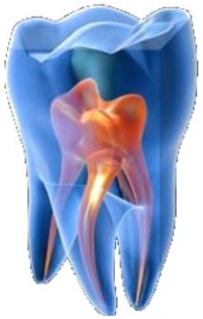
LEUKOPLAKIA. CLINICAL PICTURE. POSITIV AND DIFFERENTIAL DIAGNOSIS. TREATMENT

Lecture № 5
5 Year
10 Semester
V.Nicolaiciuc

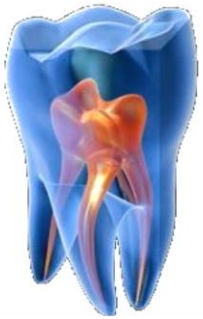


IDIOPATHIC LEUKOPLAKIA

Leukoplakia is a descriptive clinical term indicating a white patch or plaque of oral mucosa that cannot be rubbed off and cannot be characterized clinically as any other disease. This excludes lesions such as lichen planus, candidiasis, leukoedema, and obvious frictional keratosis.

Leukoplakias may have similar clinical appearances, but also have a considerable degree of microscopic heterogeneity.

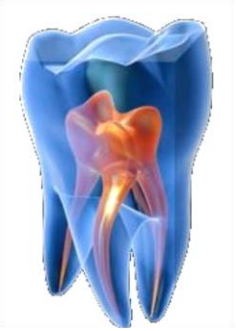
Because ***leukoplakia*** may range microscopically from benign hyperkeratosis to invasive squamous cell carcinoma, a biopsy is mandatory to establish a definitive diagnosis.



Etiology and Pathogenesis

***Many cases of leukoplakia are etiologically related*:**
Discontinue use of tobacco in smoked or smokeless forms.
Alcohol abuse;
C. albicans infection;
May have a role in the development of leukoplakia;
Nutritional factors;
Iron deficiency anemia;
Sideropenic dysphagia (Plummer-Vinson or Paterson-Kelly syndromes).

Rates of transformation to squamous cell carcinoma have varied from study to study as a result of differences in the underlying pathology and differences in the use of putative carcinogens such as tobacco.



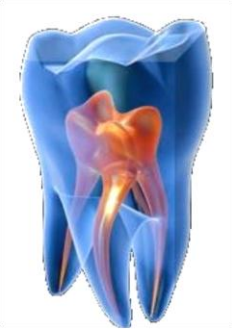
Geographic differences in the transformation rate, as well as in the prevalence and location of oral leukoplakias, are likely related to differences in tobacco habits in various parts of the world.

In U.S. populations, a majority of oral leukoplakias are benign and probably never become malignant.

Approximately 5% of leukoplakias are malignant at the time of first biopsy.

Approximately 5% of the remainder undergo subsequent malignant transformation.

From 10% to 15% of dysplasias that present as clinical leukoplakia will develop into squamous cell carcinoma. Risk of transformation of the floor of the oral cavity is higher.



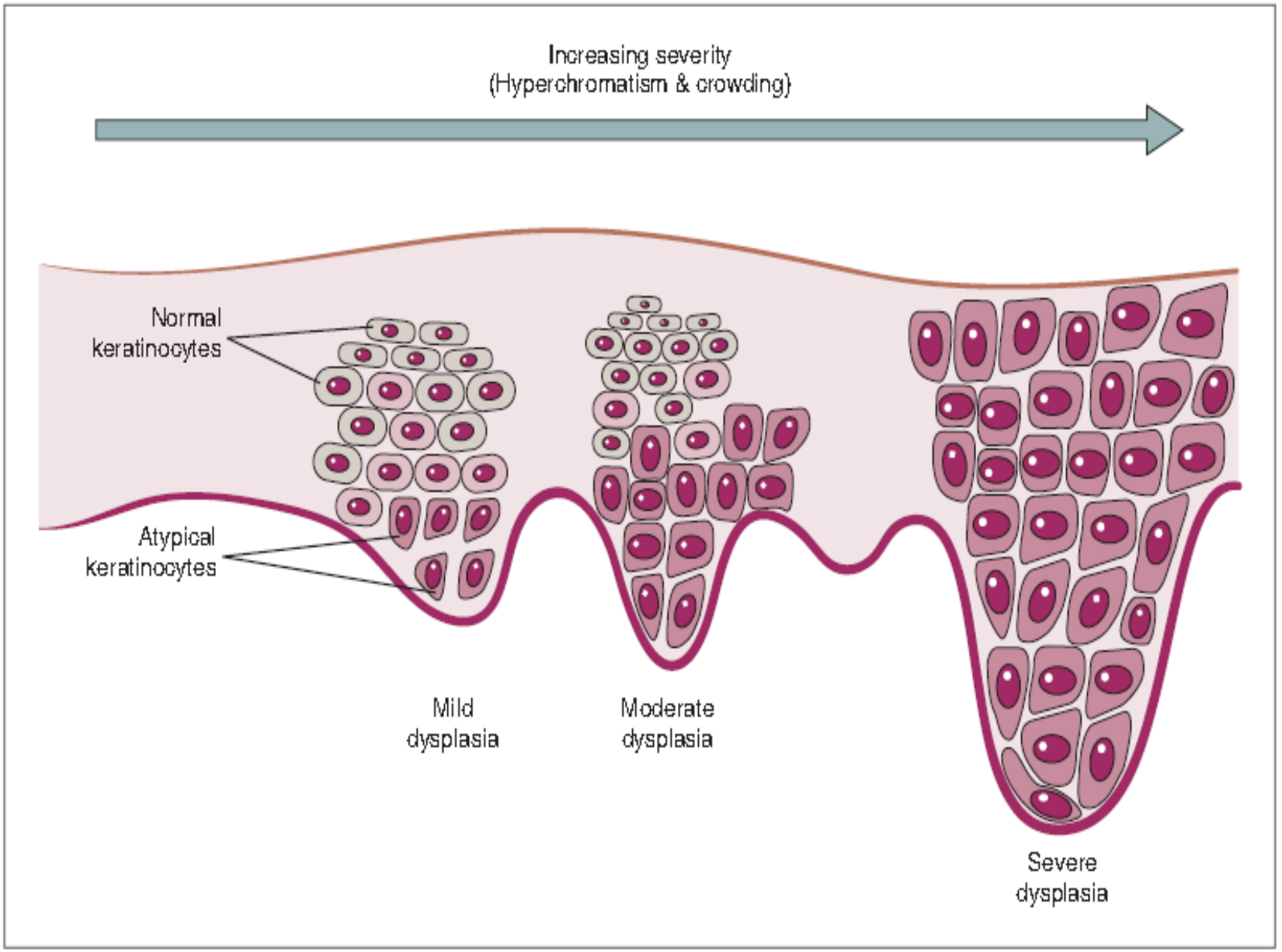
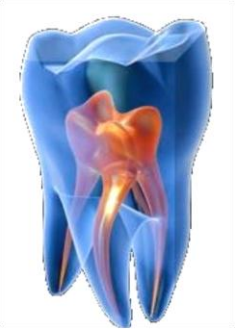


Fig. Progression of dysplasia.



Clinical Features

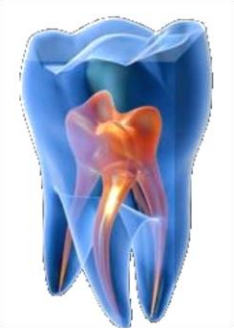
Leukoplakia is a condition ***associated with middle-aged and older populations***. A vast majority of cases occur after the age of 40 years. ***Place of localization*** of leukoplakias is placed on mandibular mucosa and the buccal mucosa (aproximately 50%).

The palate and lower lip are involved less often then floor of the mouth and retromolar sites. The relative risk of neoplastic transformation varies from one region to another.

Although the floor of the mouth accounts for a relatively small percentage (10%) of leukoplakias.

In this place by microscopy more often are found: dysplasia, carcinoma in situ, or invasive carcinoma.

Leukoplakia of the lips and tongue also exhibits a relatively high percentage of dysplastic or neoplastic change. In contrast to these sites, the retromolar area exhibits these changes in only about 10% of cases.



On visual examination, leukoplakia may changes from a barely evident, vague whiteness on a base of uninflamed, normal-appearing tissue to a definitive white, thickened, leathery, fissured, verrucous (wartlike) lesion.

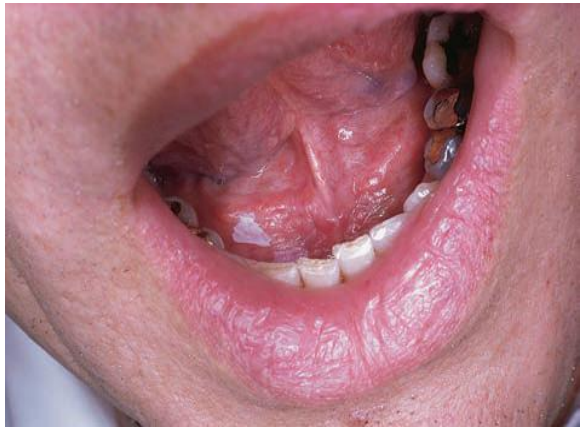


Fig. Idiopathic leukoplakia of the floor of the mouth. The microscopic diagnosis was hyperkeratosis.

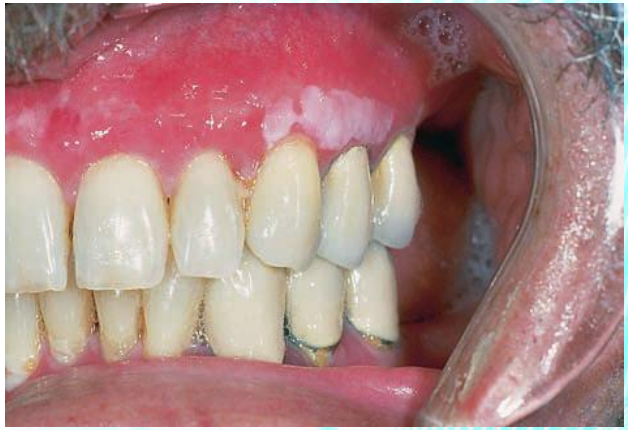


Fig. Idiopathic leukoplakia of the gingiva. The microscopic diagnosis was hyperkeratosis.

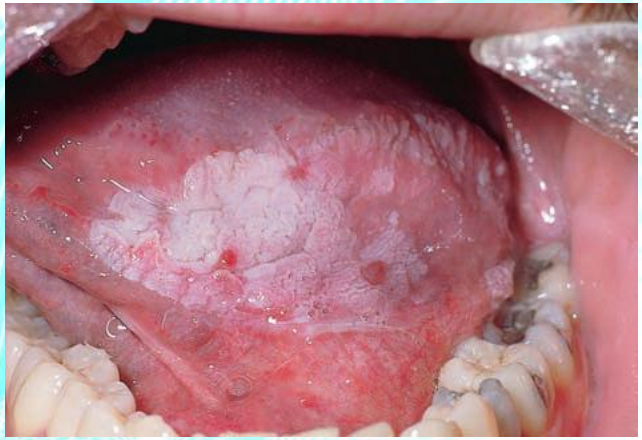
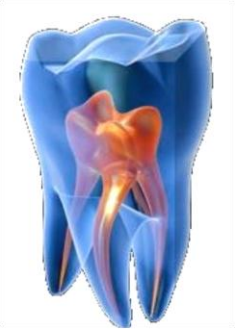


Fig. Idiopathic leukoplakia of the lateral tongue. The microscopic diagnosis was dysplasia.



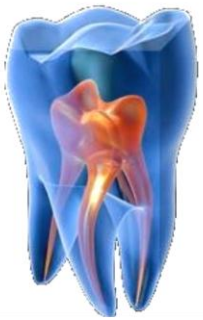
Risk of malignant transformation of speckled leukoplakia is greater than lesions that are homogeneous.

On palpation, lesions may be soft, smooth, or finely granular. Other lesions may be roughened, nodular, or indurated.

Proliferative verrucous leukoplakia (PVL) has been segregated from other leukoplakias. This type of leukoplakia, often on the gingiva, begins as simple keratosis and eventually becomes verrucous in nature.

Red zones may also be seen in some leukoplakias, prompting use of *the* ***term speckled leukoplakia (erythroleukoplakia).***

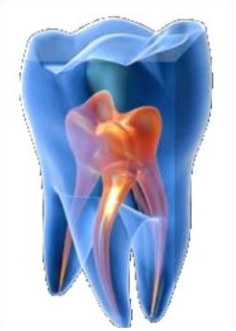
Lesions tend to be persistent, multifocal, recurrent, and sometimes locally infiltrative.



Metastasis to regional lymph nodes is uncommon. The cause of ***proliferative verrucous leukoplakia*** (***PVL***) is unknown, although early reports suggest a relationship in some lesions with ***human papillomavirus*** (***HPV***), but this association has not been substantiated.

The typical patient with ***proliferative verrucous leukoplakia*** (***PVL***) more often is female than male, and traditional risk factors attributed to oral cancer such as tobacco and alcohol use are strongly lacking.

The diagnosis is determined clinicopathologically and usually is made retrospectively. ***Malignant transformation to verrucous or squamous cell carcinoma*** from precursor lesions is greater than in epithelial dysplasia and may occur in up to 80% of cases.



Histopathology

Histologic changes range from hyperkeratosis, dysplasia, and carcinoma in situ to invasive squamous cell carcinoma.

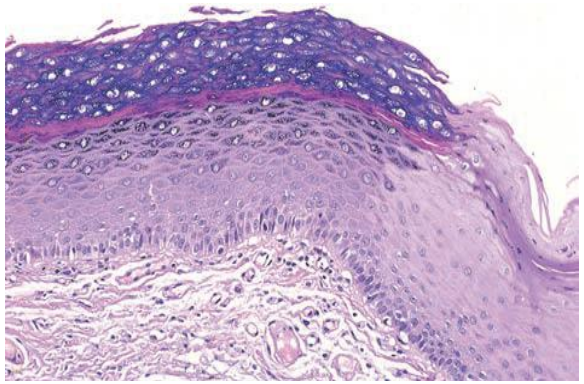


Fig. Idiopathic leukoplakia diagnosed as hyperkeratosis.

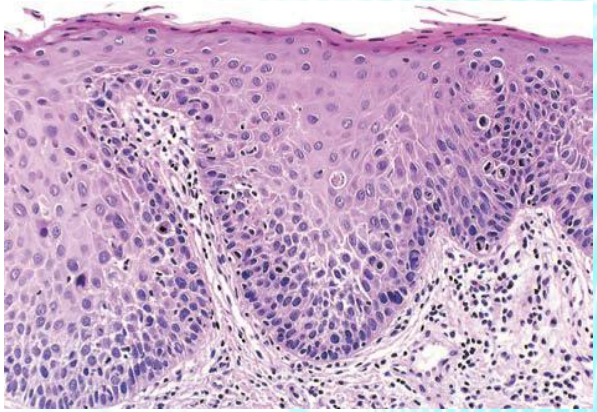


Fig. Idiopathic leukoplakia diagnosed as moderate dysplasia.

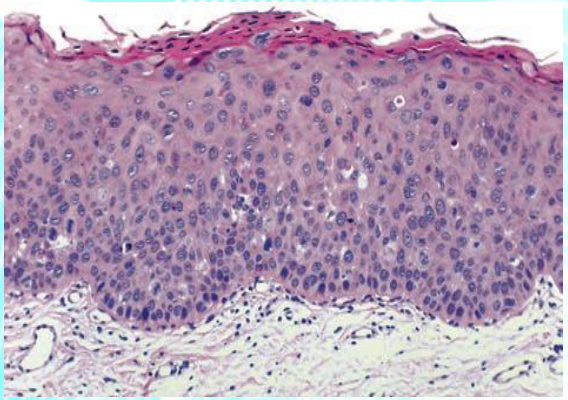
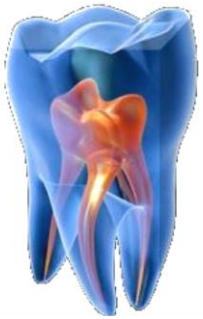


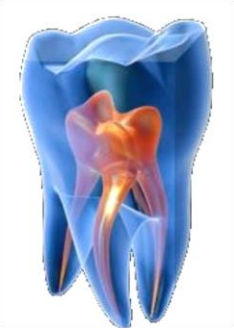
Fig. Idiopathic leukoplakia diagnosed as severe dysplasia.

The term *dysplasia* indicates an abnormal epithelium and disordered growth, whereas atypia refers to abnormal nuclear features. **Increasing degrees of dysplasia** are designated as mild, moderate, and severe and are subjectively **determined microscopically**.



Spefic microscopic characteristics of dysplasia include:
drop-shaped epithelial ridges,
basal cell crowding,
irregular stratification,
increased and abnormal mitotic figures,
premature keratinization,
nuclear pleomorphism and hyperchromatism,
an increased nuclear-cytoplasmic ratio.

It is generally accepted that the more severe the epithelial changes, the more likely a lesion is to evolve into cancer. Currently there are no microscopic or molecular methods that can predict which individual dysplasia, irrespective of grade, will progress to squamous cell carcinoma.



When the entire thickness of epithelium is involved with these changes in a so-called top-to-bottom pattern, the term ***carcinoma in situ*** may be used.

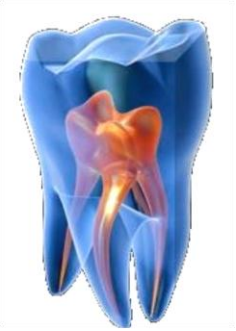
Carcinoma in situ is the concept that malignant epithelial transformation has occurred but that invasion into the stroma cannot be demonstrated.

Carcinoma in situ is not regarded as a reversible lesion, although it may take many years for invasion to occur.

A majority of squamous cell carcinomas of the upper aerodigestive tract, including the oral cavity, are preceded by epithelial dysplasia.

Conceptually, invasive carcinoma begins when a microfocus of epithelial cell invades the lamina propria 1 to 2 mm beyond the basal lamina.

At this early stage, the risk of regional metastasis is low.



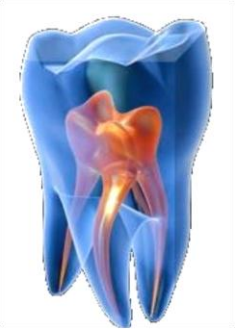
Idiopathic Leukoplakia

Risk Factors
Tobacco, alcohol, nutrition, unknown

Sites of Occurrence
Vestibule . buccal mucosa . palate . alveolar ridge . lip . tongue . floor of mouth

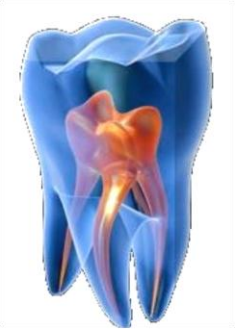
High-Risk Sites for Malignant Transformation
Floor of mouth . tongue . lip . palate . buccal mucosa
vestibule . retromolar

Age
Usually over 40 years



Microscopic Diagnoses at First Diagnosis
Hyperkeratosis—80%
Dysplasia—12%
In situ carcinoma—3%
Squamous cell carcinoma—5%

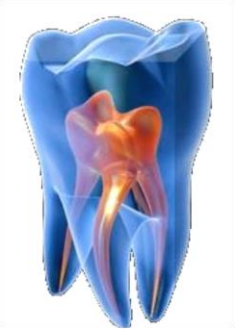
Transformation Rates
All idiopathic leukoplakias—5% to 10%
All dysplasias—10% to 15%



Dysplasia: Microscopic Features

Epithelial Architecture
Drop-shaped epithelial ridges
Basal cell crowding
Irregular stratification
Reduced intercellular adhesion

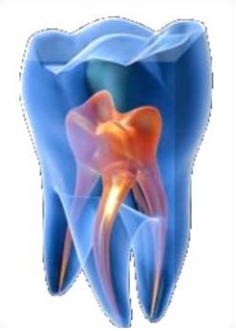
Cytologic Atypia
Pleomorphic nuclei—hyperchromatic, smudgy, angular
Increased nuclear-cytoplasmic ratios
Increased and abnormal mitoses



Differential Diagnosis

The first step in developing a differential diagnosis for a white patch (leukoplakia) on the oral mucosa is to determine whether the lesion can be removed with a gauze square or a tongue blade.

- *If the lesion can be removed*, it may represent a pseudomembrane, a fungus colony, or debris.
- If bilateral buccal mucosal disease is evident, then hereditary conditions, cheek chewing, lichen planus, and lupus erythematosus (LE) should be considered.
- If chronic trauma or tobacco use is elicited in the patient's history, frictional or tobacco-associated hyperkeratosis, respectively, should be considered. Elimination of a suspected cause should result in some clinical improvement.
- Hairy leukoplakia and geographic tongue would also be included in a differential diagnosis for tongue leukoplakia.



➢If the lesion in question is not removable and is not clinically diagnostic, it should be considered an idiopathic leukoplakia and a biopsy should be performed.

➢For extensive lesions, multiple biopsies may be necessary to avoid sample error. The clinically most suspicious areas (red, ulcerated, or indurated areas) should be included in the area to be biopsied.

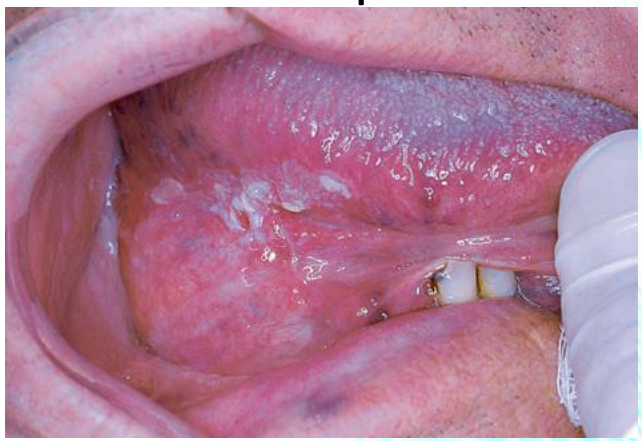


Fig. Idiopathic leukoplakia of the lateral tongue. The microscopic diagnosis was squamous cell carcinoma.

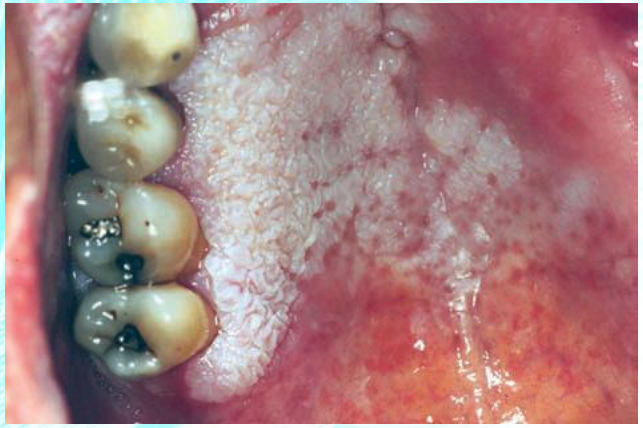
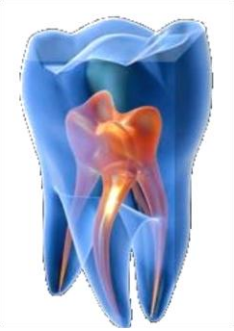
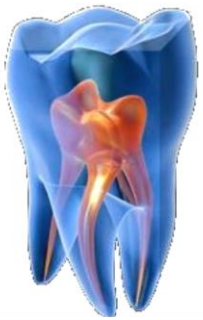


Fig. Proliferative verrucous leukoplakia.



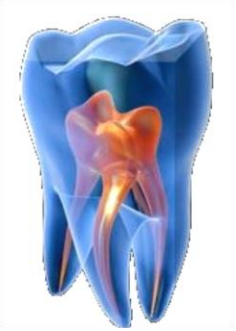
➢Clinical investigators have suggested that alveolar ridge keratosis is a distinct entity and should be separated from other oral (premalignant) leukoplakias. Alveolar ridge keratoses appear to be caused by chronic friction and when biopsied are diagnosed as benign keratosis (more than 97% have been found to represent hyperkeratosis without dysplasia).

➢Lesions present as asymptomatic white plaques or papules on the mandibular or maxillary alveolar ridges, attached gingiva or retromolar pad, or areas of frictional or occlusal trauma. Microscopically, simple hyperorthokeratosis without significant underlying inflammation is seen. Studies using immunomarkers specific for dysplasia have been negative. Clinical judgment is necessary to determine whether biopsy is in the best interest of the patient.



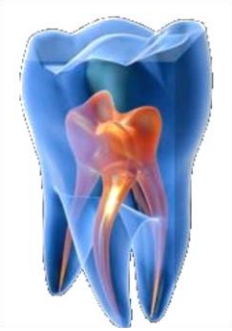
Treatment and Prognosis

1. In the absence of dysplastic or atypical epithelial changes, periodic examination and rebiopsy of new suspicious areas of leukoplakia are recommended.
2. If a lesion is mildly dysplastic, some clinical judgment should be exercised in patient management. Removal of mildly dysplastic lesions is in the patient's best interest if no causative factor is apparent and the lesion is small. If considerable morbidity would result because of the lesion's size or location, follow-up surveillance is acceptable, provided the degree of epithelial dysplasia is mild.
3. Surgical excision and other physical forms of ablation are the currently preferred treatment modalities, although it is not clear if these strategies may eliminate or significantly reduce the risk of recurrence or malignant transformation.



4. Medical management of dysplastic lesions with the use of topical agents has not proved effective. If leukoplakia is diagnosed as moderate to severe dysplasia, excision of the clinically visible lesion becomes obligatory.
5. Although surgical excision may be followed by recurrence, excision offers the opportunity to examine the lesion histologically in its entirety for the presence or absence of higher grades of dysplasia or carcinoma. Various surgical methods such as scalpel excision, cryosurgery, electrosurgery, and laser surgery seem to be equally effective in ablating these lesions.
6. For large lesions, grafting procedures may be necessary after surgery. It is important to note that many idiopathic leukoplakias may recur after complete removal.

It is impossible to predict which lesions will return and which will not. Although the risk of malignant transformation of oral leukoplakia is low, long-term follow-up is mandatory, and repeat biopsy should be considered if the clinical findings dictate.



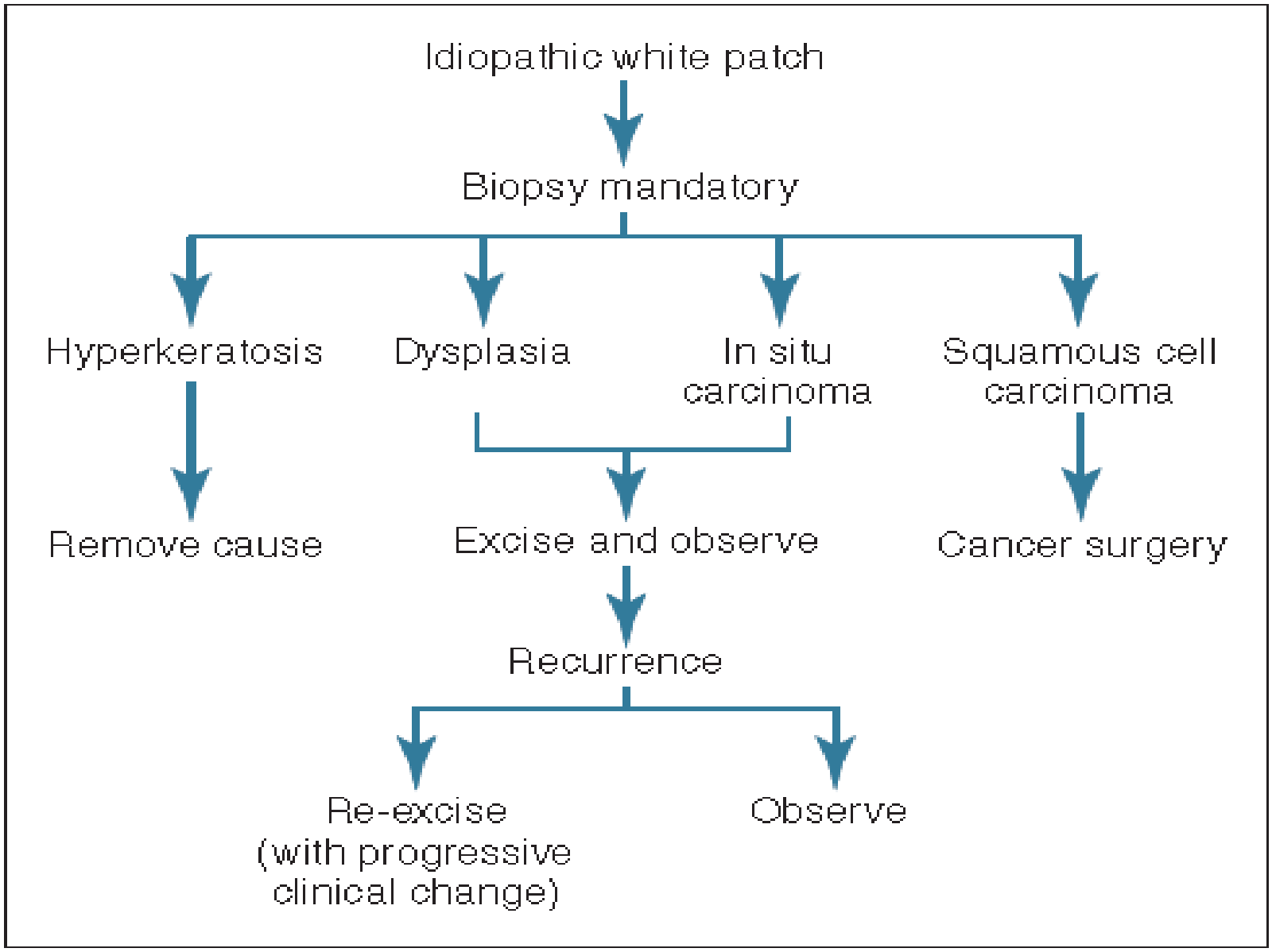
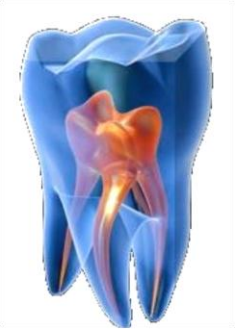


Fig. Idiopathic leukoplakia: diagnosis and management.



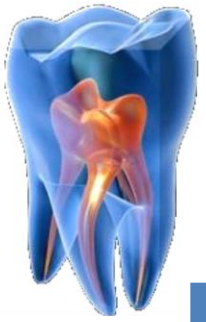
HAIRY LEUKOPLAKIA

Etiology and Pathogenesis

In 1984, an unusual white lesion along the lateral margins of the tongue, predominantly in gay men, was first described.

Evidence indicates that this particular form of leukoplakia, known as ***hairy leukoplakia***, represents an opportunistic infection that is related to the presence of **Epstein-Barr virus** (***EBV***) and is found mainly in ***human immunodeficiency virus*** (***HIV***)–infected individuals.

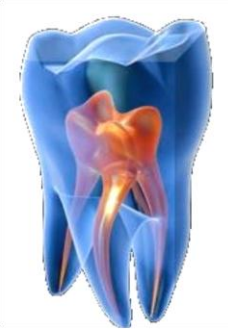
In a small percentage of cases, ***hairy leukoplakia*** may be seen in patients with other forms of immunosuppression, particularly those associated with organ transplantation (medicalinduced immunosuppression), hematologic malignancy, and long-term use of systemic or topical corticosteroids.



The prevalence of ***hairy leukoplakia*** in HIV-infected patients has been declining as a result of new chemotherapeutic regimens for HIV.

Infections
Viral: herpes simplex, herpes zoster, hairy leukoplakia, cytomegalovirus, warts
Bacterial: tuberculosis, bacillary angiomatosis
Fungal: candidiasis, histoplasmosis
Protozoan: Toxoplasmosis

Neoplasms
Kaposi's sarcoma (HHV8)
Lymphomas, high grade



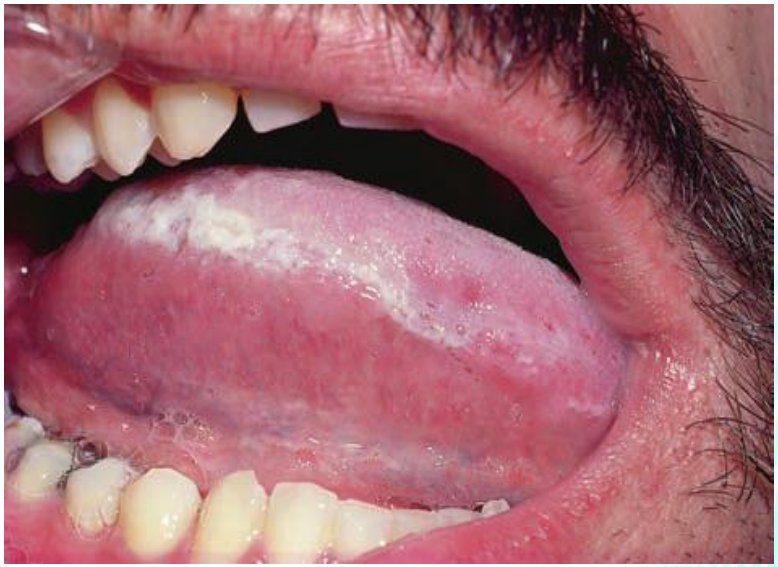
Other
Aphthous ulcers
Xerostomia
Gingivitis and periodontal disease
AIDS, Acquired immunodeficiency syndrome; *HHV8,* human herpesvirus 8.

Clinical Features

Hairy leukoplakia presents as a well-demarcated white lesion that varies in architecture from a flat to a papillary or a corrugated lesion.

It may be unilateral or bilateral. A vast majority of cases have been located along the lateral margins of the tongue, with occasional extension onto the dorsal surface. Rarely, ***hairy leukoplakia*** may be seen on the ***buccal mucosa***, ***the floor of the mouth***, or the ***palate***.

Lesions have not been seen in the vaginal or anal mucosa. ***Hairy Leukoplakia*** may be ***associated with candidiasis***.



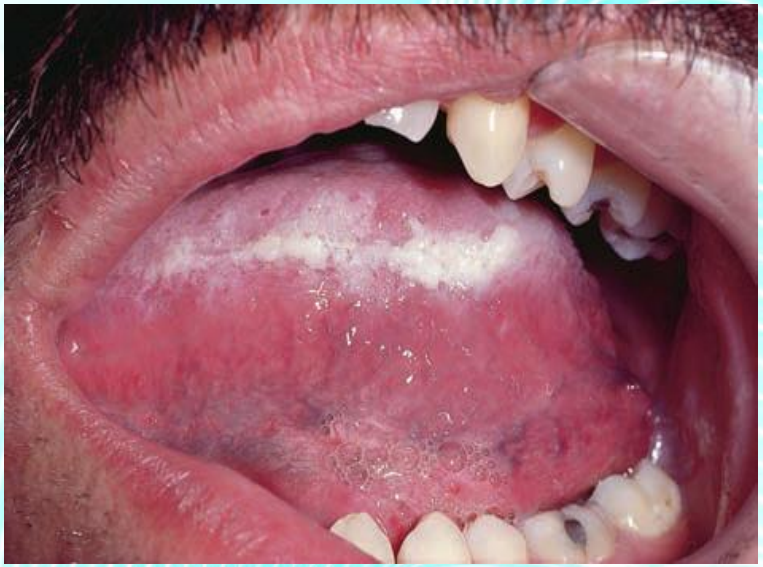


Fig. A and **B,** Hairy leukoplakia, bilateral

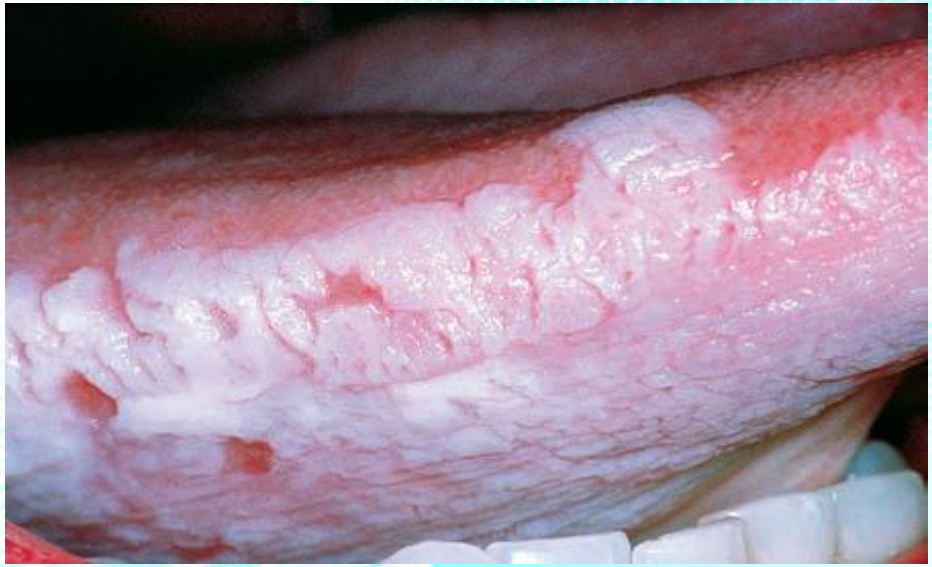
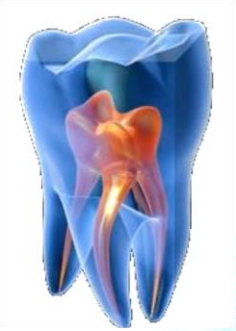


Fig. Hairy leukoplakia of the lateral and ventral tongue.



Histopathology

The characteristic microscopic feature of hairy leukoplakia is found in the nuclei of upper level keratinocytes

Viral inclusions and/or peripheral displacement of chromatin with a resultant smudgy nucleus are evident.

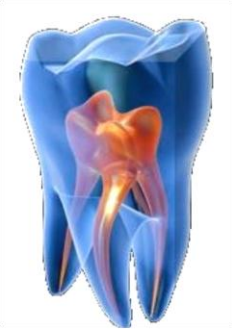
C. albicans hyphae are often seen extending into the superficial epithelial cell layers.

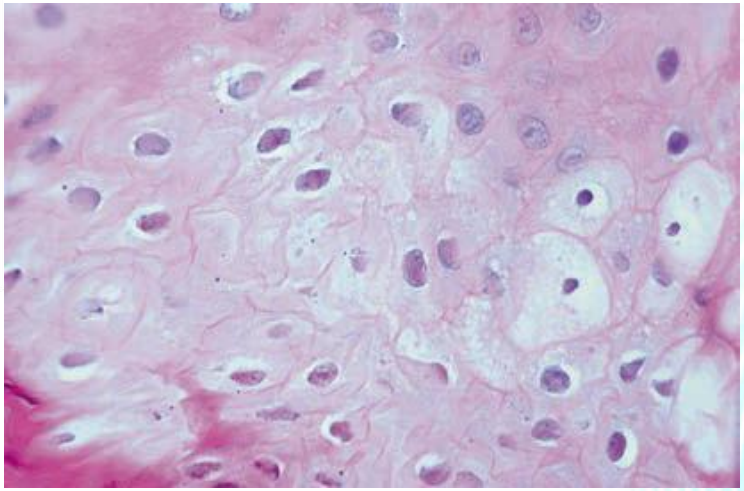
Beneath the surface, within the spinous cell layer, cells show ballooning degeneration and perinuclear clearing.

Differential Diagnosis

The clinical differential diagnosis of hairy leukoplakia includes idiopathic leukoplakia, frictional hyperkeratosis (tongue chewing), and leukoplakia associated with tobacco use.

It Need differentation with ***lichen planus, lupus erythematosus, and hyperplastic candidiasis***.





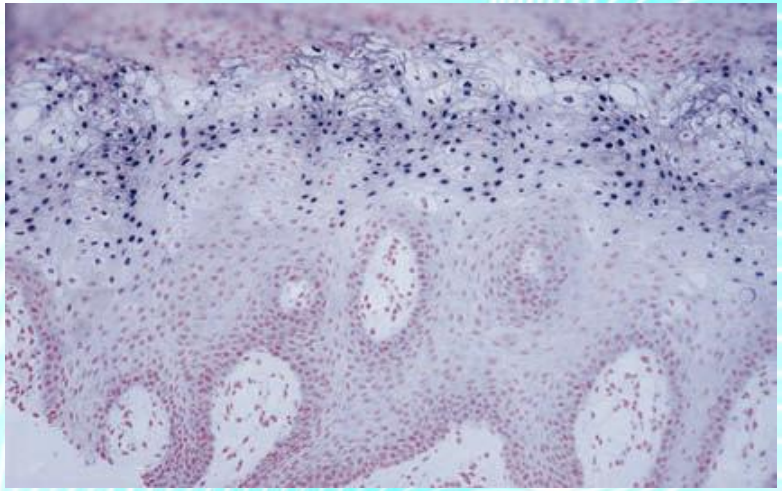
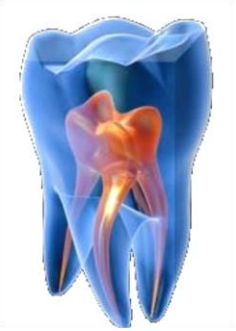


Fig. Hairy leukoplakia showing acanthosis, parakeratosis, and edema. Upper level keratinocytes showing nuclear viral inclusions.
In situ hybridization showing localization of Epstein- Barr virus (EBV) encoded small RNAs (EBER) in the infected nuclei of high level keratinocytes.



Treatment and Prognosis

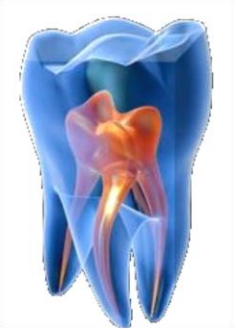
No specific treatment is available for ***hairy leukoplakia***. For patients whose immune status is unknown and in whom biopsy findings indicate hairy leukoplakia, it is necessary to conduct a study on HIV infection and find out the causes of immunosuppression..

The HIV infection is a couse of immunosuppression that can lead to ***hairy leukoplakia***.

For cosmetic reasons, patients may request treatment of their lesions.

The treatment was applied ***by acyclovir, ganciclovir, famciclovir, tretinoin, and podophyllum***. But after finishing treatment returned the lesions.

Lesions usually improve or resolve with improvement in the patients immune system.



The End