokeratinization most often) & **prominent granular cell layer**
  - **Acanthosis**
    - **Hyperplastic rete ridges around margins slope inwards towards the center of the lesion** (this is a **characteristic feature** of verruca vulgaris)
  - **Koilocytosis** → large vacuolated cells (koilocytes) with prominent Keratohyaline granules

- **Treatment:** surgical excision, cryosurgery (freezing) or chemical cautery

3. **Condyloma Accuminatum (Venereal Wart):**

- Characteristically, these warts occur in the **anogenital region** but they may be seen intraorally
- **Clinical presentation:**
  - Present as **multiple pink nodules** which grow and coalesce to form soft, **pink** (most often), **Pedunculated or sessile** (most often) **papillary lesions** similar in colour to the surrounding mucosa
- In some patients, they are an oral manifestation of HIV infection
- Most of the time venereal warts have flat surface (don’t show the warty or cauliflower appearance)
- Venereal warts are usually associated with HPV types 6, 11 and 16 infections

**Histopathological presentation:**
- Keratinization is not a feature (thus clinically they look pink)
- The dominant epithelial feature is a prominent acanthosis
  **Hyperplastic rete ridges show marked broadening and elongation**
  **Flat-topped (blunt) surface projection** (don’t show the papillary finger-like appearance)
- Koilocytosis → large vacuolated cells (koilocytes) with prominent Keratohyaline granules

4. **Focal epithelial hyperplasia (Heck’s disease):**
   - This rare disease was originally described in native north Americans but occurs in other ethnic groups and in some immune-comprised patients
   - Clinical presentation:
     - Multiple small elevated epithelial plaques
     - Most frequently involving the lower lips and buccal mucosa
     - Oral focal epithelial hyperplasias are usually associated with HPV types 13 and 32 infections
   - Histopathological presentation:
     - Hyperkeratosis
     - Acanthosis
     **Hyperplastic rete ridges tend to fuse with each other**
     - Koilocytosis → large vacuolated cells (koilocytes) with prominent Keratohyaline granules
HPV-associated lesions (SUMMARY):

<table>
<thead>
<tr>
<th>Sequamous cell Papilloma</th>
<th>Verruca vulgaris</th>
<th>Condyloma Accuminatum</th>
<th>Heck’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually single</td>
<td>Single or multiple</td>
<td>Usually multiple</td>
<td>Usually multiple</td>
</tr>
<tr>
<td>Often Pink surface</td>
<td>Often White surface</td>
<td>Often Pink surface</td>
<td>Often Pink surface</td>
</tr>
<tr>
<td>Often Pedunculated</td>
<td>Often Pedunculated</td>
<td>Often sessile</td>
<td>Often sessile</td>
</tr>
<tr>
<td>- Papillary finger-like epithelial proliferation supported by thin fibrovascular cores</td>
<td>- Papillary finger-like epithelial proliferation supported by thin fibrovascular cores (papillae may be less pronounced compared to Sequamous cell Papilloma)</td>
<td>- Keratinization is not a feature - The dominant epithelial feature is a prominent acanthosis ** Hyperplastic rete ridges show marked broadening and elongation ** Flat-topped (blunt) surface projection (don’t show the papillary finger-like appearance)</td>
<td>- Hyperkeratosis - Acanthosis ** Hyperplastic rete ridges tend to fuse with each other</td>
</tr>
<tr>
<td>- Hyperkeratosis ** Excessive keratinization (Orthokeratinization most often) &amp; prominent granular cell layer</td>
<td>- Acanthosis ** Hyperplastic rete ridges around margins slope inwards towards the center of the lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acanthosis ** Hyperplastic rete ridges show marked broadening and elongation ** Flat-topped (blunt) surface projection (don’t show the papillary finger-like appearance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koilocytosis may or may not present</td>
<td>Koilocytosis</td>
<td>Koilocytosis</td>
<td>Koilocytosis</td>
</tr>
</tbody>
</table>

Sequamous cell carcinoma (SCC):

- Epidemiology:
  - Accounts for 90% or more of all oral malignant neoplasms (the commonest oral malignancy)
  - Variable incidence worldwide (reflecting different habits & etiological factors):
    - Oral cancer \(\rightarrow\) UK & USA \(\rightarrow\) < 4% of all cancers
    - Oral Cancer \(\rightarrow\) India & South-East of Asia \(\rightarrow\) up to 40% of all cancers
  ** The incidence rates for large countries (such as the USA, UK and India) show regional and ethnic variations \(\rightarrow\) e.g. incidence rates tend to be higher in urban than rural communities in India, and higher for blacks than whites in the USA, higher in Scotland than in England and Wales in the UK

5/12
Dr. Tahani Abualteen

- **Oral cancer** is globally considered one of the 10 commonest cancers
- **Oral Cancer** on a global basis is estimated to be:
  - 4th commonest cancer in men and 6th commonest in women
    **When data for both sexes are combined it is the 6th commonest form of malignant disease**
  - 8th commonest cancer in developed, but 3rd commonest in developing countries
- **Incidence in developed countries is on the increase now** despite previous decrease in incidence and mortality rates
- **Most cases occur above age 40 years**
- **Incidence in people aged under 40 years is increasing** (age of affected patients is declining)
- **More common in men than in women but ratio is changing** (increasing in women!)
- **Geographical variations in oral sites** particularly at risk reflect different etiological factors → E.g. Tongue & floor of mouth in UK while buccal mucosa in India
- **Geographical variation in mortality rates** → 30-40% in Western societies
- Despite advances in treatment, **mortality rates have not significantly changed** (because the most important aspect in cancer is EARLY DETECTION)
- **5-year survival rates have increased significantly**

**Etiological Factors:**
- Many factors are involved in the etiology of oral cancer and these **vary in different ethnic groups**
- Studies have shown that **tobacco and alcohol** are the two most important and probably account for about 75% of intraoral cancers in the western world
  **Poor diet** probably account for another 10-15% of intraoral cancers in the western world
  1. **Tobacco:**
     - It is the first major factor in the etiology of intraoral cancer
     - Tobacco is an important factor independent of alcohol
     - **Main carcinogenic agents** in tobacco, regardless of how it is used are **nitrosamines derived from nicotine**
     - Burning of tobacco produces **polycyclic aromatic hydrocarbons** (another carcinogenic agents)
     - **Tobacco smoking:**
       - Pipes, cigars, cigarettes, reverse smoking
       - The evidence linking tobacco smoking and intraoral carcinoma is now **firmly established** regardless of the type of tobacco and method of consumption
       - Carcinogens in tobacco smoke may **dissolve in saliva** and collect in areas where saliva tends to pool, increasing risk in **floor of mouth, dorsal and ventral tongue, and soft palate** (these areas are more prone to develop cancer that others)
       - **Type of tobacco, curing methods and method of smoking may influence the relative risk of oral cancer:**
         ✓ **Pipe and cigar** are usually linked with **lip cancer**
Dr. Tahani Abualteen

- **Reverse smoking** (with the burning end inside the mouth) is associated particularly with **palate cancer** (one of the rarest sites for oral cancer)
  **Risk of oral cancer for reverse smokers is over 40 times that of non-smokers**
- **Regular smoking** is probably associated with **floor of mouth, tongue, or soft palate cancers**
  - Relative risk of oral cancer increases with the number of cigarettes smoked per day and with the duration of smoking → e.g. heavy smokers smoking 40 or more cigarettes per day have a relative risk of oral cancer 10-20 times greater than non-smokers
  **The relative risk of smokers who stop smoking falls to that of non-smokers after about 10 years**

- **Smokeless tobacco:**
  - Snuff dipping, tobacco sachets, or tobacco chewing
    **Snuff** = powdered tobacco which in addition to being inhaled, can also be placed in contact with oral mucosa in **buccal and labial sulci** (common in USA & Sweden)
    **Relative risk of oral cancer from using oral snuff is unclear**
  - **Tobacco sachets** have been suggested to be one of the factors that led to increase in oral cancer in young people
  - **Tobacco chewing** was relatively common in the UK particularly in occupations such as mining where smoking was environmentally dangerous because of possibility of explosion

2. **Betel quid (pan) & other chewing habits:**
   - Betel quid (pan) chewing is one of the most widespread habits in the world and it is particularly common in south-east Asia and Indian subcontinent
   - In **India** → Betel quid (pan) is composed of **betel nut & lime** wrapped in a betel leaf to which tobacco and various spices are often added
   - Betel quid (pan) is usually placed in the **buccal sulcus** and is frequently kept in mouth for a long time
   - As the Betel quid (pan) is chewed, **alkaloids** (carcinogenic agents) are released from **betel nut** (which aid in digestion & to produce a slight euphoric effect)
   - Betel quid (pan) chewing habit is more common in **women** than in men
Betel quid (pan) chewing habit often starts in childhood but frequency of use increases with age. Betel quid (pan) chewing habit induces leukoplakia where pan is held in the mouth and malignant transformation is usually evidenced clinically by the development of a papilliferous ulcerated mass.

The roles of the constituents of the pan in the etiology of leukoplakia & Sequamous cell carcinoma present a major problem which is compounded by the possible interactions between components of the pan making it difficult to know the role of each component alone in the development of cancer. (Are carcinogens released from betel nut, or lime or tobacco?!) **E.g., lime can hydrolyze one of the alkaloids of betel nut (arecoline) to produce (arecolidine) which has been shown to be carcinogenic.**

In Malaysia → Betel quid (pan) is composed of betel nut & lime wrapped in a betel leaf but without tobacco and this suggests that the above mechanism could play a role!!

Relative risk for oral cancer is greatly increased when tobacco is present. Chewing of betel nut (areca nut) alone is the main etiological factor in oral Submucous fibrosis which is regarded as a premalignant condition (as it leads to epithelial atrophy).

3. Alcohol:

- It is the second major factor in the etiology of intraoral cancer.
- Alcohol is an important factor independent of smoking.
- All Forms of Alcohol consumption (spirits, wines & beers) are DANGEROUS. **The relative risk for beer & wine drinkers is as high as (or maybe greater than) that for spirit drinkers.**
- There's evidence to support a dose/time relationship, but it is less obvious than seen with tobacco.
- Pure ethanol has NOT been shown to be carcinogenic, but other chemicals in the beverage, called congeners, are carcinogenetic and may be responsible for the increased risk of cancer.
- The increasing incidence of oral cancer, especially in younger groups, may be linked to increased alcohol consumption.
- The role of alcohol in the etiology of oral cancer has been complicated because of the close association between drinking and smoking habits (most heavy drinkers are heavy smokers too!!)
- Relative risk of oral cancer increases when smoking and drinking are practiced concurrently, suggesting a synergistic effect.
- The mechanisms by which alcohol consumption increases the risk of oral cancer are still unclear.
- Possible mechanisms by which Alcohol increases the risk of oral cancer:
  - Possible carcinogenic effect of chemicals other than ethanol → carcinogenic congeners present in alcoholic beverages may enhance the penetration and transport of other carcinogens across the mucosal barrier (e.g. Alcohol may act as a solvent for carcinogens present in tobacco).
It is also possible that nutritional deficiencies and impaired metabolism (which are common in heavy drinkers) may impair the mucosal barrier. It is also possible that liver disease (which is common in heavy drinkers) may impair its ability to detoxify carcinogens. It is also possible that immune-suppression (which is common in heavy drinkers) may increase the risk of developing cancer. Histological studies suggest that alcohol & tobacco usage are associated with atrophy of oral epithelium.

 Concerns have been expressed regarding the potential risk from mouthwash use. The evidence is inconclusive, but an increased risk of oral cancer is reported in subjects using high alcohol content (25% or higher) mouthwashes.

**4. Diet and Nutrition:**

 Dietary deficiencies or imbalances may account for 15% of oral cancer.

 Iron is essential for the maintenance of oral epithelium (epithelial integrity) and it is possible that atrophic changes in iron-deficiency anemia render the mucosa more susceptible to chemical carcinogens \(\rightarrow\) e.g. iron deficiency in primary Sideropenic anemia (Plummer-Vinson or Patterson-Kelly syndrome) has been linked with increased risk of esophageal, pharyngeal, and oral cancer.

 *Atrophic changes in lichen planus and tertiary syphilis render the mucosa more susceptible to chemical carcinogens too.*

 Vitamin A is also important for the maintenance of oral epithelium (epithelial integrity) and so individuals whose diets are high in the antioxidant vitamins A, C & E have a decreased risk of oral cancer.

 **The risk decreases with increasing consumption of fresh fruit and vegetables.**

**5. Dental Factors:**

 Poor oral hygiene, faulty restorations, sharp edges of teeth, and ill-fitting dentures have been incriminated in etiology of oral cancer but evidence is unclear!!

 Some oral cancer patients have poor dentitions but they also smoke and drink heavily!!

 Experiments reported that mechanical irritation can act as a cancer promoter BUT NOT as an initiator \(\rightarrow\) e.g. these dental factors may cause chronic inflammation that may release oxidants which may later on induce malignancy!!

 **Initiation comes before promotion and so we need a carcinogenic agent or mutation in certain gene to initiate cancer and then for chronic irritation to promote it.**

**6. Occupational Risks:**

 Outdoor workers (such as farmers, fishers) are at risk of high exposure to Ultraviolet light that is important in Sequamous cell carcinoma of skin, including lips (e.g. the vermilion border of lips).
Dr. Tahani Abualteen

- Lip cancer is more common in men than women
- Lip cancer is more common in lower lip than the upper lip
- Lip cancer is more common in fair-skinned males (dark-skinned males may get protection against ultraviolet light by the melanin pigment)

- Sequamous cell carcinoma of the lip may be preceded by hyperkeratotic and dysplastic changes (solar keratosis, actinic cheilitis)

** Solar keratosis or actinic cheilitis is considered a premalignant lesion
- The possible role of other occupational and environmental factors (such as atmospheric pollution by chemicals and dusts) is largely unknown

7. Viruses:
   A) Herpes Simplex Virus (HSV):
      - Has been shown to be carcinogenic or co-carcinogenic in laboratory experiments
      - Has been demonstrated in some tumors but this doesn’t necessarily mean a causal relationship
      - Rarely produce tumors
      - HSV is probably an incidental passenger virus found in some lesions
   
   B) Human Papilloma Virus (HPV):
      - HPV types 16 & 18 are important factors in Sequamous cell carcinoma of the uterine cervix
      - Evidence for role of HPV in some oral premalignant and malignant lesions is increasing
      - HPV type 16 is the most common isolate, but since it can be also detected in a relatively high proportion of normal oral mucosa, its role in oral carcinogenesis is unclear!!
      - Some HPV proteins may bind and inactivate the products of tumor-suppressor genes (p53 and Rb), which is considered a significant step in the development of oral cancer and so HPV is likely to be an important cofactor in at least some oral cancers
   
   C) Epstein Barr Virus (EBV):
      - EBV is important in development of some nasopharyngeal carcinomas and lymphomas, but a similar role in oral cancer has NOT been established
      - EBV is probably an incidental passenger virus found in some lesions

8. Immunosuppression:
   - Increased risk of lip cancer reported following renal and other organ transplants linked to immunosuppressive therapy
   - Increased incidence of oral cancer with AIDS (HIV infection) but the evidence of an increased risk in HIV-positive patients (e.g. in the early stages of AIDS) is inconclusive
   - Smoking, alcohol, and iron deficiency may impair the cell-mediated immunity, but the significance of this role in oral cancer is unknown
Dr. Tahani Abualteen

9. **Chronic Infections:**
   
   A) **Candidial infection:**
   - Chronic candidal infection is often associated with *speckled Leukoplakias* which are prone to undergo malignant transformation and it is suggested that the *fungus is responsible for this transformation*
   - Chronic hyperplastic candidosis also presents as a leukoplakia (*candidal leukoplakia*) and may have a *premalignant potential*
   - However, *other chronic oral candidal infections are not associated with malignant transformation*
   - So the role of Candida in malignant transformation is *uncertain*

   B) **Syphilis:**
   - Historically, *tertiary syphilis* (late stage) has been linked to oral cancer, especially *anterior 2/3rds of dorsal tongue*
   - *Epithelial atrophy* in late stages may render mucosa more susceptible to carcinogens
   - *Syphilitic leukoplakia* may precede invasive carcinoma
     **Syphilitic leukoplakia is considered a premalignant lesion**
   - However, late stage syphilis is now rare and its relevance to the etiology of oral cancer is *insignificant*

- **Oncogenes and Tumor-Suppressor Genes:**
  - Genes regulating cell growth and proliferation include: *growth-promoting Proto-Oncogenes* and *growth-inhibiting tumor-suppressor genes*
  - Oral cancer has a *multifactorial etiology* and is the result of *genetic damage to these genes* allowing *uncontrolled proliferation of cells*
  - Carcinogenesis is a *multistep process* involving *multiple sequential mutations* which accumulate within the cell
  - **Under normal conditions →** cellular proliferation is controlled by the *balance between growth-promoting and growth-inhibiting genes*
  - **During carcinogenesis:**
    - *Proto-oncogene* may undergo mutation and become an *activated oncogene* and/or
    - *Tumor suppressor gene* may be mutated or their product inactivated
      **The result in both cases is an increased rate of cell growth and proliferation and then malignant transformation** (tumor formation)
      **Tumors result from either activation of Oncogenes (due to mutation in Proto-Oncogenes) or inactivation of tumour-suppressor genes**
Dr. Tahani Abualteen

- **Oncogenes:**
  - Derived from mutated Proto-Oncogenes of normal cells (Oncogenes are NOT present in normal cells)
  - Code for growth promoting factors
  - Mutations results in enhanced or inappropriate gene expression
  - Excess or abnormal oncogene product may lead to uncontrolled cell growth
  - Over-expression of certain Oncogenes (c-myc, ras and erb B-1) is involved in the etiology of oral cancer

- **Tumor suppressor genes:**
  - Present in normal cells
  - Code for growth inhibiting factors
  - Mutations result in defective/deficient protein production which may lead to uncontrolled cell growth
  - Mutation of p53 gene is involved in many human cancers, including oral cancer
  - Normal p53 protein → detects DNA damage and arrests the cell cycle at G1 phase
  - Mutant p53 protein → allows cells with damaged DNA to continue the cell cycle resulting in tumor formation

- **Model for genetic progression:**
  - The development of oral cancer involves progressive accumulation of genetic changes:
  - Model for genetic progression based on loss of genetic material from specific locations on chromosomes (called loss of heterozygosity (LOH)):
    1. Normal mucosa → LOH at 9p → pre-dysplastic mucosa
    2. Pre-dysplastic mucosa → additional LOH at 3p, 17p (p53 location) → dysplastic mucosa
    3. Dysplastic mucosa → additional LOH at 13q, 11q, 14q → carcinoma in situ (CIS)
    4. Carcinoma in situ → additional LOH at p8, 4q → invasion (SCC)
  ** Dysplasia may remain unchanged or regress back to normal or progress into malignancy
  ** Carcinoma in situ = severe dysplasia involving the full thickness of the epithelium but without any invasion