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Premalignancy definition: Morphologically altered tissue in which cancer is more likely to occur than its apparently normal counter part. /WHO(1978)

They could be classified as:

1. High-risk lesions
   - Erythroplakia
   - Speckled erythroplakia
   - proliferative verrucous leukoplakia

2. Medium-risk lesions
   - Oral submucous fibrosis
   - Syphilitic glossitis
   - Sideropenic dysphagia (Paterson–Kelly syndrome)

3. Low-risk/equivocal-risk lesions
   - Oral lichen planus
   - Discoid lupus erythematosus
   - Discoid keratosis congenita

Oral leukoplakia (OL) is the most frequent precancerous lesion of the oral cavity. Oral leukoplakia is defined by WHO (1997) as “a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion”.

In 2012 van der Waal proposed a new definition which seems more opportune as it includes the histological confirmation “A predominantly white lesion or plaque of questionable behavior having excluded, clinically and histopathologically, any other definable white disease or disorder”. The lesion can not be scraped or rubbed off and is therefore primarily a diagnosis of exclusion. Lesions caused by lichen planus, white sponge nevus, nicotine stomatitis, or other plaque-causing diseases do not qualify as leukoplakia. Leukoplakia is strictly a clinical diagnosis and does not imply any specific histologic diagnosis. Leukoplakia is generally asymptomatic and clinically appears as a white or off-white lesion that may be flat, slightly elevated, rugated, or smooth lesions.

Etiology of OL is not clearly established. It is considered multifactorial:
   - smoking,
   - alcohol abuse,
   - lasting mechanical injuries,
   - chronic Candida albicans infection
   - differences of local trauma
   - galvanic potentials are reported as the most important cause factors.
Oral leukoplakia can accompany systemic disorders like hormonal disturbances, gastric juice secretion, diminished saliva secretion or iron deficiency anemia. It is also stated that EBV (is associated with oral hairy leukoplakia), HPV (16 and 18 types), HSV and HIV viruses significantly influence OL development and carcinogenic transformation.

Considering the **macroscopic appearance**, oral leukoplakia is broadly classified into homogeneous and non-homogeneous subtypes.

The distinction of these is purely clinical, based on surface colour and morphological (thickness) characteristics, and do have some bearing on the outcome or prognosis.

**Homogeneous** plaques are predominantly white, of uniform flat, thin appearance with shallow cracks of surface keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout. Despite the fact that the risk of malignant transformation is relatively low- about 5% (Silverman et al., 1984; Lind, 1987), these lesions seem to warrant careful follow-up as well (Kramer et al., 1978).

**Non-homogeneous** varieties include:

- speckled: mixed, white and red (erythroleukoplakia), but retaining predominantly white character. When observed with this morphology, they are referred to as erythroleukoplakia or “speckled erythroplakia”. These lesions also harbor an ominous potential as rates of malignant transformation have been noted of up to 23%. Speckled leukoplakias have the highest malignant potential of the leukoplakia, and these may have a candidal association, and are typically located at the commissures or on the tongue dorsum.

- nodular: small polypoid outgrowths, rounded red or white excrescences

- verrucous: wrinkled or corrugated surface appearance.

- proliferative verrucous leukoplakia (PVL)- is a subtype of verrucous leukoplakia. It involves multiple mucosal areas with confluent, exophytic and proliferative features. The PVL is characterised by an aggressive evolution, resistance to treatment, and high rate of malignant transformation.

  Verrucous or nodular keratoses have a higher malignant potential than that of homogeneous keratoses. A variant termed proliferative verrucous leukoplakia is seen especially in the buccal mucosa in older women and about one-half eventually develop carcinoma. Keratosis on the ventrum of the tongue and floor of the mouth has a higher malignant potential than similar lesions elsewhere. Seen especially in middle-aged or older women, the sublingual keratosis is usually bilateral.

Non-homogeneous lesions carry a much higher risk of malignant transformation.

Additional clinical descriptions that may assist in the characterization of oral leukoplakia are:

- Aetiological description: clearly associated with tobacco or areca nut use; idiopathic.
- Site description giving anatomical sub-site in the mouth or oropharynx.

- Size or extent of the lesion(s).
Leukoplakia is a clinical term and the lesion has no specific histology. Pathological examination of leukoplakia can show hyperkeratosis, atrophy, acanthosis and may or may not demonstrate different degrees of epithelial dysplasia. Dysplasia reflects histological changes which are followed by the loss of uniformity or of the architecture of the epithelial cells.

Oral leukoplakia can be distinguished as dysplastic and nondysplastic lesions based on histological examination. The presence of dysplasia has been associated with a risk of progression to cancer.

At the last world seminar of Oral Medicine about potentially malignant lesions, London 2010, it has been recommended a binary classification of histological changes. Lesions are graded as low risk (mild and moderate dysplasia) and high risk (severe dysplasia and carcinoma in situ) depending on the architecture and cytological changes. This aims to reduce subjectivity in grading dysplasia, thus increasing the possibility of conformity between histological interpretations of different pathologists.

Epithelial dysplasia has been regarded as one of the most important indicators of future malignant potential. Dysplastic oral leukoplakia has a 5 times higher risk of malignancy than non-dysplastic. For a period of 5 years follow-up dysplastic lesions had an incidence of malignant transformation of 41% and non-dysplastic lesions just 9.5%.

*It must be noted that oral epithelial dysplasia has no specific clinical appearance. It can be present in any apparently benign clinical white lesion.*

Despite advances in molecular biology, nowadays there are no reliable markers to predict the malignant transformation of oral leukoplakia. It has been reported that a few markers such as Ki-67 (Mib-1) and bromodeoxyuridine, and the combined biomarker score of chromosomal polysomy, p53, and loss of heterozygosity might be strong predictors for malignant transformation, but this is not generally adopted in clinical practice.
Leukoplakia with mild dysplasia of lateral border of the tongue

The risk factors for malignant transformation include age, site, size, appearance, presence of dysplasia, and abnormal DNA content, but there is no single predictive factor or any reliable biomarker predictive of malignant transformation.

**Factors associated with increased risk of malignant transformation are patients who do not smoke and are over 60 years of age; lesions that are non-homogeneous or are widespread; lesions located in high-risk areas and those larger than 200 mm²; and histopathologically confirmed epithelial dysplasia.**

High-risk areas for malignant transformation have been identified as floor of the mouth, lateral borders of the tongue and the soft palate/retromolar areas.

According to Liu W et al., (2012), high malignant incidences for patients with high-grade dysplasia occurred during the first 2–3 years of follow-up.

The patients with histologically confirmed leukoplakia are reported to have no malignant transformation in 86.6% after 3 years of follow-up and 82.0% after 5 years.

Although clinical appearance such as non-homogeneous oral leukoplakia, and anatomical site (notably the floor of the mouth and the ventral tongue) can help to identify lesions with a high risk of transformation, there are no reliable ways to predict the behaviour of individual lesions or to guide clinical management without biopsy examination.

Patients with multiple oral precancerous lesions and extensive areas of mucosa that may show signs of dysplastic change are particularly difficult to manage. Modern concepts of carcinogenesis have emphasised the existence of molecularly altered preneoplastic fields (field of cancerisation) from which multiple lesions can develop. Widespread lesions have been shown to have higher rates of malignant transformation than those that are more localised.

**Differential diagnosis**

- Hereditary

1. Leukoedema
2. White sponge nevus
3. Hereditary benign intraepithelial dyskeratosis
4. Follicular keratosis

**Reactive or inflammatory**
1. Frictional [traumatic] keratosis
2. White lesions associated with smokeless tobacco
3. Nicotine stomatitis
4. Hairy leukoplakia
5. Hairy tongue

Other white lesions

1. Geographic Tongue
2. Lichen planus
3. Lupus erythematosus

Non epithelial white lesions

1. Candidiasis
2. Mucosal burns
3. Fordyce's granules

Oral squamous cell carcinoma
Mucophagia

Herpes simplex infection

Oral condyloma

Histiocytosis
Multifocal epithelial hyperplasia/HPV associated/

White sponge nevus

**Investigations**

- Blood investigation
- Tolidine blue staining or lugol’s iodine
- Exfoliative cytology
- Biopsy- incisional, excisional
Management

Even though numerous manuscripts have dealt with management of oral leukoplakia, still there is lack of a proper protocol and no universal consensus on its management. The standard treatments for OL range from careful consideration to complete resection.

Currently, the most predictable markers of transformation to carcinoma are:

- Histology—dysplasia
- Cancer history
- Chromosomal polysomy (ploidy)
- Chromosomal loss of heterozygosity (LOH) at 3p or 9p
- p53 protein expression.

Even despite treatment the disease can recur, undergo malignant transformation, or new lesions can develop in patients treated previously.

Various non-surgical and surgical treatments have been reported, but currently there is no consensus on which is best. The main aim of oral leukoplakia management is to avoid malignant transformation.

Proper clinical examination should be done on the day of reporting of the lesion; type, size and location of lesion should be carefully recorded.

A consideration of their risk potential i.e. low risk leukoplakia and high risk leukoplakia should be done.

**Low risk leukoplakia**: Leukoplakias having no dysplastic features or having mild dysplasia associated with following features is considered as low risk leukoplakias.
- Site not in high risk area
- Size less than 200mm
- Homogenous clinical form

**High risk leukoplakia**: A leukoplakia is considered to be a high risk if it shows mild dysplasia associated with following features:
- Site in high risk area
- Size greater than 200mm
- Non homogenous clinical form

Any treatment of oral leukoplakia should begin with elimination of risk factors such as tobacco abuse, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc.

The ceasing of tobacco use is a prior action in case of tobacco associated leukoplakia. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped.

Leukoplakia induced by smokeless tobacco may resolve if the habit is stopped.

Counselling delivered by physicians and other professionals significantly increases tobacco quit rates. Even a brief (3-minute) period of counseling to urge smoker to quit results in smoking cessation rates of 5-10%.

Some candidal leukoplakias respond, at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress. In view of the evidence linking alcohol and tobacco, betel, and diet, to the development of potentially malignant and malignant oral
epithelial lesions, it would seem reasonable therefore, that habits such as the use of tobacco and alcohol should be actively discouraged, and a good diet and oral hygiene encouraged.

Clinical examination is repeated after 2-3 weeks to assess the regression in size of lesion in low risk as well as high risk leukoplakia. After 2-3 weeks of habit cessation, if there is regression in size of leukoplakia than follow up is done initially every three months followed by every 6-12 months.

Low risk lesion which is not regressing in size even after habit cessation or in cases of high risk lesion, biopsy is mandatory in order to assess the degree of epithelial dysplasia.

In cases which show no signs of dysplasia, then conservative treatment is advised. In cases of mild, moderate or severe dysplasia, both conservative and surgical treatment are advised.

Oral leukoplakia presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient’s engagement in smoking cessation.

In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended.

Non-surgical treatment can be considered as a good choice in homogenic OL without dysplasia or as an initial treatment in other cases of OL.

Non-surgical treatments cause minimal adverse effects, particularly in patients with widespread oral leukoplakia that involves a large area of the oral mucosa, or in those with medical problems who have high surgical risks, or when patients refuse surgical intervention.

Conservative treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (beta-carotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, metformin, curcumin etc.

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy, thus reducing the morbidity and mortality associated with it.

The use of photodynamic therapy have been also reported.

Careful and routine follow-up observations of leukoplakia are appropriate in conjunction with elimination of any risk-associated behavior or habits. In case of no improvement, treatment should become more invasive.

Surgical treatment still remains one of the most common treatment methods in OL and should be the method of choice in OL with histologically diagnosed epithelial dysplasia.

Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation).

Surgical treatment for OL may prevent the development of oral squamous cell carcinoma, provided by assuring that the resection margins are adequately thick and free of epithelial abnormalities. However, it has been shown that surgical intervention does not appear to prevent OL from developing recurrence. Malignant transformation of these lesions is independent of drug or laser therapy.

Non-surgical treatment of oral leukoplakia

1. Carotenoids

1.1. Beta-Carotene

Beta-carotene is a vitamin A precursor. This carotenoid is commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges.

The use of beta-carotene has been recommended for the prevention of potential malignant lesions, such as OL. The potential benefits and protective effects against cancer are possibly related to its antioxidant action.
This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals.

It has been shown that beta-carotene has a better therapeutic clinical response in preventing oral leukoplakia lesions in smokers than in nonsmokers.

1.2. Lycopene

Lycopene is a fat-soluble red pigment found in some fruit and vegetables. The greatest known source of lycopene is tomatoes.

There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardio-vascular diseases.

Lycopene appears to be a very promising antioxidant as a treatment modality in oral leukoplakia and can protect cells against damage.

In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to play a protective role against progression of dysplasia by inhibiting tumor cell proliferation.

In vitro experiments have shown the inhibition of the process of human neoplastic cellular growth by lycopene, since this protein interferes in growth factor receptor signaling and, thus, in cellular cycle progression. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb anti oncogenes and stop cell division at the G0-G1 cell cycle phase.

Zakrzewska concluded that lycopene brings about histological changes of a significant degree in patients with oral leukoplakia.

2. Vitamins

2.1. Retinoids (Vitamin A/ Retinol)

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A.

The most biologically, naturally occurring retinoid is vitamin-A. Vitamin A, also known as retinol, is an alcohol that can be converted into an aldehyde (retinal) or retinoic acid.

Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins.

Vitamin A is required in the normal pathway of epithelial cell differentiation and production of keratin. An association between vitamin A deficiency and the enhanced susceptibility to carcinogenesis was reported with an increased risk for developing different epithelial carcinomas.

Supplementation with retinoids for oral leukoplakia treatment begin in the 1960s, however, this treatment was not widely accepted due to its side effects-hypervitaminosis, teratogenic effects, toxicity, and alterations in various organic systems.

Topical retinoid were initially tested against diseases related to keratinization. The topical use of 13-cis retinoic acid has been shown to be effective in resolving oral leukoplakia. But they are limited because recurrences appear after short periods of cessation of the treatment.

2.2. Vitamin E

Vitamin-E is the collective term for a family of chemical substances that are structurally related to alpha-tocopherol. Alpha-tocopherol, the major constituent of Vitamin E has antitumor proliferation capacity as well as function as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids.
It is found in plant oil, margarine, and green leaves. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women.

2.3. L-Ascorbic Acid (L-AA)/ Vitamin C

L-AA has antioxidizing properties and reacts with superoxide produced as a result of the cells’ normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. Vitamin C can be found in citrus fruits such as kiwi, strawberries, papaya, mango etc.

The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes.

L-AA toxicity does not occur, since vitamin is water-soluble.

The ability of L-AA to maintain oral mucosa integrity is very little documented. There are no studies regarding the efficacy of the use of L-AA alone for OL treatment.

3. Anti-neoplastic agents:

3.1. Bleomycin

Bleomycin is a cytotoxic antibiotic which was first used for the treatment of neoplasms. It can be used as an alternative for treatment of oral leukoplakia. It is not very often used in practice for its adverse effects.

The most commonly adverse effects are muco-cutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin.

Topical bleomycin in treatment of OL was used in dosages of 0.5%/day for 12 to 15 days or 1%/day for 14 days.

Topical administration of bleomycin usually reduces lesion size and has little toxic side effects. It is beneficial to use bleomycin adjuvant with the surgical procedure for extensive leukoplakia to decrease the size of lesion before surgery. This helps to avoid grafting after removal of the lesion and prevent the dysplastic change of benign form of lesion.

5. Photodynamic Therapy (PDT)

Photodynamic therapy is a non-invasive method of treatment for head and neck tumors and premalignant lesions. It is based on photo-chemical reaction, initiated by light activation of a photosensitizing drug causing tumor cell death. It requires the simultaneous presence of a photosensitizing drug (photosensitizer), oxygen, and visible light and it is a non-thermal reaction.

The photosensitizer is administered systemically by intravenous injection or can be topically applied.

After a period to allow the photo sensitizer to collect in the target tissue, the photosensitizer is activated by exposure to low-power visible light of a drug specific wavelength.

Intracellular activation of the photosensitizer results either in the production of radicals (type I mechanism) or the formation of intracellular singlet oxygen (type II
mechanism), which causes cell death by vascular shut down mechanisms and intracellular oxygenation.

_Surgical treatment of oral leukoplakia_

Surgery is an obvious option for the management of leukoplakia, certainly for patients with high predisposition to malignant transformation, such as leukoplakias that are:
1. speckled
2. verrucous
3. from high-risk sites, including the floor of the mouth/ventrum of the tongue, or soft palate/fauces
4. in a patient with previous cancer in the upper aerodigestive tract
5. dysplastic
6. polysomic (aneuploidy or tetraploidy)
7. tested positive for genetic markers such as mutated tumour suppressor factor p53, or LOH on chromosomes 3p or 9p.

1. **Conventional surgery - excision**

   Conventional surgery refers to scalpel excision of the lesion. This is followed by a primary closure or secondary healing in case of reduced mucosal defects or with a transposition of local mucosal flaps or even skin graft in case of large defects.

   Conventional surgery may not feasible for extensive lesions or those in certain anatomical locations. The associated morbidity of surgery also makes it less appealing for extensive lesions.

   The use of a scalpel may induce wide areas of denudated mucosa with unfavorable scarring changes and secondary functional alterations as surgical sequelae.

   It should be noted however that curative surgical resection has the potential to be effective as a prophylactic treatment of lesions on the tongue having a tendency to develop cancer.

2. **Electrocoagulation**

   Electrocoagulation can be used alone or as an adjuvant to scalpel surgery. Electrocoagulation produces thermal damage in the underlying and surrounding tissue, which causes postoperative pain and oedema, and leads to considerable tissue scarring. Postoperative pain and oedema are also severe after cryosurgery.

3. **Cryosurgery**

   Cryosurgery is a method of treatment which involves controlled tissue damage caused by low temperatures. This method locally destroys lesional tissues by freezing in situ.

   - by liquid nitrogen (N) or dinitrogen dioxide (N2O2).

   Arnott, a British physician, was the first person to use cryosurgery in the year 1851. Initially, its use was limited to the treatment of cancer of the lip and oral cavity. At present,
cryosurgery has an extensive application in the treatment of both benign and malignant lesions in the head and neck region.

4. Laser surgery (excision or evaporation)
The laser surgery has been reported as most appreciated in the last 30 years.

Carbon dioxide, neodymium:yttrium-aluminium garnet (Nd:YAG), argon, and potassium-titanyl-phosphate (KTP) lasers are used in the management - vaporization or excision of oral leukoplakia lesion.

Their precision allows a conservative and site-specific, minimally invasive surgery with sterilization of the surgical area and minimal intraoperative hemorrhage. These lasers also permit a better postoperative period, with less swelling and pain and healing with minimal scarring. This can be performed even for extensive lesions.

Wound healing is excellent because of limited contraction; it produces satisfactory mobility of the oral mucosa and minimum oral dysfunction.

Additional advantages of lasers include an optimal visualization of the surgical area, seal of lymphatic, and nerve endings which minimizes the chances for neoplastic cells seeding and the elimination of precancerous fields (dysplasia) neighboring the leukoplakia with minimal surgical morbidity.

The degree of epithelial dysplasia is mandatory for the correct choice of the treatment. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. Mild dysplasia or the absence of dysplasia can be completely removed or not. In this case the decision should consider clinical factors such as location, size and the patient’s engagement in smoking cessation.

All individuals with leukoplakia, and those who were treated for it, should be followed-up regularly, regardless of their response to topical or systemic treatment, including clinical resolution.

Follow-up patients should be regularly checked at 3, 6 and 12 months, and then annually for any:

- size change
- appearance of red lesions
- ulceration
- recurrences
- new lesions.

Erythroplasia (erythroplakia) is the oral lesion with the most severe epithelial dysplasia and greatest predilection to develop to carcinoma. Almost all true erythroplakia demonstrates dysplasia, carcinoma in situ, or invasive carcinoma. Shafer and Waldron’s review of biopsies submitted under this clinical diagnosis revealed that 51% were invasive SCC, 40% were carcinoma in situ or severe dysplasia, and just 9% were mild to moderate dysplasia.
As with leukoplakia, **erythroplakia** is defined as a red patch that cannot be clinically or pathologically diagnosed as any other condition. Queyrat originally used the term *erythroplasia* to describe a precancerous red lesion that develops on the penis. Oral erythroplakia is clinically and histopathologically similar to the genital process.

The point prevalence rate (number of persons with active lesions at a given point in time) of oral erythroplakia has been estimated as 1 per 2500 adults.

Erythroplakia also may occur in conjunction with leukoplakia and has been found concurrently with a large proportion of early invasive oral carcinomas. Erythroplakia is less common than leukoplakia but has a much greater potential to be severely dysplastic at the time of biopsy or to develop invasive malignancy at a later time.

**Aetiopathogenesis**

The etiology of these lesions is unknown but thought to be the same as that for leukoplakia and the same as those associated with invasive squamous cell carcinoma of the mouth. Tobacco and alcohol use are often implicated.

**Clinical features**

Erythroplakia is predominantly a disease of middle-aged to older adults with no significant gender predilection.

The floor of mouth, tongue, and soft palate are the most common sites of involvement, and multiple lesions may be present.

Erythroplastic lesions are well-defined velvety red plaques. Some erythroplakias are associated with white patches, and are then termed speckled leukoplakia. Erythroplasia is seen mainly in older males, usually in the buccal mucosa or palate. The most common sites of occurrence are the floor of the mouth and retromolar trigone. Lesions appear as bright red, are frequently “velvety” in appearance, and have a sharply demarcated border. Frequently these lesions are noted to be nonhomogeneous in appearance with adjacent or intralesional leukoplakia. When observed with this morphology, they are referred to as erythroleukoplakia or “speckled erythroplakia”. These lesions also harbor an ominous potential as rates of malignant transformation have been noted of up to 23%.
Nonspecific mucositis, candidiasis, psoriasis, or vascular lesions may clinically mimic erythroplakia, and biopsy often is required to distinguish between them.

According to one large clinicopathologic investigation, 90% of erythroplakic lesions histopathologically represent severe epithelial dysplasia carcinoma in situ or superficially invasive squamous cell carcinoma. The epithelium shows a lack of keratin production and often is atrophic, but it may be hyperplastic. This lack of keratinization, especially when combined with epithelial thinness, allows the underlying microvasculature to show through, thereby explaining the red color and underlying connective tissue often demonstrates chronic inflammation.

Red lesions of the oral mucosa, especially those of the oral floor and ventral or lateral tongue, should be viewed with suspicion, and a biopsy should be performed. If a source of irritation can be identified and removed, then biopsy of such a lesion may be delayed for 2 weeks to allow a clinically similar inflammatory lesion time to regress. As with leukoplakia, the treatment of erythroplakia is guided by the definitive diagnosis obtained by biopsy. Lesions exhibiting moderate dysplasia or worse must be removed completely. It is best to preserve most of the specimen for microscopic examination because of the possibility that a focal invasive carcinoma might be missed in the initial biopsy material. Recurrence and multifocal oral mucosal involvement are common with erythroplakia; hence, long-term follow-up is suggested for treated patients.

When present, these dysplastic changes typically begin in the basilar and parabasilar portions of the epithelium. The more dysplastic the epithelium becomes, the more the atypical epithelial changes extend to involve the entire thickness of the epithelium. The histopathologic alterations of dysplastic epithelial cells are similar to those of squamous cell carcinoma and may include the following:

- Enlarged nuclei and cells
- Large and prominent nucleoli
- Increased nuclear-to-cytoplasmic ratio
- Hyperchromatic (excessively dark-staining) nuclei
- Pleomorphic (abnormally shaped) nuclei and cells
- Dyskeratosis (premature keratinization of individual cells)
- Increased mitotic activity (excessive numbers of mitoses)
- Abnormal mitotic figures (tripolar or star-shaped mitoses or mitotic figures above the basal layer) In addition, histomorphologic alterations of dysplastic epithelium are evident at low-power magnification, including the following:

  a/ Bulbous or teardrop-shaped rete ridges
  b/ Loss of polarity (lack of progressive maturation toward the surface)
  c/ Keratin or epithelial pearls (focal, round collections of concentrically layered keratinized cells)
  d/ Loss of typical epithelial cell cohesiveness

When epithelial dysplasia is present, the pathologist provides a descriptive adjective relating to its “severity” or intensity.
**Mild epithelial dysplasia** refers to alterations limited principally to the basal and parabasal layers.

**Moderate epithelial dysplasia** demonstrates involvement from the basal layer to the midportion of the spinous layer.

**Severe epithelial dysplasia** demonstrates alterations from the basal layer to a level above the midpoint of the epithelium. Sometimes dysplasia will be seen to extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth.

When the entire thickness of the epithelium is involved, the term **carcinoma in situ** is used. Carcinoma *in situ* is defined as dysplastic epithelial cells that extend from the basal layer to the surface of the mucosa. In this light, it should be mentioned that keratin pearl formation is rare in carcinoma *in situ* and may indicate the presence of a focus of invasive squamous cell carcinoma in the adjacent tissue.

Sometimes dysplasia will be seen extending down the ducts of the minor salivary glands, especially in lesions in the floor of the mouth. When ductal dysplasia occurs in a precancerous surface dysplasia, the recurrence rate is increased. The depth of ductal dysplasia does not appear to be a significant factor.

**Diagnosis**

Similar clinical appearances can be seen in inflammatory and atrophic lesions (e.g. in deficiency anaemias, geographic tongue and lichen planus). A biopsy should be undertaken to confirm the diagnosis and histopathologically detect epithelial dysplasia or carcinoma.

**Management**

Any possible causal factor such as tobacco use should be stopped. The lesion should be removed, though there is no reliable evidence for the efficacy of this approach. It is likely that similar disease will develop at the same, or another, oral mucosal site at some time following removal of the original lesion.

There is also no hard evidence as to the ideal frequency of follow-up, but it has been suggested that patients with mucosal potentially malignant disorders be clinically re-examined:

- within 1 month
- at 3 months
- at 6 months
- at 12 months
- at least annually thereafter.

**Always note any changes in colour and texture of all soft tissues or any swelling. If you detect an abnormality, determine the history of the lesion; if the abnormality has been of more than 2 weeks duration, take appropriate action to obtain a biopsy.**

- **Follow up to ensure a definitive diagnosis of an abnormality.**
- Teach your patients about the signs and symptoms of oral cancer and precancer.
- If a patient uses tobacco products, provide appropriate counseling or refer patient for counseling.
- Advice patients for reduction of alcohol consumption and good oral hygiene

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