Oral epithelial dysplasia

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Oral epithelial dysplasia

- Leukoplakia and erythroplakia are the most common precursor lesions of oral squamous cell carcinoma (OSCC)
- Histopathological term “epithelial dysplasia” is applied when there is a disturbance of architecture and cellular atypia(Barnes et al, 2005)
- Presence of epithelial dysplasia is one of the prognostic features of malignant transformation of premalignant, precancerous, or potentially malignant lesions
- However: nondysplastic lesions **may become malignant** and **not all dysplastic lesions** become malignant(Reibel, 2003; Holmstrup et al, 2006)

Idiopathic “true” Leaukoplakia

- Definition:
- ‘ A white patch or plaque that cannot be characterized clinically or histopathologically as any other disease’ **WHO 1978**
- : ‘ A predominantly white lesion of the oral mucosa which cannot be characterized as any other definable lesion; some oral leaukoplakias will transform into cancer’ Pindborg 1994.
- “The term leukoplakia should be used to recognize white plaques of questionable risk having excluded (Other) known diseases or disorders that carry no increased risk of cancer”- Warnakulasuriya et al 2007

- It is a clinical term with no histological connotation!! (Silverman et al, 1996)

Idiopathic “true” Leaukoplakia

Precancerous lesion: ‘Morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart’ **WHO 1972.**

Precancerous Condition ‘A generalized state associated with a significantly increased risk of cancer

Etiological agents : tobacco, alcohol, candidosis, possible HSV, HPV (18, 16), sunlight (vermillion border)

Idiopathic “true” Leaukoplakia

Previously:

Precancerous lesion: ‘Morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart’ **WHO 1972.**

- **ie cancer arises at site of lesion**

Precancerous Condition ‘A generalized state associated with a significantly increased risk of cancer

- Ie Cancer arises in any site of person with condition

Better term is :

“Potentially malignant Disorder”

Idiopathic "true" Leaukoplakia

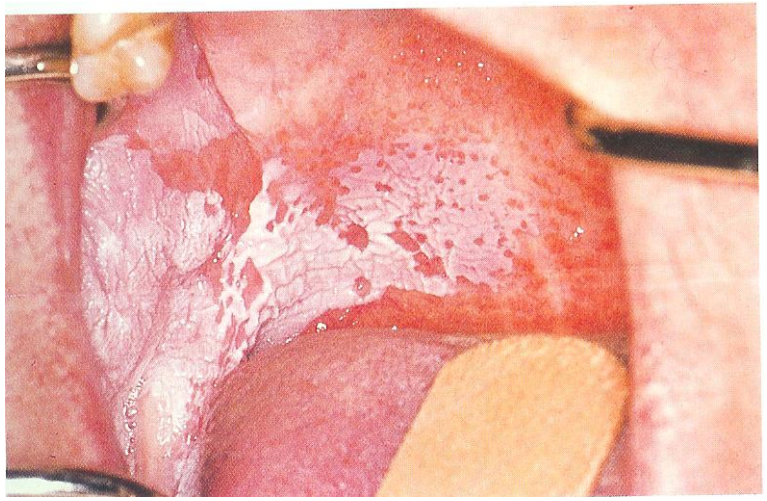
Subtypes:

1. ***Homogenous***

Idiopathic "true" Leaukoplakia

Subtypes:

1. ***Homogenous***



Idiopathic "true" Leaukoplakia

Subtypes:

1. *Homogenous*
2. ***Nodular***

Idiopathic “true” Leaukoplakia

Subtypes:

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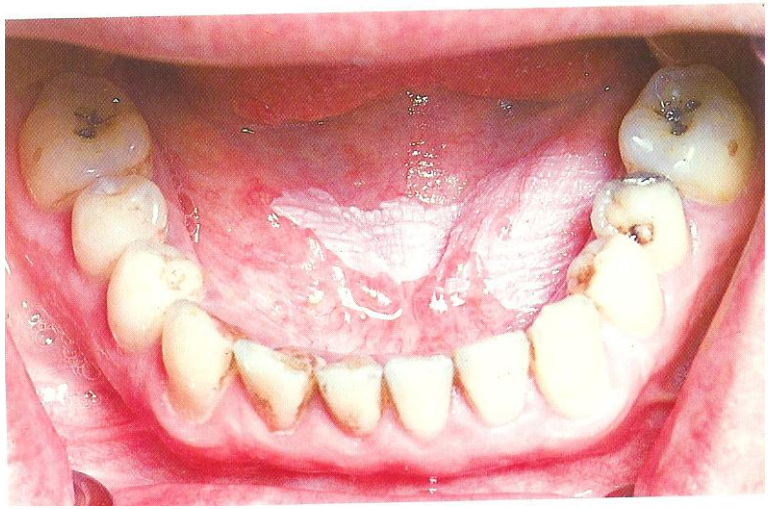
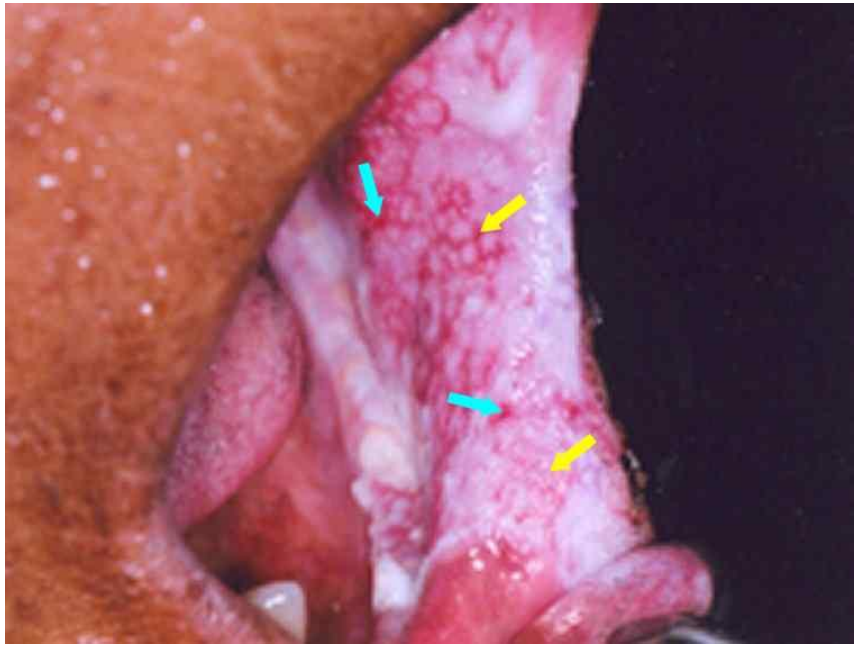
2. ***Nodular***



Idiopathic “true” Leaukoplakia

Subtypes:

1. *Homogenous*
2. ***Nodular***



Nodular leukoplakia on the left buccal mucosa extending posteriorly from the commissure. Note the small nodules (yellow arrows) on an erythematous base (blue arrows).

Idiopathic "true" Leaukoplakia

Subtypes:

1. *Homogenous*
2. *Nodular*
3. ***Verrucous***

Idiopathic "true" Leaukoplakia

Subtypes:

1. *Homogenous*
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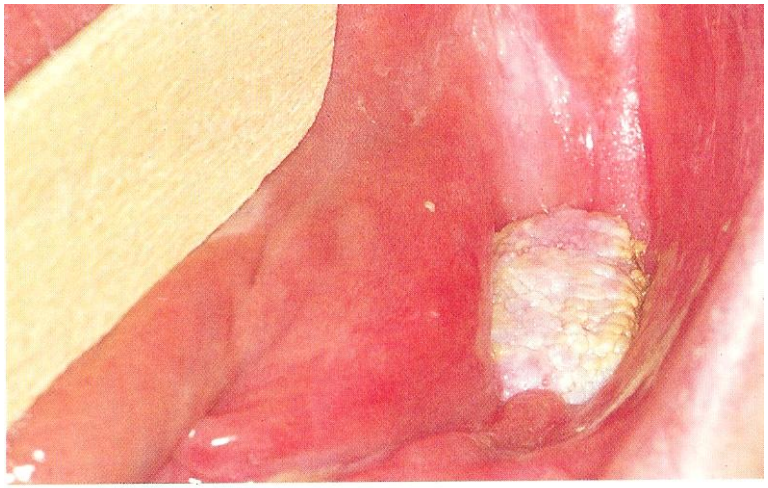
3. ***Verrucous***



Idiopathic “true” Leaukoplakia

Subtypes:

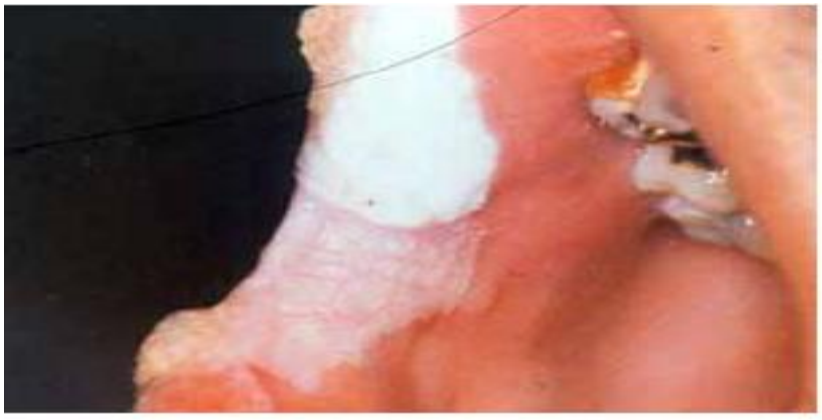
Again better to think in terms of

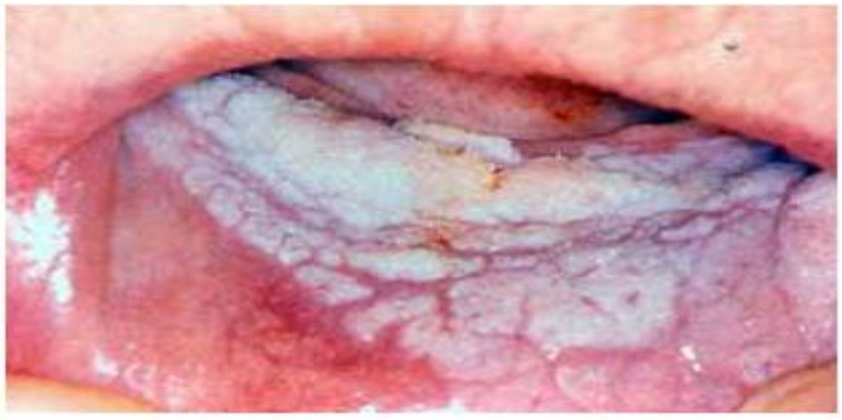
1. Homogeneous
2. **Erythro leukoplakia- higher risk of malignant change**

Idiopathic “true” Leaukoplakia

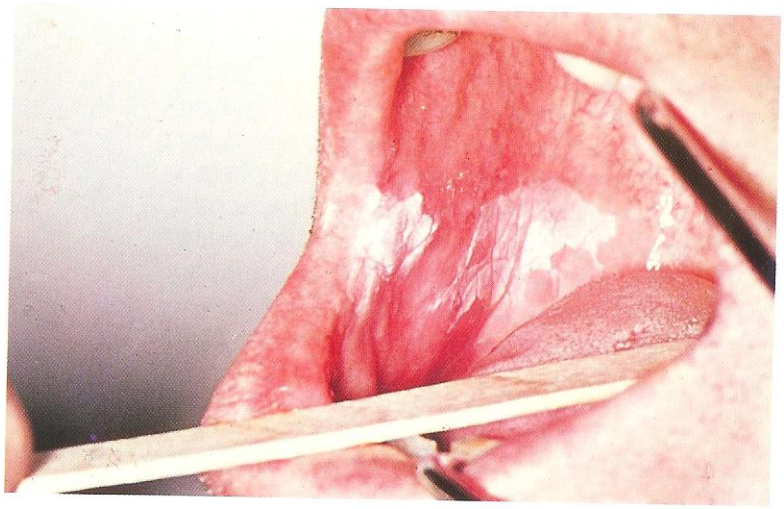
Subtypes:

1. Homogenous
2. Nodular
3. Verrucous
4. **Proliferative Verrucous Leaukoplakia (Hansen et al, 1985).**

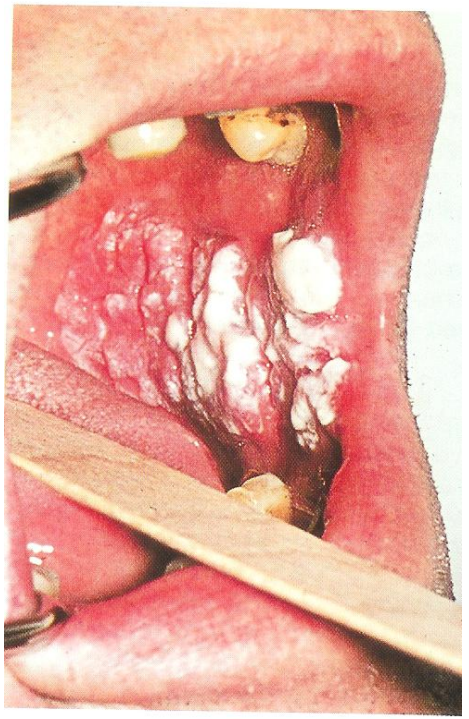




Bowens disease- Intra epithelial carcinoma in situ, that is full epithelial thickness dysplasia



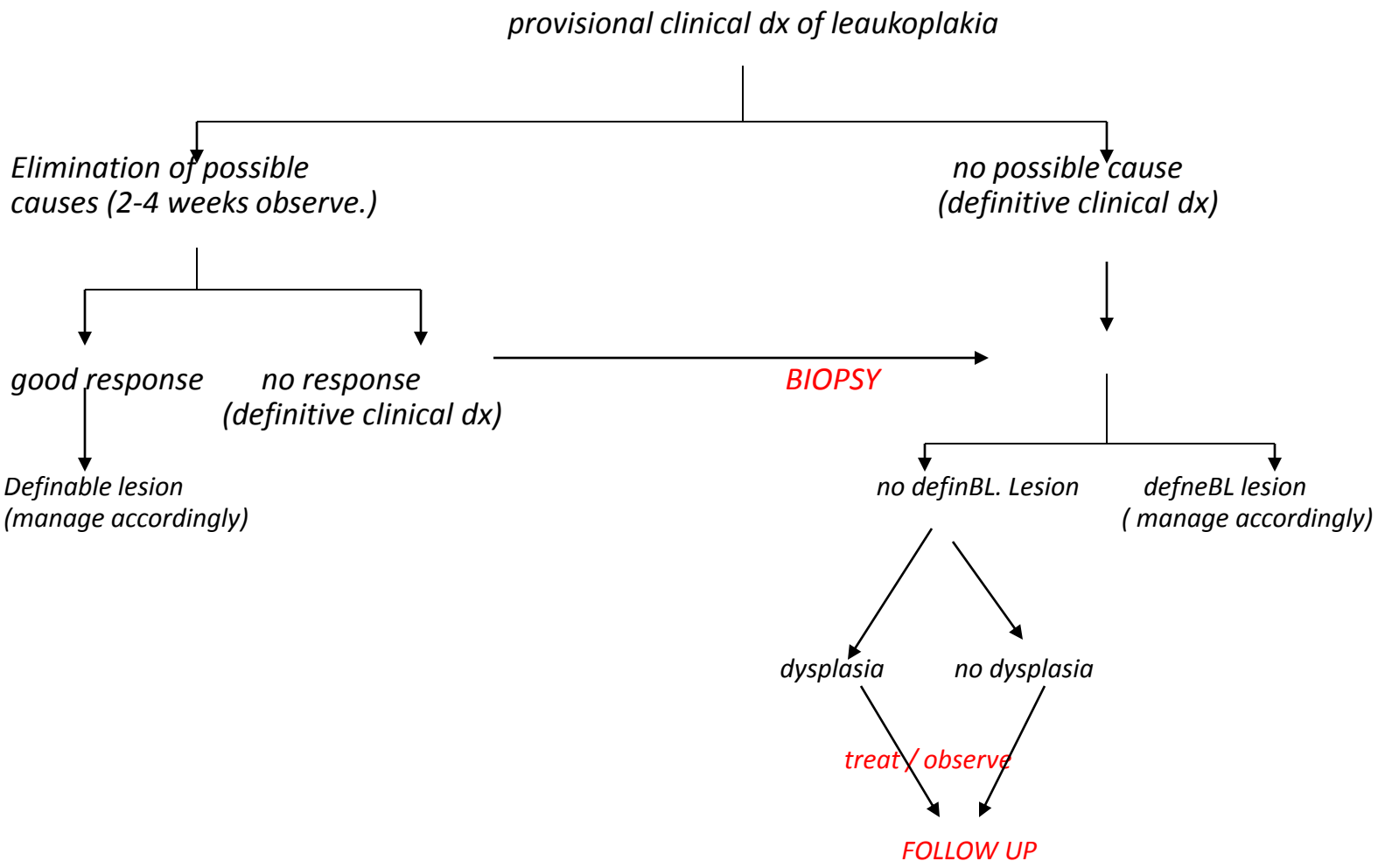
Leakoplakia R side



"Ca in Situ" L side

Leukoplakia

Leaukoplakia (Van der Waal et al.)



Leaukoplakia- Wanakulasuriya et al 2007

Disorders that need exclusion to diagnose leukoplakia

Disorder	*Diagnostic features*	*Biopsy*
White sponge nevus	Noted in early life, family history, large areas involved, genital mucosa may be affected	Biopsy not indicated
Frictional keratosis	History of trauma, mostly along the occlusal plane, an etiological cause apparent, mostly reversible on removing the cause	Biopsy if persistent after elimination of cause particularly in a tobacco user
Morsicatio buccarum	Habitual cheek – lip biting known, irregular whitish flakes with jagged out line	Biopsy not indicated
Chemical injury	Known history, site of lesion corresponds to chemical injury, painful, resolves rapidly	Not indicated
Acute pseudomembranous candidosis	The membrane can be scraped off leaving an erythematous/raw surface	Swab for culture
Leukoedema	Bilateral on buccal mucosa, could be made to disappear on stretching (retracting), racial	Not indicated
Lichen planus (plaque type)	Other forms of lichen planus (reticular) found in association	Biopsy consistent with lichen planus
Lichenoid reaction	Drug history, e.g. close to an amalgam restoration	Biopsy consistent with lichen planus or lichenoid reaction
Discoid lupus erythematosus	Circumscribed lesion with central erythema, white lines radiating	Biopsy consistent with DLE supported by immunofloresence and other investigations
Skin graft	Known history	Not indicated
Hairy leukoplakia	Bilateral tongue keratosis	Specific histopathology with koilocytosis; EBV demonstrable on ISH
Leukokeratosis nicotina palate	Smoking history, greyish white palate	Not indicated

Leaukoplakia- Wanakulasuriya et al 2007

Palatal lesions in reverse smokers

- *Smoking the lit end of cigar, cigarette or cheroot inside the mouth*
- *Red, white or mixed lesions of the palate*

Oral submucous fibrosis (OSF)

- *Chronic disorder characterized by fibrosis of the lining mucosa of oral cavity and upper digestive tract*

- *Fibrosis of lamina propria*
  - *Early signs may have burning sensation, blanching of mucosa, leathery mucosa*
  - *Late signs may show fibrous bands within mucosa, limited mouth opening, woody changes of mucosa and tongue*

Leaukoplakia- Wanakulasuriya et al 2007

Oral Lichen planus

Discoid Lupus Erythematosus

Hereditary disorders

- Dyskeratosis congenita
- Epidermolysis bullosa

Erythroplakia

Defn- ‘ Bright red velvety plaque or patch which cannot be characterized clinically or pathologically as being due to any other condition’ (Brightman et al, 1997**).**

- Erythroplakias esp. in floor of mouth, ventral tongue, soft palate and anterior pillars of tonsils exhibit a high frequency of pre-malignant and malignant change, (Mashberg et al, 1995).

- Differential Dx-
  erythematous candidosis, mechanical irritation, denture stomatits, vascular lesion and non-specific inflammatory lesions

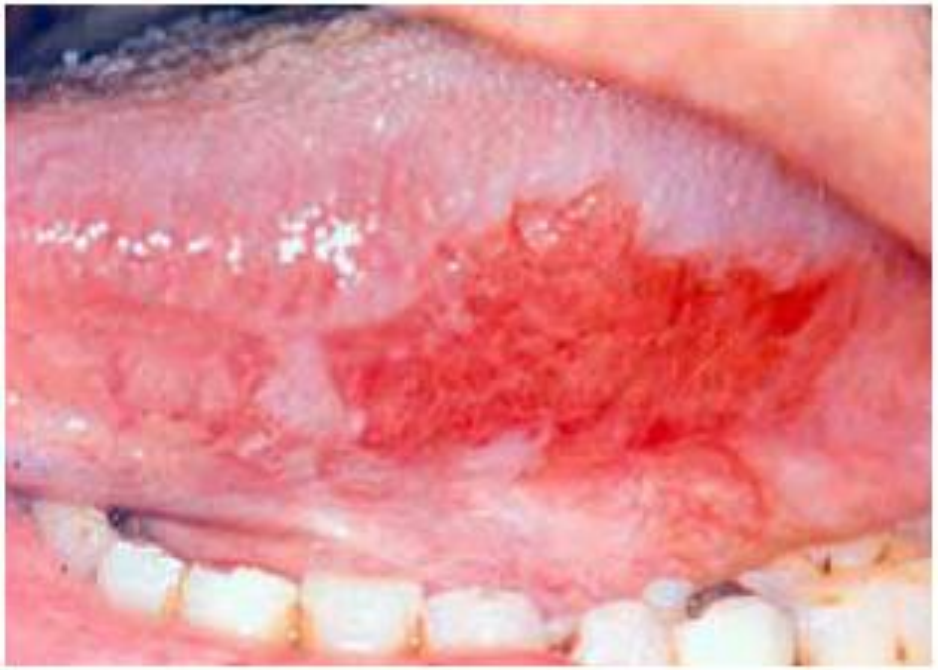
Erythroplakia

Name of condition	***Diagnostic category***
Inflammatory/ immune disorders	*Desquamative gingivitis* *Erythematous lichen planus* *Discoid Lupus* *Pemphigoid* *Hypersensitive reactions*
Infections	*Erythematous candidosis* *Histoplasmosis*
Harmartomas/ neoplasms	*Hemangiomas* *Kaposi's sarcoma*

From: Reichart et al 2005

Erythroplakia

- Velvety red patch that cannot be clinically or microscopically be defined as any other disease
- Premalignant (may be earliest sign of OMSCC)



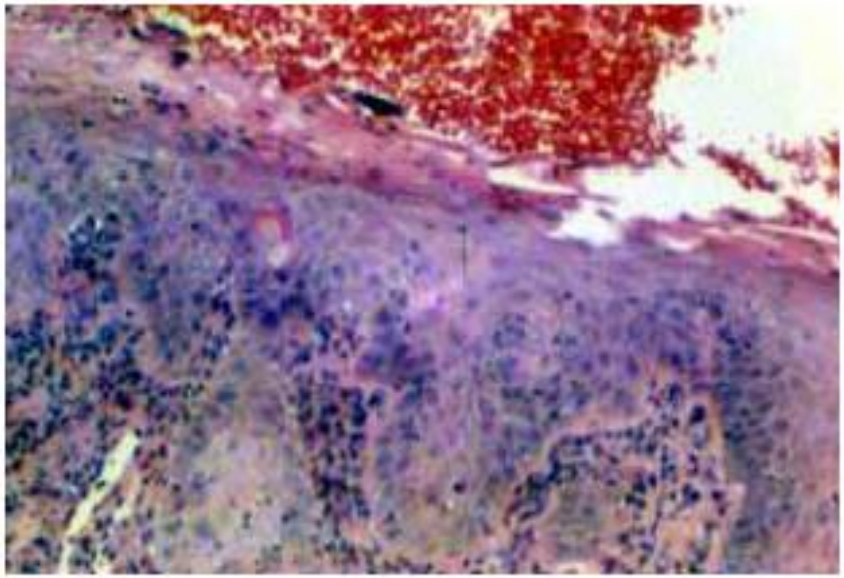
Oral epithelial dysplasia- diagnostic dilemma

Determining whether a dysplastic lesion will progress to OSCC may in future reqire molecular markers indicative of risk for disease progression, these may also serve as therapeutic targets for future management strategies (Brennan et al, 2007)

Some of these may be:

- **Microarray technology** :numerous inflammatory related genes of the arachdonic acid metabolism pathway have altered expression(Banerjee et al, 2005)
- **Loss of heterozygosity**: at 3p and/or 9p increased the risk of progression of dysplasia to OSCC (Zhou et al, 2005)
- **Apoptosis and cell cycle alterations**: apoptosis decreases with more severe dysplasia and OSCC (Kovsi et al, 2003)
- **Metrix metalloproteinases**: (MMP)-1 and -9 more commonly expressed indysplastic tissue that progressed to OSCC (Jordan et al,2004 ; Vigneswaran et al, 2006)
- **Cytokeratin**: K4 and K13 were suppressed and K 14, K 17 expression elevated OSCC and Dysplasia(Ohkura et al, 2005)
- **Integrins**: $\alpha_v \beta_6$ integrin was associated with malignant transformation of dysplastic oral leaukoplakias but also expressed in OLP (Hamidi et al,2000)

Oral epithelial dysplasia- diagnostic dilemma



Oral epithelial dysplasia- clinical dilemma

Management (Brennan et al 2007)

- Surgery including lasers: lack of RCTs for evidence-base recommendation
- Topical bleomycin and systemic cis-retinoic acid:no evidence based recommendation(Epstein et al , 1994)
- Systemic lycopene may have some efficacy for short term resolution of oral epithelial dysplasia as seen in subcontinent Indian populations (Singh et al, 2004)
- Attention should be given to the diagnostic usefulness of Toludine blue application (Zhang et al, 2005; Gandolfo et al, 2006)

Oral Lichen Planus and Lichenoid Lesions

- Oral Lichen Planus is a chronic systemic disease of established immune-mediated pathogenesis

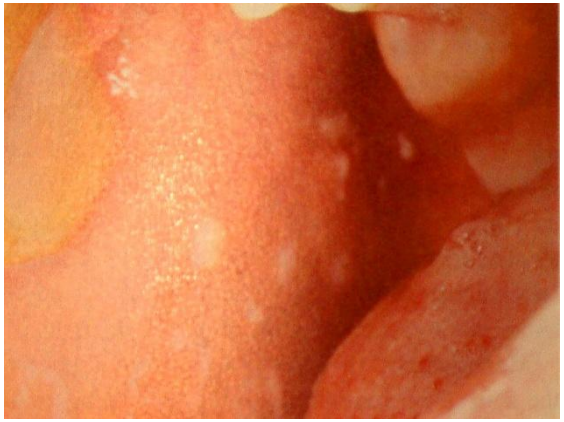
- Disease commonly affects oral mucosa (0.7%-1.8%), skin, genital, scalp (alopecia) and nails (Axĕll et al, 1987)

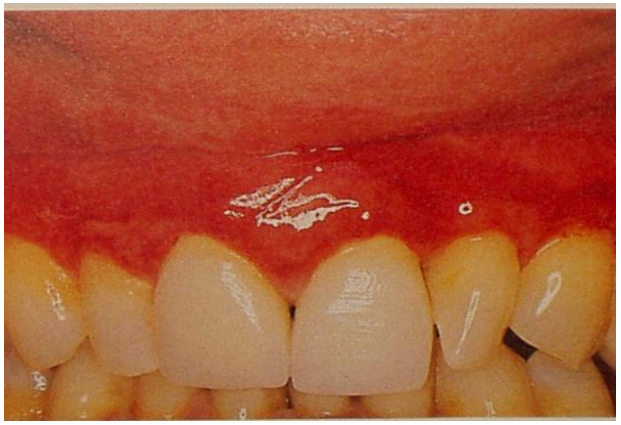
- Age 30 to 60 years, mainly females

Oral Lichen Planus and Lichenoid Lesions

Presentation

- Usually bilateral, symmetrical distribution
- White papules, which may become reticular, annular or plaque–like pattern





Oral Lichen Planus and Lichenoid Lesions

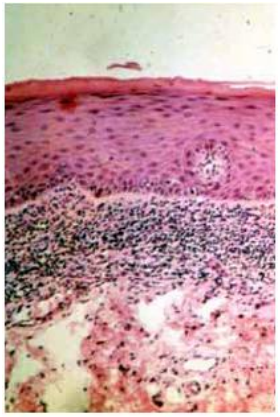
Histopathology

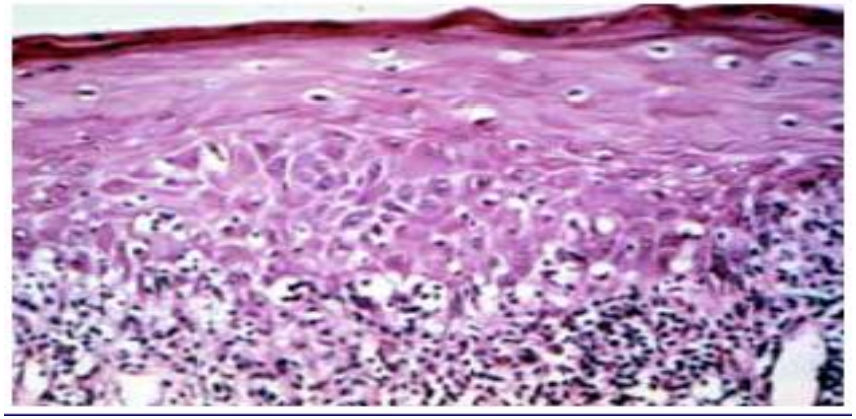
Keratinsed suqmous epithelium

Basal cell degeneration
(liquafactive degeneration with apoptotic bodies {civatte})

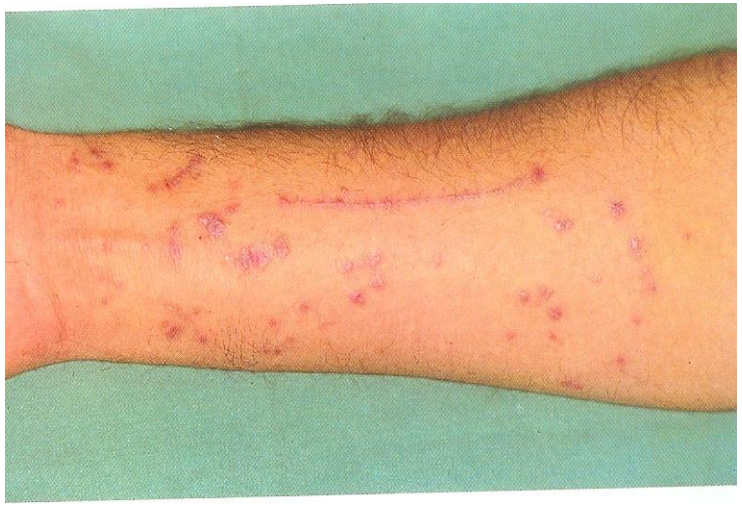
Band of chronic inflamatory (lymphocytes no plama cells) infiltrate

Immunofluoresence will show fibrinogen along BMZ





Lichen planus of skin



Oral Lichen Planus and Lichenoid Lesions

- Diagnosis may be made on clinical grounds, but if features not typical the biopsy is mandatory

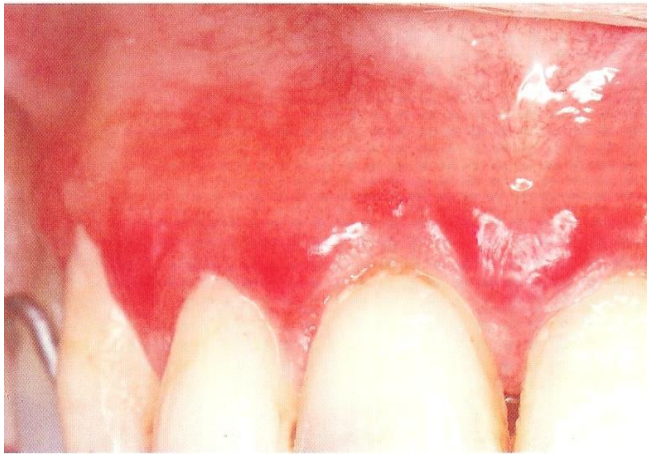
- Lichenoid Dysplasia is a term for a lesion with premalignant process (with features resembling OLP, not OLP with dysplastic features (Eiseberg et al, 2000)

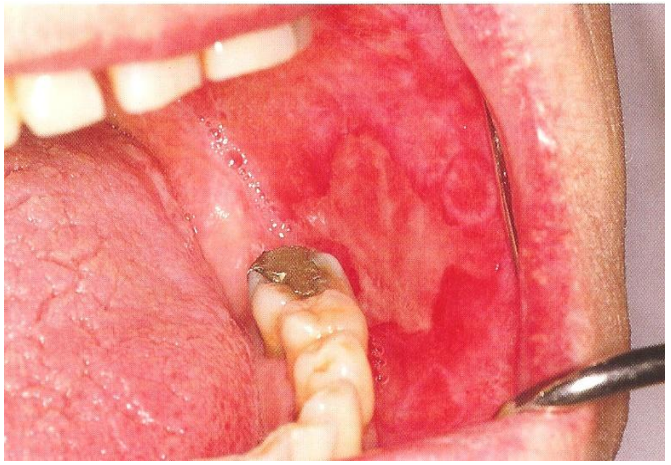
Oral Lichen Planus and Lichenoid Lesions

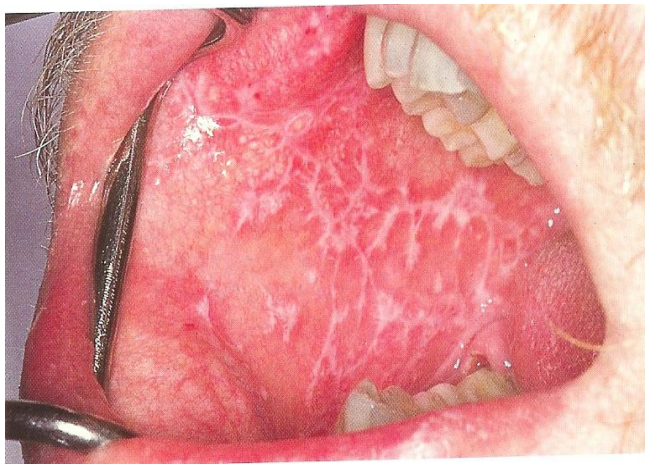
Other lesions that resemble OLP

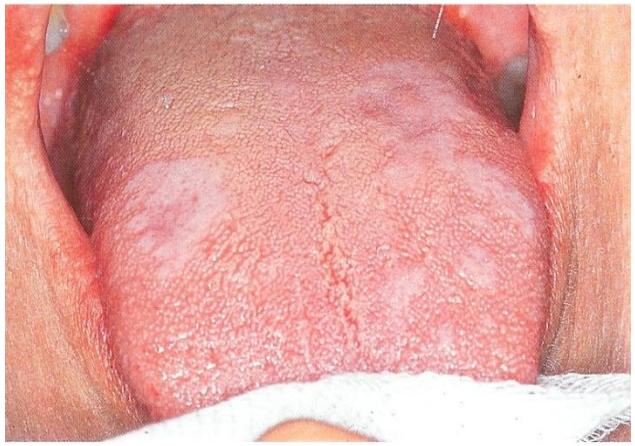
1. Oral Lichenoid Contact lesion (OLCL)- immune-mediated hypersenitivity, eg dental materials such as Amalgam, also cinnamon
2. Oral Lichenoid Drug Reactions (OLDR)- oral hypoglyccaemic agents, ACE inhibitors,NSAIDS
3. Oral Lichenoid Lesions of Graft versus Host (OLL-GVHD)- Acute(<100days) and Chronic(> 100 days after transplant)

Lichen Planus

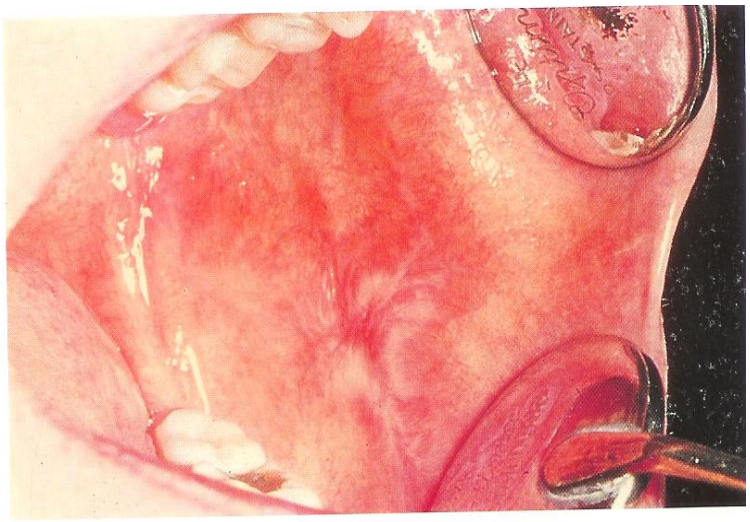


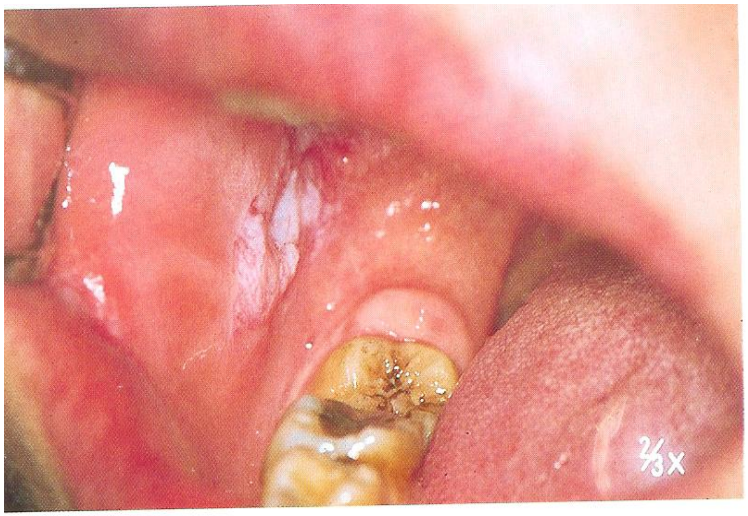






Lupus Erythematoses





Oral Lichen Planus and Lichenoid Lesions

Treatment (Chan et al, 2005)

1. Corticosteroids
2. Retinoids
3. Calcineurin-inhibitors (Cyclosporins, Tacrolimus)- Topical or systemic
4. Others- Lysosomotrophic amines, azothioprines and mycophenolate mofitil

Oral Lichen Planus and Lichenoid Lesions

1. **Corticosteroids** (Campisi et al, 2004)
   Topical corticosteroids +/- antimycotics are the first line of treatment
2. **Retinoids** (Scardina et al, 2006)-Potentially effective but inferior to topical corticosteroids
3. **Calcineurin inhibitors** (Byrd et al, 2004)- Tacrolimus and pimecrolimus may perform better than topical cyclosporin. FDA warning about possible increased risk of OSCC and Lymphoma.
4. **Phototherapy** (Psoralen ultra violet A light (PUVA) is not reccomended for OLP (Oncogenic potential).
5. **Hydroxychloroquine** (Eisen et al, 2003)- retinal dammage and **Azothioprine** (Verma et al, 1999)- Marrow aplasia
6. **Mycophenolate mofetil**- insufficient evidence

Oral Lichen Planus and Lichenoid Lesions

OLCL- topographic relationship to suspected causative agent eg Amalgam

OLDR- No clinical or histopathological features to distinguish

OLL-GVHD- Major complication of allogeneic hematopoietic stem cell bone marrow transplants.

- Acte- affects 3 specific organ systems (Skin, liver and GIT including oral cavity). Often managed with systemic steroids
- Chronic- greater number of organs involved eg salivary glands.Topical steroids (others include dexamethasone mouth rinse, Tacrolimus topical)

Oral Lichen Planus and Lichenoid Lesions

OLCL: (Ibtisam et al 2007)

- Histological confirmation is recommended, especially if clinically atypical (to exclude dysplasia and/or malignancy)
- Skin patch testing of materials and any to be used as a substitute may be useful (readings at 3,7 and 14 and later as delayed reactions may occur)
- Tx- removal/replacement or coverage of possible causative restorations

Oral Lichen Planus and Lichenoid Lesions

OLDR: (Ibtisam et al 2007)

Diagnosis may be difficult as:

- lack of specific clinical and/or histopath features to distinguish from OLP

- May be hazardous to replace offending drug

- May take several months for clinical change to be observed.

Oral Lichen Planus and Lichenoid Lesions

OLL-GVHD: (Ibtisam et al 2007)

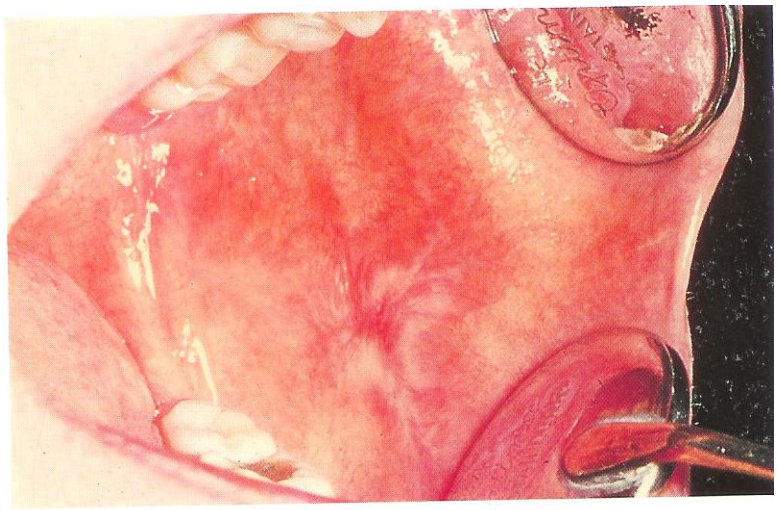
- Histological confirmation is required esp in absence of other organ or system involvement. Atypical cases should exclude dysplasia/malignancy
- First line tx: Topical steroids +/- topical antimycotics as adjunct to systemic tx or for isolated lesions
- Second line tx: Topical calcineurin inhibitors Tacrolimus and pimecrolimus may perform better than cyclosporine)
- UV light irradiation (PUVA) not recommended

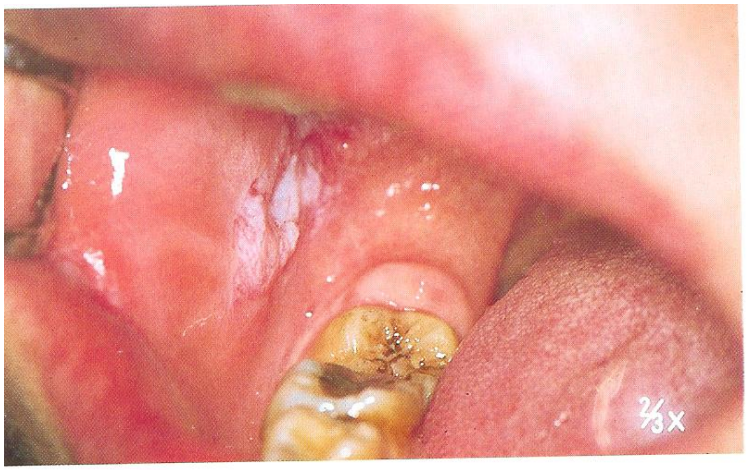
Lupus Erythematoses

- Immunologically mediated inflammatory condition that causes multi organ damage
- Two types –discoid LE

  - Systemic LE
- Lesions frequently appear lichenoid or may resemble leakoplakia, vesiculobullous or granulomatous lesion
- Systemic will show anti-DNA antibodies
- Immunofluorescence will show deposition of various immunoglobulins and C3 in a granular band involving the basement membrane zone seen also in uninvolved skin (called Lupus band test), not seen in Discoid.

Lupus Erythematoses

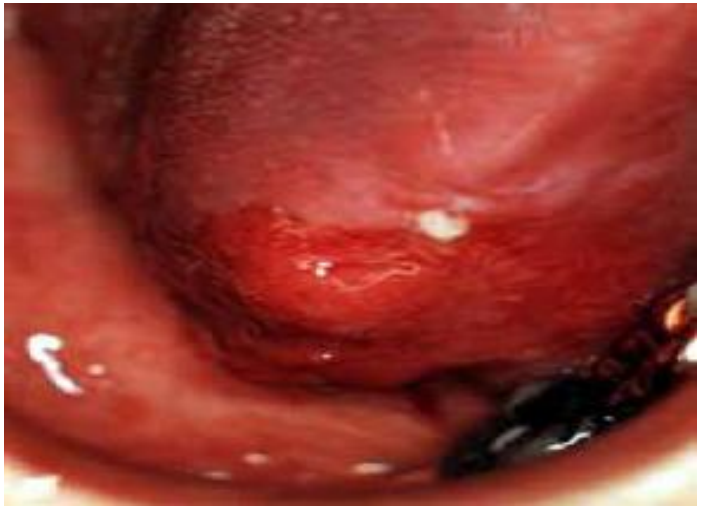


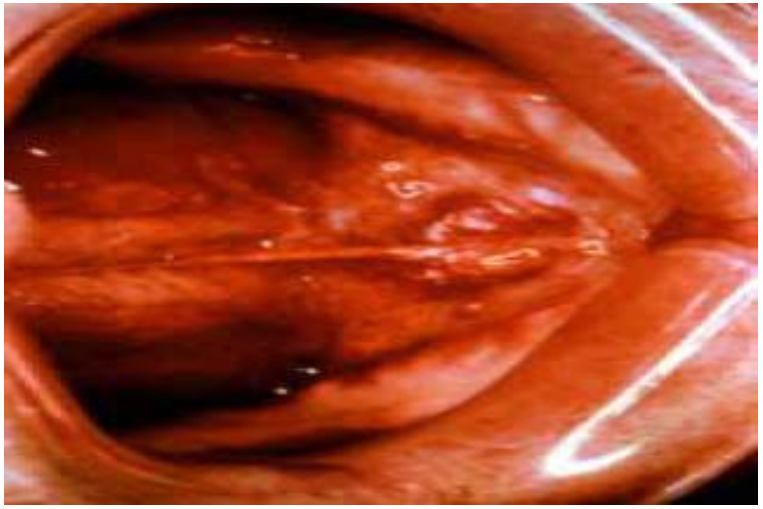


Carcinoma-In-Situ

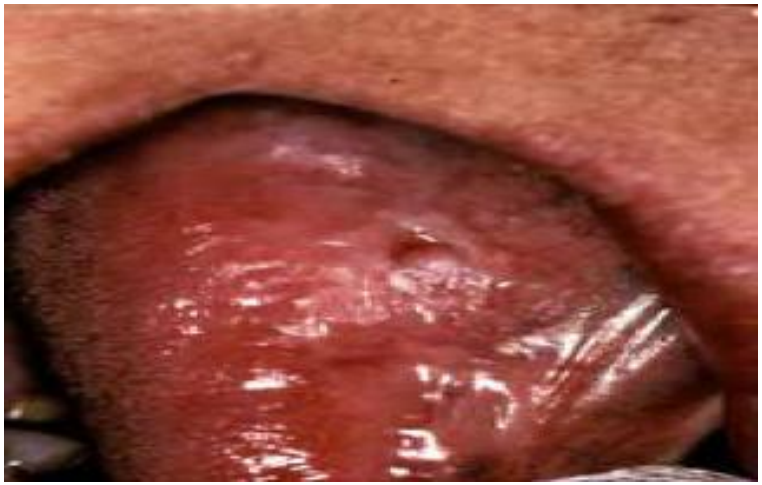
- Top to bottom epithelial cytologic changes characteristic of malignancy, but no CT invasion.
- The distinction between severe dysplasia and CIS is arbitrary.
- Erythroplakic lesions more often show dysplasia or CIS than leukoplakia (Marshberg & Meyers)

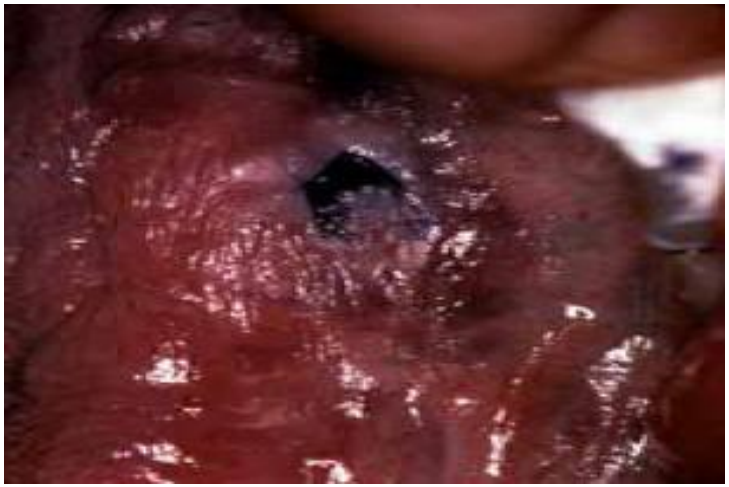
Carcinoma-In-Situ



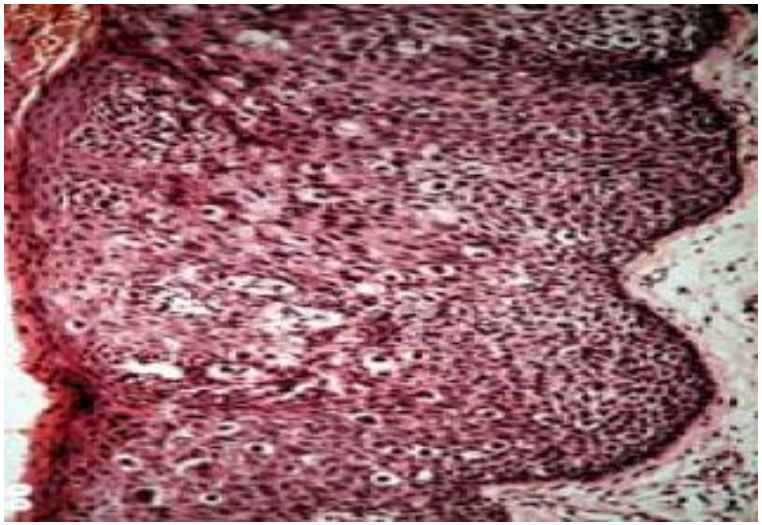


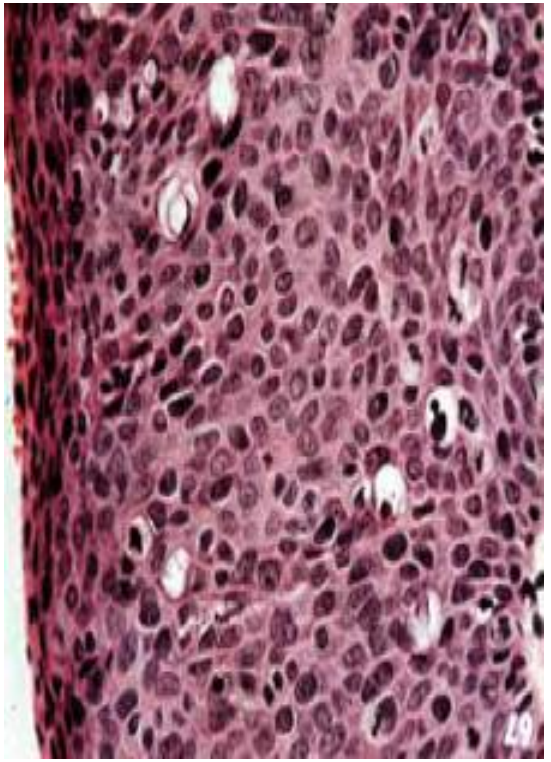
Carcinoma-In-Situ





Histopathology





OMSCC: Verrucous Carcinoma

- Verrucous carcinoma is a well differentiated malignancy
- Microscopic diagnosis may not be obvious

  -Basement membrane often intact No obvious anaplasia

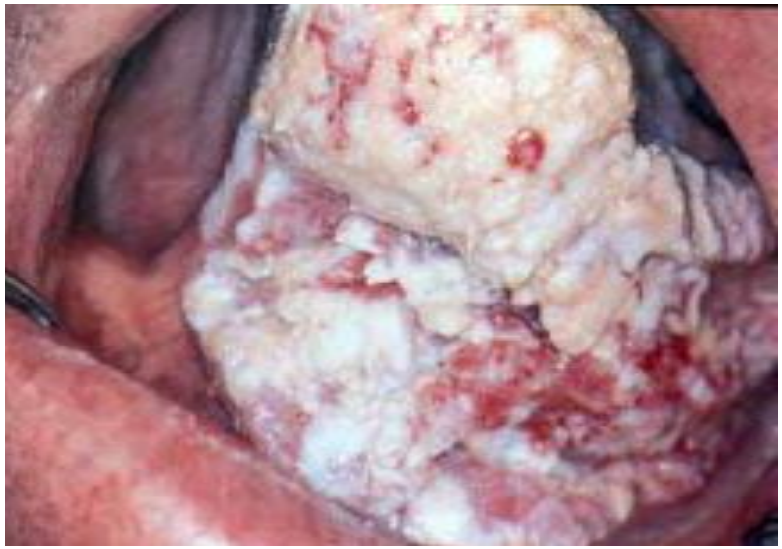
  - Proliferates on a broad front
- One must carefully evaluate multiple sections of an adequate tissue sample to render a proper dx
- Mimics other conditions

  – Squamous papilloma

  - Pseudoepitheliomatous hyperplasia

  - Oral florid papillomatosis

OMSCC: Verrucous Carcinoma



Oral Mucosal Squamous Cell Carcinoma (OMSCC)

- 30,000 new cases of oral cancer each year
- Includes lip, tongue, floor of mouth,salivary glands, pharynx

- 7% of new U.S. cancer cases
  - – 6.2% in males
  - - 1.9% in females
- 50% of all malignancies in some parts of Asia
- Less than 35% of oral cancer case are cured
- Up to 90% cure rates when discovered early

OMSCC: Tobacco

- Cigarette smoking considered a major cause of U.S. oral cancers (SCC)
- Pipe/cigar smoking increases risk at the same rate as cigarettes
- Smokeless tobacco puts patients at minimal risk, regardless of reported studies

OMSCC: Alcohol

- Relationship to cancer induction not as strong as tobacco
- Heavy users often are heavy smokers
- How alcohol produces cancer is poorly understood
  - – Is it carcinogenic agent?
  - Is it a solvent for other carcinogens?
  - Does it increase exposure to oxidants?
  - Does it suppress the immune system?

OMSCC: Actinic Radiation

- Sunlight (actinic radiation) plays a role in causing cancer of the lip vermilion
- Skin pigment also seems important
  - Actinic cancers higher in those with fair skin
  - Actinic cancers lower in those with dark skin
  - Melanin may play a protective role

OMSCC: Nutrition

- Nutritional deficiencies or excesses have been linked to cancers elsewhere (e.g., colon)
- Iron deficiency linked to oral-pharyngeal cancers (Plummer Vinson syndrome)
- Some evidence that fruit consumption is oral cancer protective (vitamins A, B, C, E may play a protective role)

OMSCC: Oral Dental & Occupational Factors

- No evidence that trauma from dentures, poor oral hygiene, defective restorations, etc. can promote oral cancer

- Animal studies:

  – Show trauma + carcinogen causes cancer more readily than no trauma

  - Probably not transferable to humans

OMSCC

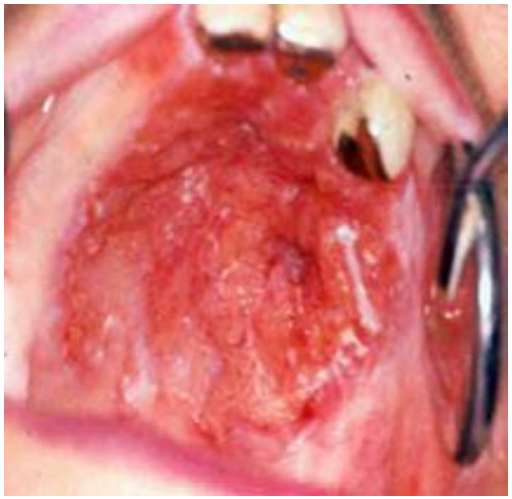
- Oncogenes, growth factors, and suppressor genes have been implicated (H ras, c-myc, c-erb-B-1 oncogenes,EGF, TGF-a, TGF-b, P53 oncosurppressor gene)
- Viruses- HPV & HSV may be synergistic in OMSCC; EBV & CMV have been demonstrated in OMSCC.

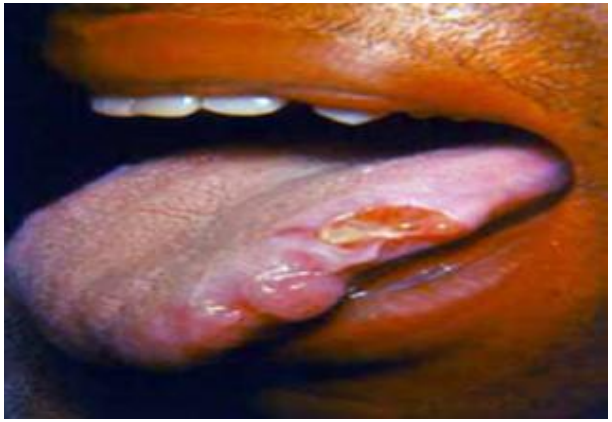
  - HPV antigens and gene products have been detected in biopsies of OMSCC. HPV identified in metastatic lesions
- Immune competence

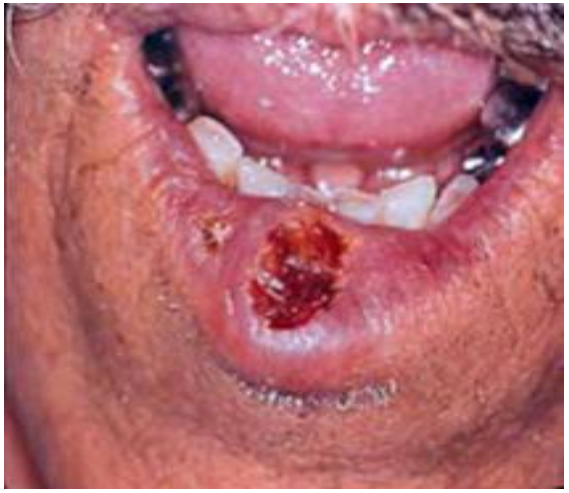
OMSCC

- Clinically varied presentation of red, white, ulceration (raised rolled edges) and tumour masses.
- If bone involvement produces irregular radiolucency

OMSCC





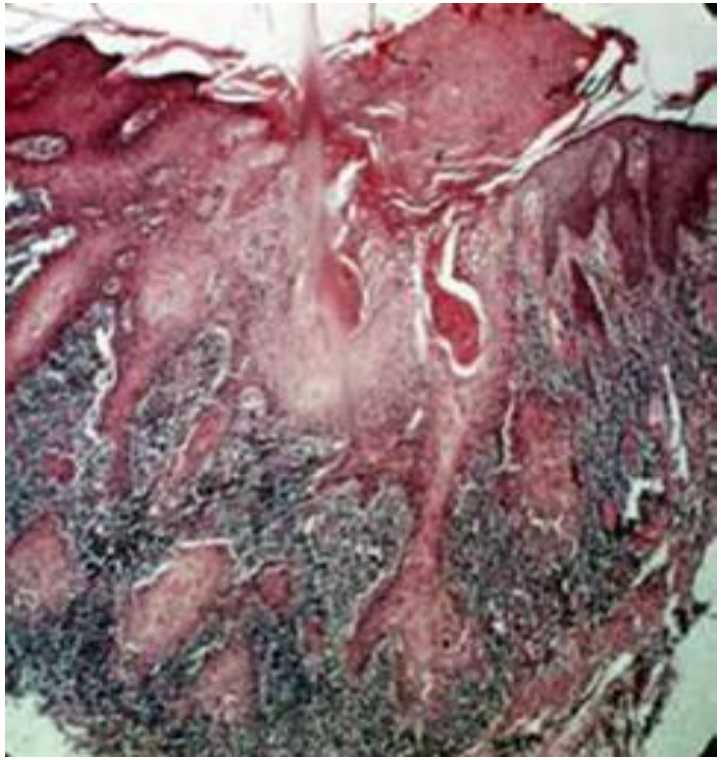


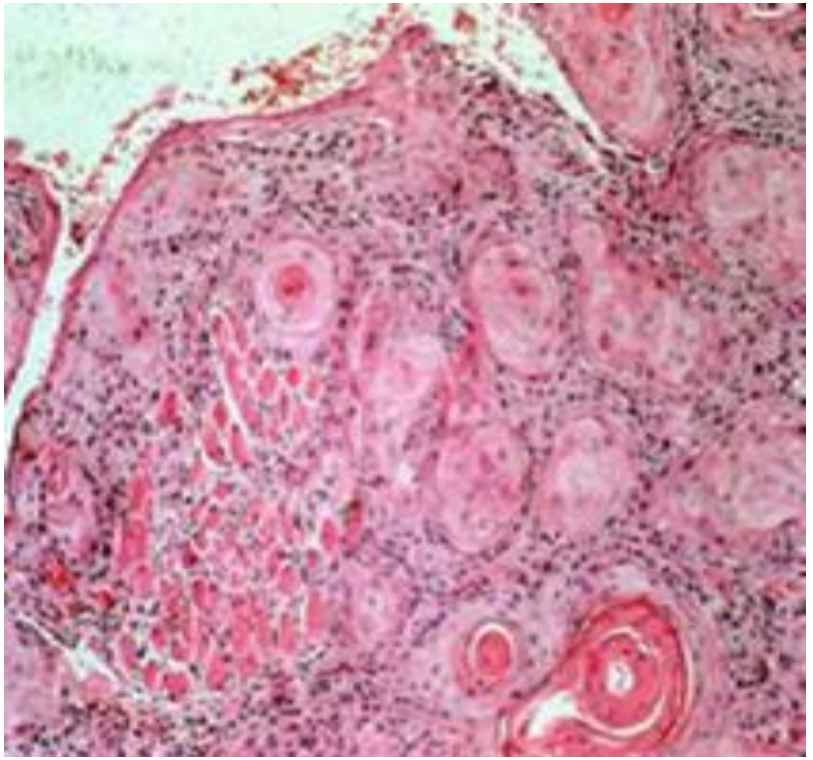
OMSCC- Histological features and prognosis

- Cervical lymph node metastasis, angiolymphatic invasion, perineural invasion = grave prognosis

- Tumor Margins:
  - 12-No tumor in margins = 12
  - Tumor in margins = 80% recurrence rate 18% recurrence rate
  - Biologic markers may be used to evaluate margins for tumor cells; ie p53, HPV, p16

OMSCC- Histopathology





OMSCC- Histopathology

Histological features of dysplasia

- Nuclear hyperchromatism
- Increased nuclear: cytoplasmic ratio
- Mitoses in prickle cell layer
- Abnormal mitoses
- Loss of polarity of basal cells
- Deep cell keratinization
- Loss of definition between basal and prickle cells
- Diminished intercelluar adherence
- Drop-shaped rete pegs

Carcinoma will show these features but also invasion of underlying tissue. Keratin whorls may occur

Metastatic tumous

- Metastasis to the Oral Cavity An infrequent finding: 1% of oral neoplasms
- 25 of 2,400 oral malignancies (Meyer & Shklar)
- Lung and breast most common primary sites
- Other sites: kidney, thyroid, prostate, liver, testis, bladder, cervix/uterus Metastasis to jaws
- more common than to oral soft tissues
- Gingiva and tongue most common soft tissue sites

Thank You