Oral Medicine

Lecture 7

Red and White Lesions of the Oral Mucosa

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Learning Objectives

One challenging aspect of Oral Medicine is that many lesions of different conditions look alike, with the same diagnosis may be manifested in various ways.

The objectives are to :

1. Know that white and red oral lesions are the most commonly color changes.
2. Observe changes in the color of oral mucosa from a normal-looking mucosa.
3. Know the different ways of classifying oral mucosal lesions.
4. Know that different colors may indicate pathologic changes and they guide us in the diagnosis.

Learning Objectives

One challenging aspect of oral medicine is that many lesions of different conditions look alike. The same diagnosis may also manifest in various ways.

Thus, in order to become a successful clinician in differential diagnosis, appreciation of the very versatile appearances of the same disease requires considerable clinical acumen and experience. It is also important to appreciate that the oral mucosa in some patients may appear to be different from what we perceive as normal-looking mucosa.

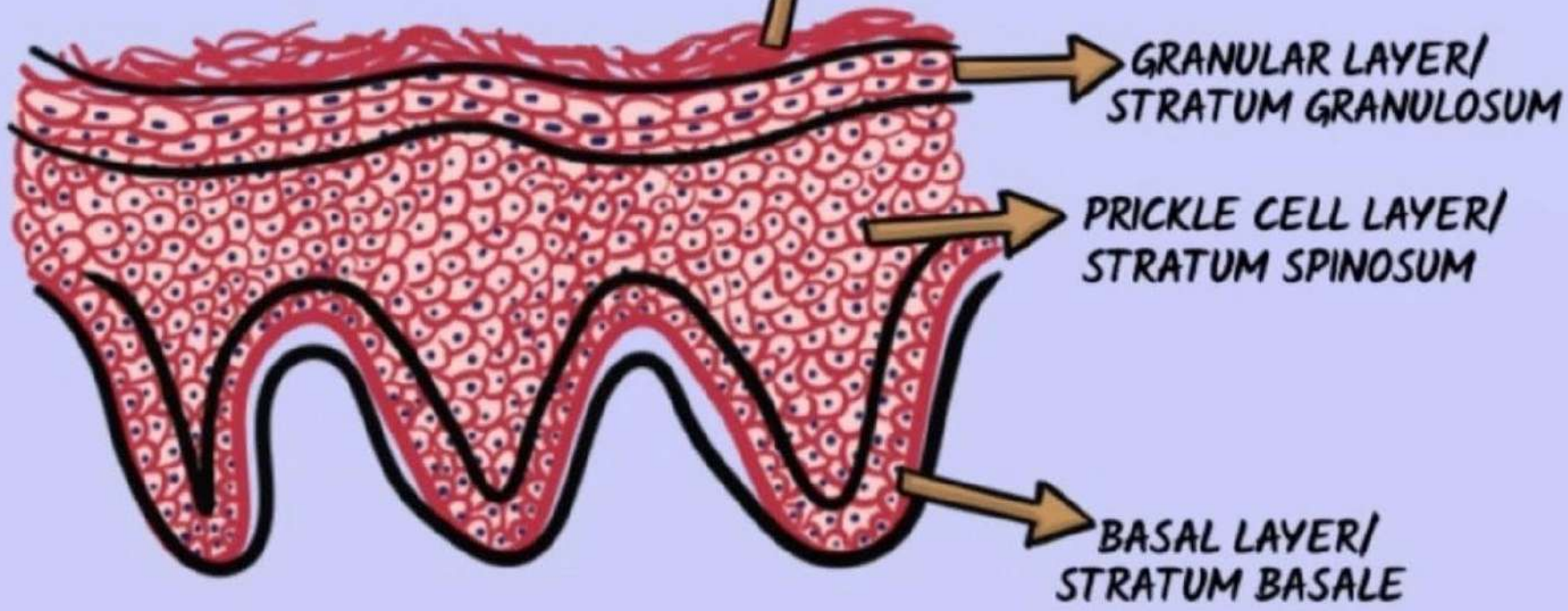
White lesions of oral mucosa are white as a consequence of several possible structural occurrences:

1. Increased thickness of the corneal layer (keratinized epithelium).

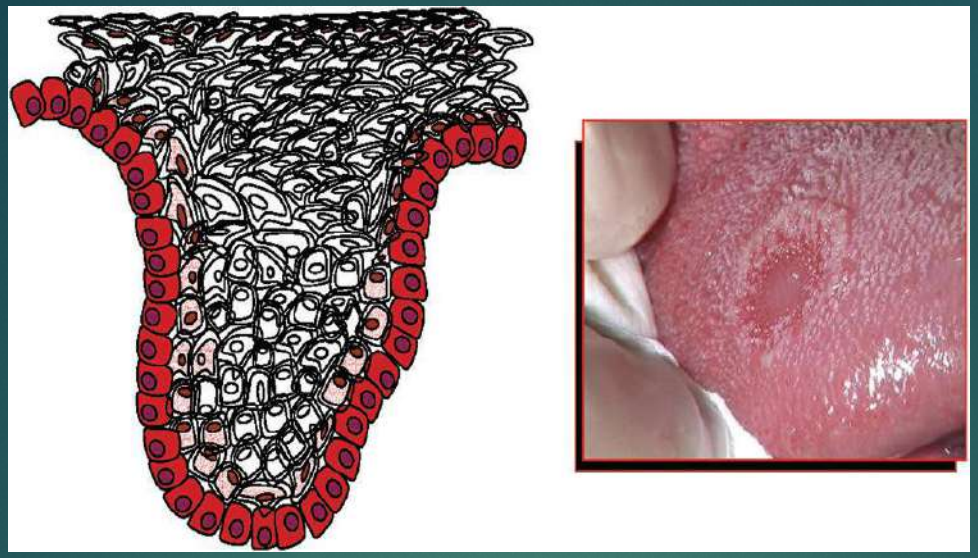
2.Keratinization of epithelium that does not normally contain a corneal layer (non-keratinized epithelium).
Both (1&2) manifest as **hyperkeratosis**.

3. Formation of abnormal keratin.
4.Epithelial edema: intra- and extracellular accumulation of fluid in the epithelium may also result in clinical whitening
5.Abnormal keratinization occurring prematurely within individual cells or groups below the stratum granulosum (dyskeratosis often also contains hyperkeratosis).
6. Subepithelial superficial fibrosis, which with its decreased vascularity network causes a diffuse whitish appearance.

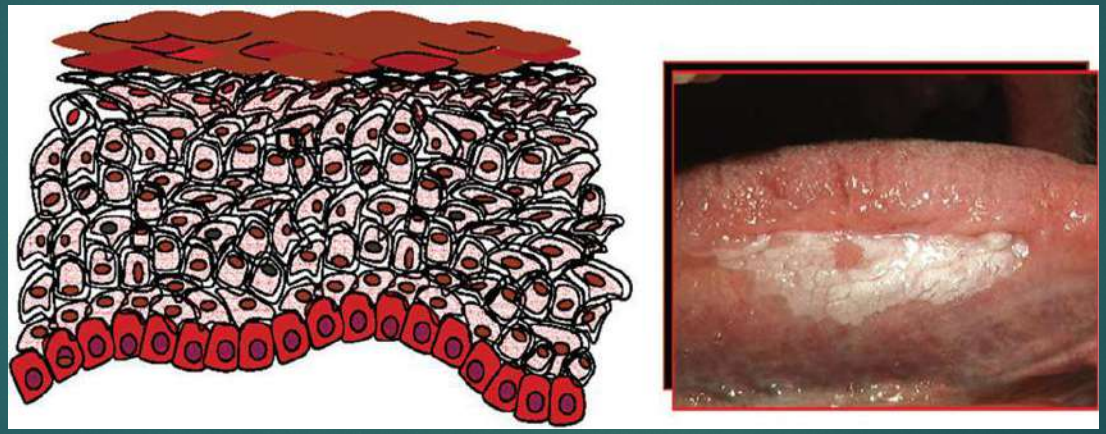
KERATINIZED EPITHELIUM



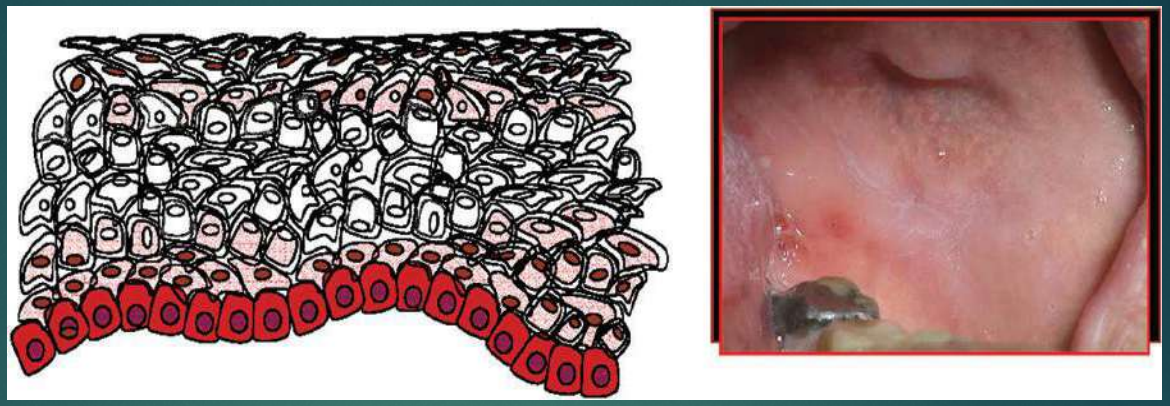
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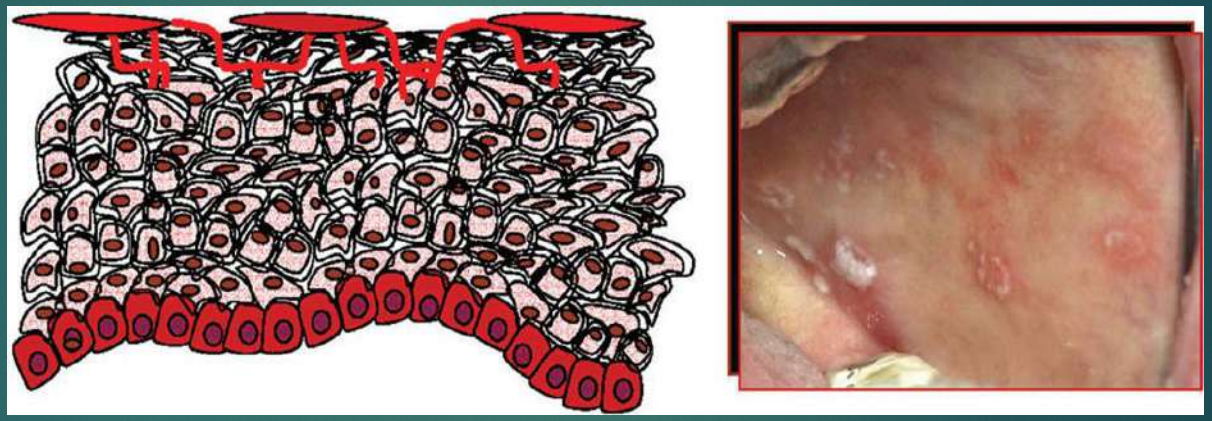
Mechanisms leading to a white appearance of the oral mucosa due to an abnormal but benign thickening of stratum spinosum (acanthosis).



Mechanisms leading to a white appearance of the oral mucosa due to an increased production of keratin (hyperkeratosis).



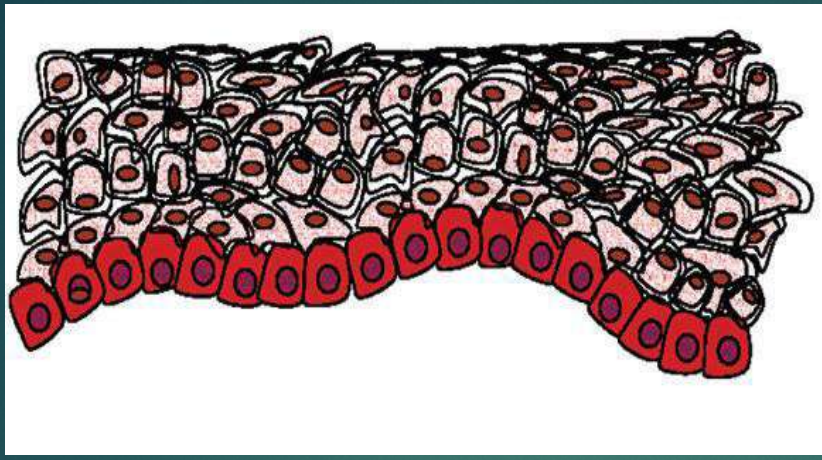
Mechanisms leading to a transparent white appearance of the oral mucosa due to intra- and extracellular accumulation of fluid in the epithelium (leukodema)



Mechanisms of a white appearance of the oral mucosa due to microbes, particularly fungi, which can produce whitish pseudomembranes consisting of sloughed epithelial cells, fungal mycelium, and neutrophils, which are loosely attached to the oral mucosa (plaques).

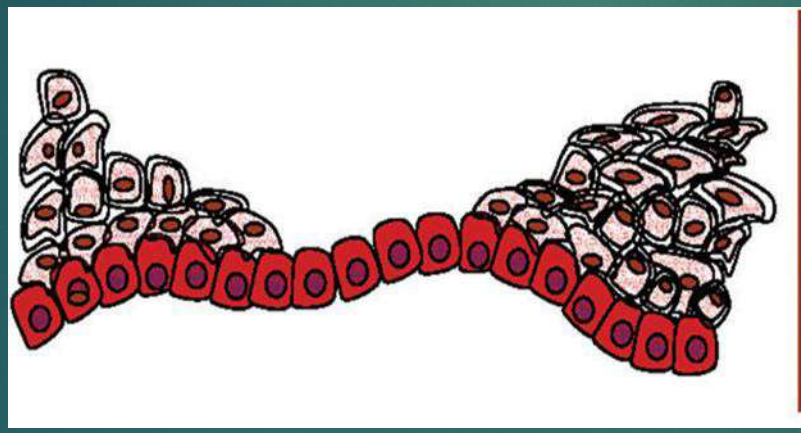
A red lesion of the oral mucosa may develop as a result of:

1. Atrophic epithelium characterized by a reduction in the **number** of epithelial cells
2. Loss of the superficial cell layers (superficial erosion)
3. Increased vascularization due to proliferation of vessels
4. Redness or erythema may further be caused by dilatation of vessels associated with inflammation of the oral mucosa.
5. **Reduced** epithelial keratinization, and, importantly, cellular proliferation signifying a possible malignancy.





Mechanisms leading to a red appearance of the oral mucosa; a red lesion of the oral mucosa may develop as the result of an atrophic epithelium (atrophy).





Mechanisms leading to a red appearance of the oral mucosa characterized by a result of loss of the superficial cell layers (superficial erosion) **or increased vascularization; that is, dilatation of vessels and/or proliferation of vessels.**

Oral mucosal lesions may be classified according to different characteristics

- **Infectious Diseases**

Oral Candidiasis
Oral Hairy Leukoplakia

- **Oral Potentially Malignant Disorders**

Oral Leukoplakia
Proliferative Verrucous Leukoplakia
Oral Erythroplakia
Oral Submucous Fibrosis

- **Immunopathologic Diseases**

Oral Lichen Planus
Oral Disease Severity Scoring
Oral Lichenoid Drug Eruptions
Lichenoid Reactions of Graft-versus-host Disease
Lupus Erythematosus

Allergic Reactions

Oral Lichenoid Contact Reactions

Reactions to Dentifrice and Chlorhexidine

Toxic Reactions

Reactions to Smokeless Tobacco

Smoker's Keratosis

Smoker's Palate

Reactions to Mechanical Trauma

Morsicatio (Mucosal Nibbling)

Frictional Hyperkeratosis

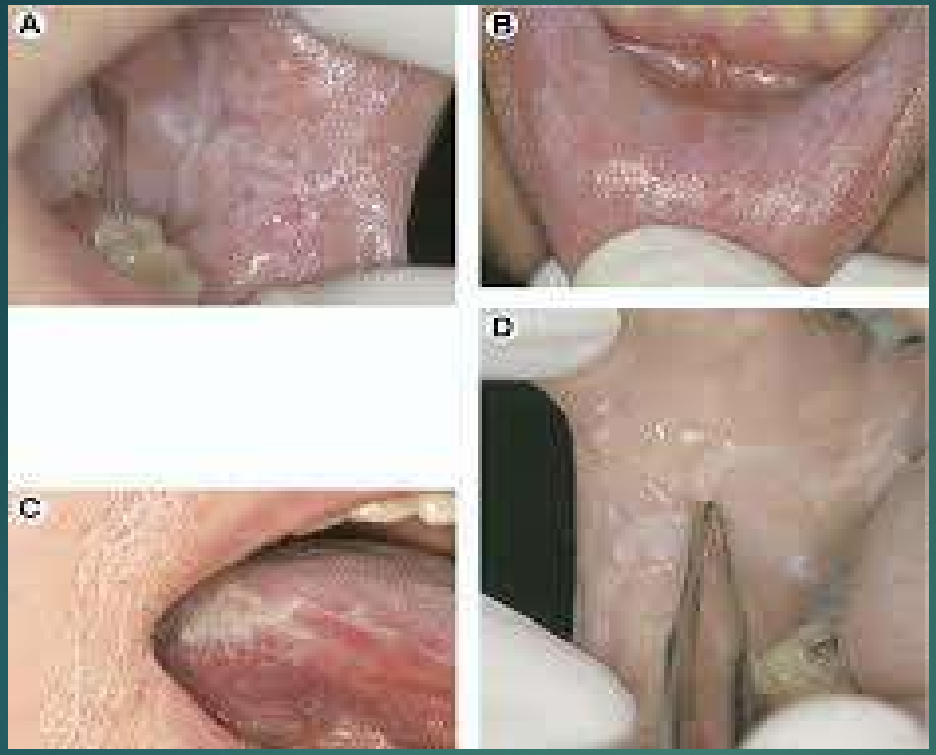
Other Red and White Lesions

Benign Migratory Glossitis (Geographic Tongue)

Leukoedema

White Sponge Nevus

Hairy Tongue



Morsicatio (Mucosal Nibbling)

Main clinical characteristics of Red or White lesions.

1. Is pain present?
2. Are lesions single or multiple?
3. Are lesions bilateral or unilateral?
4. Is the distribution of lesions linked to mucosal type?
5. Are lesion borders defined or indistinct?
6. Date of onset
7. Are lesions associated with changes of the skin?
8. Duration of lesion
9. Any changes in shape, size, or texture with time?
10. Any previous response to therapy?
11. What makes the pain or the lesions worse?
12. Have lesions healed and recurred?

Infectious Diseases

Oral Candidiasis

Oral candidiasis the most prevalent opportunistic infection affecting the oral mucosa. In the vast majority of cases, the lesions are caused by ***Candida albican***.

The pathogenesis is not fully understood, but a number of predisposing factors have been shown to convert *C. albicans* from the normal commensal flora (saprophytic stage) to a pathogenic organism (parasitic stage).

Candidiasis is said to affect in particular
the very young,the very old, the very dry, and the very sick **Most** candidal infections only affect mucosal linings, but **rare** systemic manifestations may have a fatal course.

- Oral candidiasis is divided into **primary & secondary** infections
  - The primary infections are restricted to the oral and perioral sites,
  - whereas secondary infections are accompanied by systemic mucocutaneous manifestations.

Etiology and Pathogenesis

Candida albicans, *C. tropicalis*, and *C. glabrata* comprise together over 80% of the species isolated from human candidal infections.

- **To invade** the mucosal lining, the microorganisms must **adhere** to the epithelial surface; therefore, candidal strains with **better adhesion** potential are more **virulen**t than strains with **poorer adhesion** ability.

- The yeasts' penetration of the epithelial cells is facilitated by their **production of lipases**
- and for the yeasts to remain within the epithelium, they **must overcome constant desquamation of surface** epithelial cells.

Predisposing Factors for Oral Candidiasis and Candida-Associated Lesions

Local factors

Those local factors include

- Lack of saliva (medications causing dry mouth, autoimmune diseases, head and neck radiotherapy),
- Denture wearing,
- Topical steroid use,
- Use of antibiotics
- Immunosuppressive medications

Systemic conditions including

- Diabetes,
- Immunosuppressive diseases-HIV
- Impaired health status
- Chemotherapy
- Endocrine disorders
- Anemia-Hematinic deficiencies

Rare systemic manifestations of candidal infections may have a **fatal course** and are major causes of morbidity and mortality, causing variety of diseases from mucosal infections to deep tissue disease, which may lead toward **candidemia** and **organ involvement.**

Local Predisposing Factors for Oral Candidiasis and Candida-Associated Lesions

Denture wearing
Smoking
Inhalation steroids
Topical steroids
Hyperkeratosis
Quality and quantity of saliva
Atopic constitution
Imbalance of the oral microflora

General Predisposing Factors for Oral Candidiasis

Immunosuppressive diseases
Immunosuppressive medications
Chemotherapy
Endocrine disorders(diabetes)
Hematinic deficiencies
Systemic antibiotics
Impaired health status

Classification of oral candidiasis.

Type	Examples
Pseudomembranous—acute	Thrush
Pseudomembranous—chronic	With inhalers
Erythematous—acute atrophic	After antibiotic therapy
Erythematous—chronic atrophic	Denture stomatitis; in HIV
Chronic hyperplastic (nodular and plaque-like subtypes)	Candidal leukoplakia, median rhomboid glossitis
Candida-associated lesions	Denture stomatitis; angular cheilitis

Candidiasis affecting extr-aoral sites and conditions predisposing to candidiasis.

- Familial chronic mucocutaneous candidiasis
- Diffuse chronic mucocutaneous candidiasis
- Erythematous candidiasis endocrinopathy syndrome
- Chronic severe combined immunodeficiency
- DiGeorge syndrome
- Chronic granulomatous disease
- HIV disease

Epidemioloy

- Part of the commensal oral flora
- Large geographic variations
- Candidal strains are more frequently isolated from **women**.
- **A seasonal variation** has been observed, with an increase during **summer** months.
- **Hospitalized patients** have a higher prevalence of the yeasts.
- In healthy individuals, blood group O and non-secretion of blood group antigens are separate and cumulative risk factors for oral carriage of *C. albicans*.
- In complete denture-wearers, the prevalence of denture stomatitis has been reported as nearly 70%.
- Candidiasis is frequently **over-reported** in those without experience of the normal anatomy of the oral cavity.

Thus, even slight elongation of the filiform papillae on the dorsum of the tongue may be erroneously diagnosed as candidiasis.

Clinical Findings

➢ Pseudomembranous Candidiasis

- Acute form of pseudomembranous candidiasis (thrush) is grouped with the primary oral candidiasis and is recognized as the classic candidal infection.
- The infection predominantly affects patients taking antibiotics, immunosuppressant agents, or having a disease that suppresses the immune system.



Erythematous Candidiasis

- Was previously referred to as atrophic oral candidiasis erythematous surface may not just reflect atrophy but can also be explained by increased vascularization.
- The lesion has **a diffuse border** which helps distinguish it from .erythroplakia which usually has a sharper demarcation

- The infection is predominantly seen in the **palate** and the **dorsum of the tongue** of patients who are using **inhalation steroids.**
- Other predisposing factors that can cause erythematous candidiasis are **smoking** and treatment with **broad-spectrum antibiotics**.



There is also a chronic form of pseudomembranous candidiasis, often associated with immunodeficiency.

The clinical presentations of acute and chronicpseudomembranous candidiasis are indistinguishable.

The chronic form may emerge as the result of HIV infection, as patients with this disease may be affected by a pseudomembranous candidal infection for a long period of time.

Patients treated with steroid inhalers may also show pseudomembranous lesions of a chronic nature.



Erythematous candidiasis caused by inhalation steroids (A) on the dorsum of the tongue and (B) the associated contact (kissing) lesion on the hard palate.

➢ Chronic Plaque-Type and Nodular Candidiasis

Replaces the older term, **candidal leukoplakia**.

- ❑ A white irremovable plaque
- ❑ Characterizes the typical clinical presentation, which may be **indistinguishable** from oral leukoplakia
- ❑ A positive correlation between oral candidiasis and **moderate to severe** epithelial dysplasia

- ❑ Both the chronic plaque-type and the nodular type of oral candidiasis have been associated with **malignant transformation**, but the possible role of yeasts in oral carcinogenesis is unclear.

- ❑ It has been hypothesized that it may act through its capacity to catalyze **nitrosamin** production.

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Denture Stomatitis

Denture stomatitis is classified into **three different types**.

- ✓ **Type I** is limited to minor erythematous sites caused by trauma from the denture.
- ✓ **Type II** affects a major part of the denture-covered mucosa
- ✓ In addition to the features of type II, **type III** has a granular mucosa.

The denture serves as a vehicle that accumulates sloughed epithelial cells and protects the microorganism from physical influences such as salivary flow.

The microflora is complex and may, in addition to *C. albicans* contain bacteria from several genera, such as *streptococcus-*, *Veillonella-*, *Lactobacillus-*, *Prevotella-* *Actinomyces-strains*.

It is not known to what extent these bacteria participate in the pathogenesis of denture stomatitis

Denture stomatitis is classified into 3 different types:

Type I is limited to erythematous sites caused by trauma from the denture.

type II affects a major part of the denture-covered mucosa

Type III has a granular mucosa (reactive proliferation of underlying fibrous tissue) in addition to the features of type II..



Chronic atrophic candidiasis (denture stomatitis) type III with a granular mucosa in the central part of the palate

The clinical appearance of denture stomatitis. (A) Type I denture stomatitis, characterized by a localized inflammation and/or pinpoint hyperaemia. (B) Type II denture stomatitis, characterized by diffuse erythema. (C) Type III denture stomatitis, characterized by papillary hyperplasia.

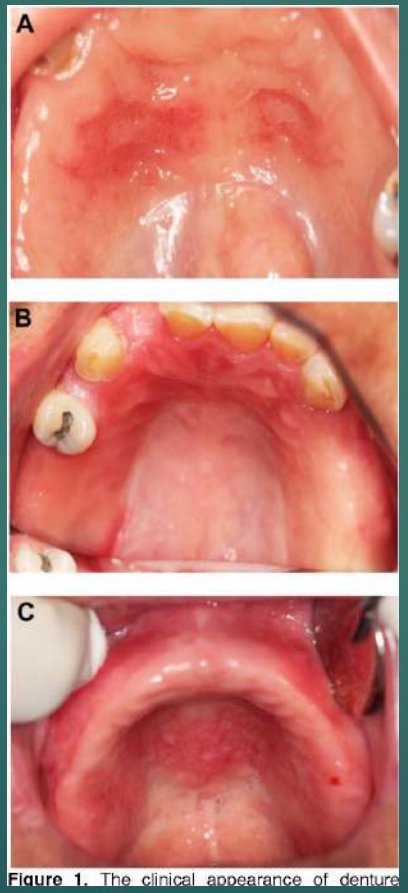


Figure 1. The clinical appearance of denture

➢ Angular Cheilitis

Angular cheilitis presents as **infected fissures of the commissures** of the mouth, often surrounded by erythema

The lesions are frequently infected with both *Candida albicans* and *Staphylococcus aureus*.
Vitamin B12 deficiency, iron deficiencies, and loss of vertical dimension have been associated with this disorder.
Dry skin may promote the development of fissures in the commissures, allowing invasion by the microorganisms.
Approximatly, 30% of patients with denture stomatitis also have angular cheilitis, but this infection is only seen in 10% of denture-wearing



Candida-induced bilateral angular cheilitis.
Treatment must include the intraoral Candida reservoir.

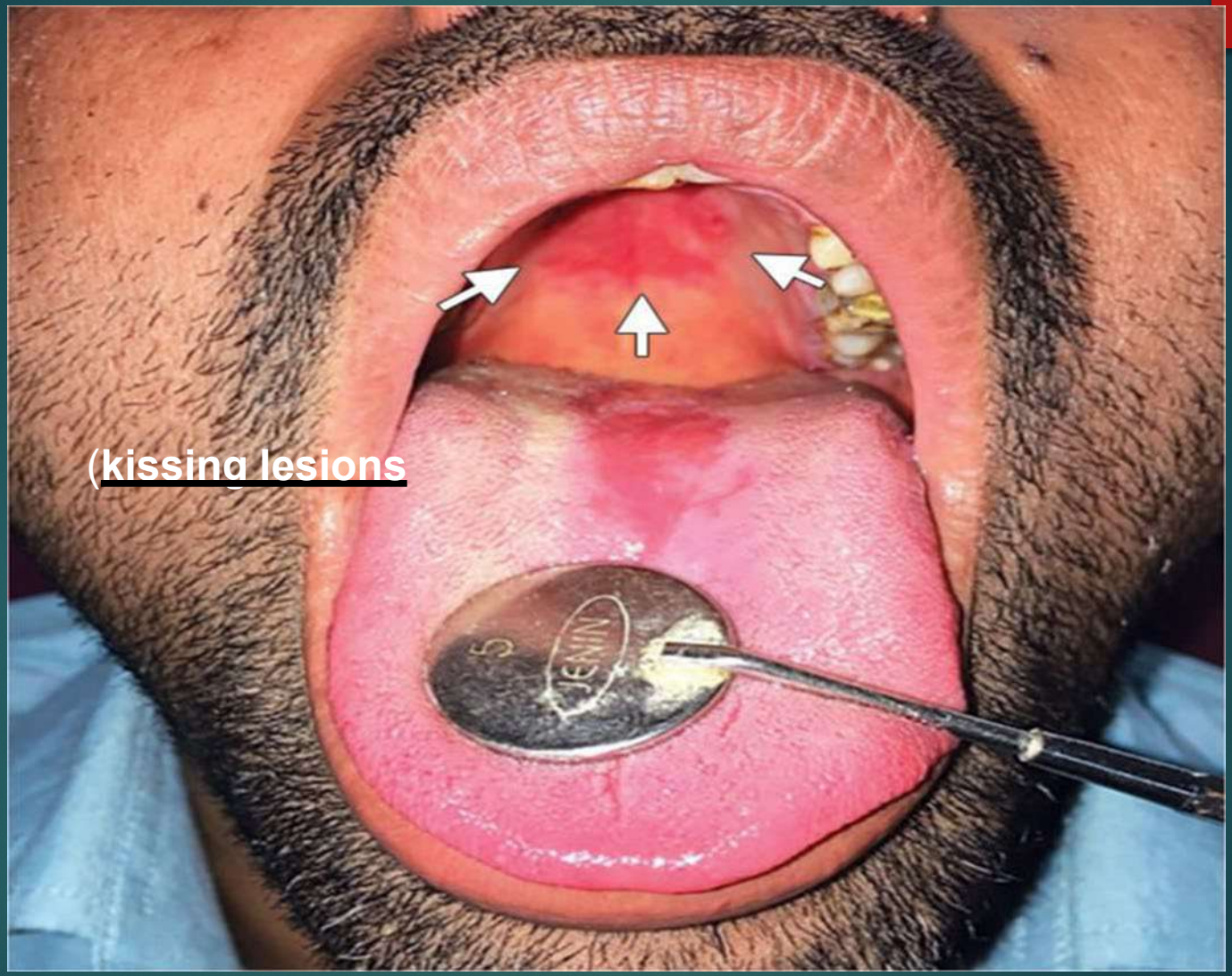
➢ Median Rhomboid Glossitis

- Clinically characterized by an erythematous lesion in the center of the posterior part of the dorsum of the tongue;
- An oval configuration.
- This area of erythema results from atrophy of the filiform papillae and the surface may be lobulated.
- The etiology is not fully clarified, but the lesion frequently shows a mixed bacterial/fungal microflora.
- Biopsies yield candidal hyphae in more than **85%** of the lesions.
- Smokers and denture-wearers have an increase risk of developing it.
- Patients using inhalation steroids.
- Sometimes a concurrent erythematous lesion may be observed in the palatal mucosa called (**kissing lesions**).
- It is asymptomatic, and management is restricted to a reduction of predisposing factors.

- The lesion does not entail any increased risk for malignant transformation.



Median rhomboid glossitis apparently arising from the junction of the posterior third and anterior two-thirds of the tongue. Histology confirmed chronic hyperplastic candidiasis.


(kissing lesions
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➢ Oral Candidiasis Associated with HIV

- More than **90%** of acquired immune deficiency syndrome (AIDS) patients have had oral candidiasis during the course of their HIV infection.
- The infection is considered a portent of AIDS development

The most common types of oral candidiasis in conjunction with HIV are

1. Pseudomembranous candidiasis,
2. Erythematous candidiasis,
3. Angular cheilitis,
4. Chronic plaque-like candidiasis.

As a result of the **Highly Active Antiretroviral Therapy** (HAART), the prevalence of oral candidiasis has decreased substantially.

Chronic mucocutaneous candidiasis (CMC)

- Involves a heterogeneous group of disorders, which, in addition to oral candidiasis, also affect the **skin**, typically the **nail** and other mucosal linings, such as the **genital mucosa**.
- The **face and scalp** may be involved.
- Approximately **90%** of the patients with CMC also present with oral candidiasis.
- The oral manifestations may involve the tongue, and lesions are seen in conjunction with fissures.
- CMC can occur as part of endocrine disorders, including hyperparathyroidism and Addison's disease.

- **Recent studies revealed that an impairment of interleukin-17 (IL-17) immunity underlies the development of CMC .**

- T-helper 17 cells produce IL-17 and play an important role in host mucosal immunity to Candida.

- Impaired phagocytic function by neutrophilic granulocytes and macrophages caused by myeloperoxidase (MPO) deficiency (oxidative stress plays a key role in the release of MPO from these cells).

- **Severe combined immunodeficiency** (SCID) syndrome is characterized by a defect in the function of the cell-mediated arm of the immune system.
- Patients with this disorder frequently contract disseminated candidal infections.

- **Thymoma i**s a neoplasm of thymic epithelial cells that also entails systemic candidiasis.
- Thus, both the native and adaptive immune systems are critical to prevent development of systemic mucocutaneous candidiasis.





Chronic candidiasis of (A) dorsum of tongue and (B) fingernails of a patient with chronic mucocutaneous candidiasis

Diagnosis and Laboratory Findings

The presence of candidal microorganisms as a member of the commensal flora complicates the discrimination of the normal state from infection.
The detection of yeast organisms in the form of hyphae- or pseudohyphae-like structures is usually considered a sign of infection although these structures have also been identified in normal oral mucosa.

To increase the sensitivity, a second scrape can be transferred to a transport medium followed by cultivation on **Sabouraud agar**. To discriminate between different candidal species, an additional examination can be performed on **Pagano-Levin agar**
The result is expressed as colony forming units per cubic millimeter **(CFU/mm$_2$).**

This method is a valuable adjunct in the diagnostic process of erythematous candidiasis and denture stomatitis as these infections consist of fairly homogeneous erythematous lesions.

Salivary culture techniques are primarily used in parallel with other diagnostic methods to obtain an adequate quantification of candidal organisms.
Patients who display **clinical signs of oral candidiasis** usually have **more than 500 CFU/mL**.

Candida cells can be found in 60% of people in numbers of up to 500 cfu/mL as **normal commensals**.

However, **in infection**, these numbers may increase to over 10,000 cfu/mL and any increase to over 1000 cfu/Ml may be seen in candidal infections.

In chronic plaque-type and nodular candidiasis, cultivation techniques have to be supplemented by a histopathologic examination.

This examination is primarily performed to identify the presence of **epithelial dysplasia** and to identify invading **candidal organisms by PAS staining**.

Routine tests for patients with suspected oral candidiasis.

1) Smears (cytology)
2) Swabs
3) Culture of saliva (or saline rinses) for cfu/mL
4) Biopsies
5) Hematology
6) Full blood picture, liver function tests
7) Hematinics (iron/ferritin, folate, vitamin B12)
8) Immunology, endocrinology

Management

- Treatment for fungal infections, which usually include **antifungal regimens**, **will not** always be successful **unless** the clinician addresses **predisposing factors** that may cause **recurrence**.
- **Local factors** are often easy to identify but sometimes not possible to reduce or eradicate.
  - **In smokers**, cessation of the habit may result in disappearance of the infection even without antifungal treatment.
  - Antifungal belong to the groups of **polyenes or azoles**

Polyenes such as nystatin and amphotericin B are usually the **first choices** in treatment of primary oral candidiasis and are both well tolerated.

- Elimination or reduction of predisposing factors should always be the **first goal** for treatment
- This involves improved denture hygiene, not to use the denture while sleeping.

- The denture hygiene is important to remove nutrients, including desquamated epithelial cells, which may serve as a **source of nitrogen** essential for the growth of the yeasts.

- Denture cleaning also **disturbs the maturity** of a microbial environment established under the denture.

- **Porosities** in the denture can harbor microorganisms, which may not be removed by physical cleaning, the denture should b**e stored in antimicrobial solutions during the night**

Different solutions.including:
Alkaline peroxides, alkaline hypochlorites,acids, disinfectants, and enzymes, have been suggested.
The latter seems to be most effective against candidal strains.
Chlorhexidine may also be used but can discolor the denture and also counteracts the effect of nystatin.

- **Type III denture stomatitis** may be treated with **surgical excision** in an attempt to eradicate microorganisms present in the deeper fissures of the granular tissue. If this is not sufficient, continuous treatment with topical antifungal drugs should be considered.

- **Topical** treatment with **azoles** such as **miconazole** is the treatment of choice for **angular cheilitis** often infected by both *S. aureus* and candidal strains. (biostatic effect on *S. aureus* in and fungistatic effect).

- If angular cheilitis comprises an erythema surrounding the fissure, a **mild steroid ointment** may be required to suppress the inflammation.
- To prevent recurrences, patients have to apply a moisturizing cream, which may prevent new fissure formation.

- **Systemic azoles** may be used for deeply seated primary candidiasis, such as **chronic hyperplastic candidiasis**, **denture stomatitis**, and **median rhomboid glossitis** with a granular appearance,

There are several disadvantages with the use of azoles.

- They are known to interact with **warfarin**, leading to an increased bleeding propensity.
- Topical application as the azoles **are fully or partly resorbed from the GIT**.
- **Development of resistance** is particularly compelling for **fluconazole** in individuals with HIV disease. In such cases, **ketoconazole and itraconazole** have been recommended as alternatives.
- The **azoles** are also used in the treatment of secondary oral candidiasis associated with systemic predisposing factors and for systemic candidiasis.

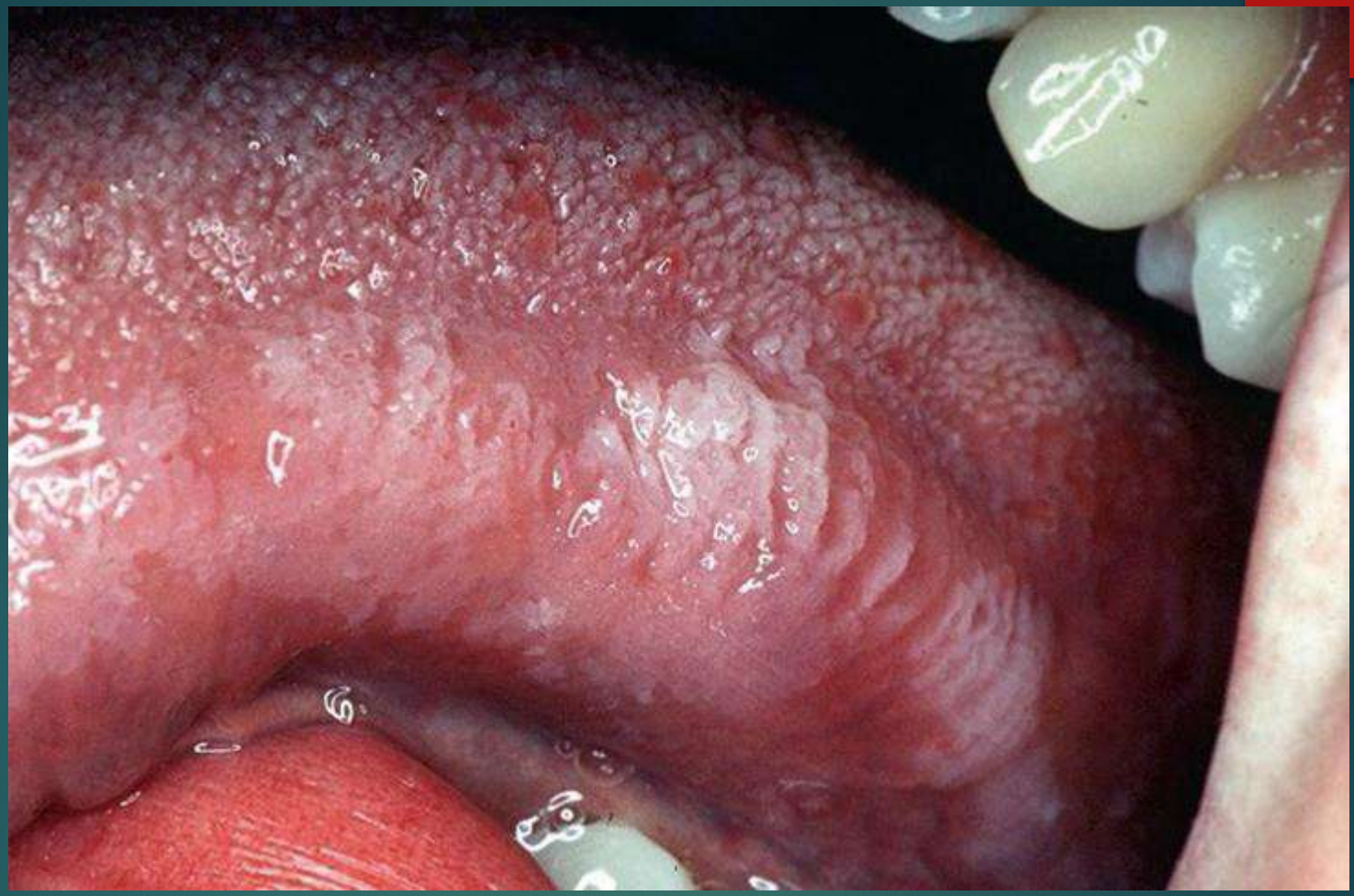
Prognosis of oral candidiasis good when predisposing factors are reduced or eliminated.
Persistent chronic plaque-type and nodular candidiasis have been suggested to be associated with an increased risk for malignant transformation compared with leukoplakia, not infected by candidal strains.

Oral Hairy Leukoplakia(OHL)

- Is the **second** most common HIV-associated oral mucosal lesion.
- HL has been used as a marker of disease activity since the lesion is associated with low CD4+ T-lymphocyte counts.
- The lesion **is not** pathognomonic for HIV disease since other states of immune deficiencies, such as caused by immunosuppressive agents

- Is strongly associated with **Epstein-Barr virus (EBV)** and with **low** levels of CD4+ T lymphocytes.
- Antiviral medication, which prevents EBV replication, is **curative**

- In AIDS, the prevalence may be as high as 80%.
- In children the prevalence is lower compared with adults (2%).
- Is more frequently in men, but the reason for this predisposition is not known.
- A correlation between smoking and OHL has also been observed
- immunosuppressive medications and cancer chemotherapy, have also been associated with OHL



Hairy leukoplakia at the left lateral border of tongue in an AIDS patient showing vertical keratotic corrugations.

- ✓ Is **frequently** encountered on the lateral borders of the tongue but may also be observed on the dorsum and in the buccal mucosa
- ✓ Is a symptomatic, although symptoms may be present when the lesion is superinfected with candidal strains
- ✓ **It is important to always consider mucosal lesion whenever the border of the tongue is affected by white lesions, particularly in immunocompromised patients**

Diagnosis

A diagnosis of OHL is usually based on clinical characteristics, but histopathologic examination and detection of EBV can be performed to confirm the clinical diagnosis.

Management

- ➢ It can be treated successfully with **antiviral medication**, but this is not often indicated as this disorder is not associated with adverse symptoms.
- ➢ The disorder may show spontaneous regression.
- ➢ OHL is not related to increased risk of malignant transformation

Medication with Antiretroviral therapy (ART) has reduced the number of OHL to a few percent in HIV-infected patients