



# A Comprehensive Guide to Diagnosing Oral Mucosal Lesions: Part II. Infectious Processes

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## Abstract

The clinical features of infectious oral mucosal lesions (OMLs) vary widely and frequently overlap, making diagnosis more difficult. Syphilis, tuberculosis, herpesviruses, HPV, HIV-related lesions, candidiasis, histoplasmosis, and blastomycosis are among the most important bacterial, viral, and fungal infections that affect the mouth. Clinical evaluation, patient history, and confirmatory tests are necessary for an accurate diagnosis. For prompt treatment and prevention of complications, especially in immunocompromised patients, early identification of these infections is essential.

## Subject Areas

Dentistry

## Keywords

Oral Medicine, Oral Lesion, Oral Manifestations, Infection

## 1. Introduction

Oral mucosal lesions (OMLs) represent a frequent diagnostic challenge in clinical practice. Following the clinical examination and combining the patient's history with clinical findings, the practitioner is in a position to formulate diagnostic hypotheses as to the etiology of the lesions observed. Soft tissue disorders of the oral cavity are generally classified into three broad categories: infectious, non-infectious, and neoplastic processes. Among these categories, infections of bacterial, viral and fungal origin make up a large and varied proportion of OML. They present a diversity of clinical features, pathophysiological mechanisms and diagnostic modalities, making their identification and management sometimes complex. This part of the review presents the main infections affecting the oral mucosa,

detailing their clinical manifestations, the diagnostic methods available and the differential diagnoses to be considered.

## 2. Bacterial Infections

### 2.1. Syphilis

#### Description:

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum* most seen in young adults. It is characterized by several stages—primary, secondary, latent, and tertiary.

The primary, secondary, and tertiary phases have all been associated with oral lesions.

#### Clinical manifestations:

- **Primary stage:** A painless, centrally ulcerated granulomatous papule with raised indurated borders called chancre, lasting three to seven weeks and eventually heal without scarring. Lesions are highly infectious [1].
- **Secondary stage:** Diverse occasionally painful OML: pharyngitis; mucous patches as glistening patches covered by a grey-white necrotic membrane on the soft palate, tongue, buccal mucosa and rarely the gingiva; oral ulcers.
- **Tertiary stage:** Gummas as locally destructive granulomas or as glossitis with mucosal atrophy [2].

#### Diagnosis:

- Diagnosis relies on thorough clinical examination supported by serological testing, including both treponemal and non-treponemal assays [2].
- The differential diagnosis of syphilitic lesions should consider herpetic cold sores, deep fungal infections, mycobacterial ulcers, malignancies, and traumatic ulcers. [1].

#### Management:

According to the World Health Organization (WHO), syphilis is treated primarily with intramuscular benzathine benzylpenicillin, which remains the gold standard. For early syphilis, a single dose (2.4 million units) is effective, while late latent or tertiary syphilis typically requires three weekly doses. In penicillin-allergic patients, doxycycline or azithromycin may be alternatives, though with caution due to resistance concerns [3].

### 2.2. Tuberculosis (TB)

#### Description:

Tuberculosis (TB) is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*. Although it mainly affects the lungs, it can affect any organ in the body. The disease is mainly airborne, via droplets expelled by a person with an active form of the infection [4].

#### Clinical manifestations:

Oral manifestations of all TB infections are rare and account for 0.5% - 1% [5].

OML of pulmonary TB are either primary or secondary in occurrence:

- Primary lesions are uncommon, seen in younger patients, and present as single painless ulcer with regional lymph node enlargement.
- The secondary lesions are common, usually present as single, indurated, irregular, painful ulcer covered with inflammatory exudate, affecting patients of any age [4].

OML of oral TB are most common on the tongue and gingiva. Other sites include the palate, lips, buccal mucosa, palatine tonsil, and floor of the mouth.

- Primary lesions on the gingiva presents mostly as single or multiple irregular and painless ulcers; with surrounding erythema without induration. As for lesions on the tongue, they can be found on the lateral margins, midline and base. They present as deep painless ulcers with a thick mucus material at the base of the lesion [5].
- Secondary lesions are seen as irregular, superficial, or deep, painful ulcers that tend to increase slowly in size. Other occasional mucosal lesions can show swelling, granulation or fissuration, but no obvious clinical ulcerations [4].

#### **Diagnosis:**

Diagnosis of *Mycobacterium tuberculosis* infection is based on the patient's medical history and clinical examination, the detection of acid-fast mycobacteria in clinical samples, a delayed hypersensitivity skin reaction (tuberculin test) to the purified protein derivative, and chest X-rays. Mycobacterial culture from sputum remains the most reliable diagnostic method [1].

The aphthous ulcers, traumatic ulcers, syphilitic ulcers, and malignancy, including primary squamous cell carcinoma, lymphoma, and metastases are the differential diagnosis of the tubercular ulcer of the oral cavity [5].

#### **Management:**

Therapeutic management of oral tuberculosis follows national or WHO protocols. It consists of a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase with isoniazid and rifampicin. Local care may include antiseptics, mouth rinses, and pain management. Because tuberculosis is a notifiable disease in most countries, proper isolation and mandatory reporting are also required to prevent transmission [6].

### **3. Viral Infections**

#### **3.1. Herpesvirus Infections**

The Herpesviridae group includes over 80 types of viruses, 8 of which have humans as their natural host. Among these human herpesviruses, the most frequently responsible for oral infections are herpes simplex virus type 1 (HSV-1), type 2 (HSV-2), as well as varicella and varicella zoster viruses (VZV) [7] [8].

Herpesviruses cause a primary infection, then remain in a latent state in the host's cells throughout their life. During this latent phase, the virus can reactivate, leading to recurrent infection, either symptomatic or asymptomatic; which translates into mucocutaneous infections [1].

## HSV-1 and HSV-2

- **Description:**

HSV-1 and HSV-2 viruses are transmitted from a person to another by direct contact with saliva or genital secretions, often being excreted by asymptomatic carriers; with HSV-1 being responsible for most primary and recurrent oral infections [1] [2] [9].

- **Clinical manifestations:**

Primary HSV infection affect children from 1 to 5 years old mostly. Symptoms include lymphadenopathies, fever, sore throat, loss of appetite, vesiculo-ulcerative lesions affection of the oral mucosa and the perioral region; and an acute marginal gingivitis [8]. The history of the disease should count a negative past of recurrent herpes infection and a positive history of direct intimate contact with a person with past infection (Figure 1) [9].



**Figure 1.** Vesiculo-ulcerative lesions in the oral mucosa and on the labial commissure with acute marginal gingivitis.

After the primary infection, HSV may persist in a latent state in the trigeminal ganglion and later reactivate as herpes simplex labialis, by internal and external triggers such as stress, fatigue, fever, menstruation, immunosuppression, and exposure to heat, cold, or sunlight [10]. The latter manifests as groups of lesions that evolve from red papules and vesicles to erosive ulcerations, mainly localized on the labial tissue and vermilion (Figure 2) [2]. Recurrence of intra-oral stomatitis caused by the HSV is also possible yet rare, it can lead to the formation of vesicles followed by erosions on keratinized surfaces [2] [10].



**Figure 2.** Reactivated HSV affection as herpes simplex labialis.

- **Diagnosis:**

Diagnosis of primary HSV infection is usually straightforward when patients present with a classic clinical picture, with generalized symptoms followed by an eruption of oral vesicles, round, shallow, symmetrical ulcerations and acute marginal gingivitis. In these cases, laboratory tests are rarely required.

Differential diagnosis includes aphthous ulcers, traumatic ulcers, acute necrotizing ulcerative gingivitis, erythema multiforme and acute eruptions of vesiculo-bullous diseases.

- **Management:**

Early diagnosis and prompt initiation of antiviral therapy (e.g., acyclovir, valacyclovir, or famciclovir) within 72 hours of symptom onset are essential to reduce the severity and duration of the disease and to prevent complications. Recommended antiviral regimens include acyclovir 800 mg five times daily for 7 - 10 days, famciclovir 500 mg three times daily, or valacyclovir 1000 mg three times daily for seven days. Adjunctive treatments may include analgesics, corticosteroids, and neuropathic pain agents (e.g., gabapentin) depending on symptom severity [11].

#### **Varicella Zoster Virus (VZV)**

- **Description:**

Initial exposure to varicella-zoster virus (VZV) in a non-immunized person causes an acute illness called varicella (chickenpox), transmitted mainly via the respiratory tract or conjunctiva.

Reactivation of latent VZV in a sensory nerve ganglion, such as the trigeminal nerve, leads to the onset of herpes zoster (HZ) [7]. Risk factors for reactivation include cytotoxic treatments, immunosuppression, internal cancers and aging.

- **Clinical manifestations:**

Though varicella classically affects the skin, oral ulcerations may also occur. As a primary infection, it presents a prodrome of 2 to 4 days that may precede the appearance of a generalized, itchy rash, which spreads centripetally. Fever and malaise may also occur. Lesions progress through macular, papular, vesicular, pustular and crusted ulcerated stages with healing taking place in 2 to 3 weeks [1] [8].

In reactivated HZ, the appearance of lesions may be accompanied by fever and malaise. Vesicles rapidly rupture to form ulcerations with prominent red edges, similar to aphthae. These lesions are distributed unilaterally along the affected nerve. Paresthesia, pain and sensitivity are the first symptoms of herpes zoster, which may appear prodromally 3 to 5 days before the lesions [1].

- **Diagnosis:**

Oral herpes zoster (HZ) can be confused with recurrent intraoral herpes (RIH). However, HZ is generally distinguished by a more intense prodrome, well-defined unilateral outbreaks, a rash on the same side, and potential complications such as postherpetic neuralgia.

When herpes zoster (HZ) presents with pain and unilateral vesicles, the diag-

nosis is generally uncomplicated. Diagnostic difficulties arise during the prodromal phase, when only pain is present without the appearance of lesions [8].

### 3.2. Hand-Foot-Mouth Disease

Hand-foot-mouth disease is a moderately contagious disease caused by various Coxsackie viruses of groups A and B. It mainly affects children, but can also affect young adults, with a higher prevalence in spring and summer. It is characterized by small ulcerations in the mouth, accompanied by an erythematous rash on the skin of the hands, fingers and soles of the feet [1] [12]. Nearly three-quarters of patients also develop non-pruritic, copper-colored papules and vesicles on the dorsal and lateral surfaces of the hands and feet [8].

### 3.3. Human Papillomavirus (HPV)

- **Description:**

HPV are DNA viruses with a particular affinity for mucocutaneous tissue, causing lesions in various parts of the body, including the genitals, nasal cavity, larynx, trachea, esophagus and oral cavity [1]. They are transmitted through close vaginal, anal, or oral contact [2].

- **Clinical manifestations:**

The oral lesions typically associated with human papillomavirus are as follows:

Squamous papilloma: Cauliflower-shaped lesion with a narrow base. It is a small pink outgrowth of the oral mucosa [13].

- *Condyloma acuminatum*: it presents multiple small, soft, pale, sessile lesions with a cauliflower-like surface similar to squamous papilloma [2].
- *Verruca vulgaris*: or the common wart, is a narrow exophytic growth, wider at the base, sessile and firm. It usually occurs on the gingiva, labial mucosa, commissure, hard palate or tongue [8].
- *Focal epithelial hyperplasia (Heck's disease)*: usually appears as multiple papular or patchy, flat or convex lesions on the mucosa, especially in children. Color can vary from red to white or gray, and lesions are found exclusively on the oral mucosa [1].

- **Diagnosis:**

Diagnosis of HPV lesions is based on histopathological analysis. Characteristic features include koilocytosis, acanthosis and papillomatosis, which, in association with the clinical appearance, indicate infection [1].

- **Management:**

Benign HPV-induced oral lesions are usually treated by surgical excision (e.g., scalpel, laser, or cryotherapy), with histopathological examination to rule out dysplasia or malignancy. Recurrence is possible, especially in immunocompromised individuals. In some cases, topical agents like imiquimod or podophyllotoxin may be used for accessible lesions, although their efficacy in the oral cavity is limited. Prevention through HPV vaccination (e.g., Gardasil 9) is effective against both high-risk and low-risk HPV types and is recommended prior to exposure [14].

### 3.4. Human Immunodeficiency Virus HIV/AIDS

Nearly 50% of HIV-infected patients and up to 80% of those with AIDS develop oral lesions, mainly due to opportunistic infections [15].

Infections such as candidiasis, periodontal disease (necrotizing ulcerative gingivitis, periodontitis and linear gingival erythema), Kaposi's sarcoma—the most common oral neoplasia associated with HIV—as well as hairy leukoplakia, are considered useful early clinical signs for the screening, diagnosis and treatment of HIV/AIDS patients (**Figure 3**) [16] [17].



**Figure 3.** Necrotizing ulcerative periodontitis as a sign of HIV infection.

## 4. Fungal Infections

### 4.1. Oral Candidiasis (OC)

#### Description:

OC is the most common fungal infection of mucosal membranes caused by *Candida albicans*. This infection has many predisposing factors including malnutrition, endocrine disorders, patients who are immunocompromised, those with diabetes mellitus, or pernicious anemia; and those undergoing systemic chemotherapy or radiation to the head and neck. In addition to general conditions, xerostomia, the use of oral antibiotics, broad-spectrum antibiotics, corticosteroids, or immunosuppressives can promote the development of OC [2] [10] [12] [16].

#### Clinical manifestations:

OC can present in various forms:

- Milky white plaques (acute pseudomembranous candidiasis) on the oral mucosa (buccal mucosa, palate, and tongue). The plaques are easily wiped off, leaving a red, raw, painful surface (**Figure 4**).
- Or, as erythematous lesions that are especially common under dentures and presents as denture stomatitis [2] [16].
- Median Rhomboid Glossitis as erythematous patches of atrophic papillae located in the central area of the dorsum of the tongue [9].
- Angular cheilitis that manifests as desquamation and fissuring of surface epithelium of lip commissures (**Figure 5**) [12].

#### Diagnosis:

Diagnosis can be confirmed with oral exfoliative cytology (stained with periodic acid-Schiff or potassium hydroxide), biopsy, or culture [10].



**Figure 4.** Pseudo membranous candidiasis on the tongue.



**Figure 5.** Angular cheilitis in an edentulous patient.

Differential diagnosis includes leukoplakia, geographic tongue and squamous cell carcinoma [16].

**Management:**

The management of OC involves eliminating predisposing factors (such as poor oral hygiene, immunosuppression, or denture use) and using antifungal therapy. Topical agents like *nystatin suspension* or *clotrimazole troches* are commonly used for mild cases, while systemic antifungals such as *fluconazole* or *itraconazole* are prescribed for more severe or recurrent infections. Proper denture hygiene, discontinuation of inhaled corticosteroids (or rinsing the mouth afterward), and controlling underlying conditions like diabetes are crucial to prevent recurrence [18].

## 4.2. Histoplasmosis

**Description:**

Histoplasmosis is a systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic fungus that grows in the yeast form. This endemic infection results from

inhaling dust contaminated with droppings, particularly from infected birds or bats.

Histoplasmosis has been classified into three forms:

1) a primary acute pulmonary form that is usually asymptomatic but with flu-like symptoms; 2) a chronic pulmonary form that is usually associated with underlying pulmonary disease; and 3) the rare severe disseminated form tends to occur in the immunocompromised patient or in patients at the extremes of age [9] [19].

**Clinical manifestations:**

Oral mucosal lesions may appear as:

- A papule, a nodule, an ulcer, or a vegetation. If a single lesion is left untreated, it progresses from a firm papule to a nodule, which ulcerates and slowly enlarges.
- Or, non-healing granulomatous lesions and ulcerations as large as 2.5 cm [19]. Enlarged and firm lymphadenopathies are noted as well [9].

**Diagnosis:**

Definitive diagnosis is made by a culture of infected tissues or exudates. Biopsy of infected tissue is also recommended [9]. Differential diagnoses are carcinomas and tuberculosis [19].

**Management:**

Mild cases of histoplasmosis are mainly treated with itraconazole (200 mg once or twice daily) for several weeks to months, while amphotericin B is used for severe or immunocompromised patients followed by itraconazole for maintenance. Treatment duration varies, and managing underlying conditions is essential to prevent recurrence [20].

### 4.3. Blastomycosis

**Description:**

Blastomycosis is a rare fungal infection caused by *Blastomyces dermatitidis*. A fungus mainly found in north America, more specifically in agricultural workers. This infection is responsible of primary pulmonary affection [19].

**Clinical manifestations:**

Oral manifestations are rarely primary sites of infection, but when present they appear as nonspecific painless verrucous and nonhealing ulcer with indurated borders, often mistaken for squamous cell carcinoma [9].

**Diagnosis:**

- Diagnosis is made based on biopsy and on culturing the organism from tissue, while taking note of the agricultural background of the patient [9].

**Management:**

Like histoplasmosis, mild to moderate cases of blastomycosis are typically managed with oral itraconazole, while more severe or disseminated forms may require initial treatment with amphotericin B. Both conditions demand early diagnosis and prolonged antifungal therapy to ensure complete resolution and prevent re-

lapse [21].

## 5. Conclusion

The diversity of oral lesions of infectious origin, whether bacterial, viral or fungal, calls for a rigorous and methodical diagnostic approach. Each pathology presents clinical signs that are more or less specific, but often mimic other conditions, which complicates their identification. Thorough questioning, a detailed clinical examination and the use of complementary tests (serologies, cultures, biopsies) are essential to establish a precise diagnosis. In addition, a good knowledge of the epidemiological characteristics, risk factors and oral manifestations of the disease will help to guide the clinician. Finally, early recognition of these infections is essential for appropriate management and to prevent complications, especially in high-risk populations such as immunocompromised individuals.

## Conflicts of Interest

The authors declare no conflicts of interest.

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