Viral infection

Viruses

are among the simplest and smallest microorganisms that infect humans. They consist of a single or double strand of DNA or RNA surrounded by a protein coat termed a capsid. The core virion is the viral component responsible for infection. A virus is an obligate parasite, because it must enter a host cell of a higher life form to replicate and undertake macromolecular synthesis.

LATENCY: A prolonged stage of some viral infections in which the viral core is integrated within cellular components, but its presence is not detectable clinically or with the use of laboratory methods.

Viral latency is considered to play an important role in carcinogenesis, acting as a predisposing cofactor necessary for the development of a large array of neoplasms. Latency is considered the reason for long delays in the onset of symptoms of patients infected with the human immunodeficiency virus 1 (HIV-1).

The three most commonly encountered families of viruses within the oral cavity are

(1) herpes virus,

(2) coxsackie virus, and

(3) papova virus.

HERPES VIRUSES

The herpes family of viruses consists of the following:

- **Herpes simplex virus 1 (HSV-1)**
- **Herpes simplex virus 2 (HSV-2)**
- **Varicella-zoster virus (VZV)**
- **Epstein-Barr virus (EBV)**
- **Cytomegalovirus (CMV)**

Of the herpesvirus family, HSV-1, HSV-2, and VZV are neurotropic and EBV, CMV, are lymphotropic. All herpes viruses are capable of entering and replicating in epithelial cells, and some have been associated with malignancies. EBV is also associated with epithelial and lymphoid malignancies. HHV-8 is highly associated with the malignant endothelial cells of Kaposi sarcoma

Herpes Simplex Virus

The core of HSV consists of a single strand of DNA. The chromatid contains more than 80 genes that are divided into three groups according to their function during replication. The virus is lytic to human epithelial cells and latent in neural tissue. Replication occurs primarily in epithelial cells, resulting in cell death and the release of up to 200,000 virions.

- **CLINICAL FEATURES**

HSV usually enters the body through breaks in the skin, although considerable evidence suggests that it can penetrate intact mucous membranes. HSV-1 occurs primarily in lesions located above the waist, and HSV-2 occurs primarily in lesions below the waist. In approximately 10% of the cases, HSV-2 can be found in oral lesions and HSV-1 can be found in genital lesion.

Patients infected with HSV-1 or HSV-2 experience an initial primary infection followed by a state of latency.

Most cases of initial (primary) herpes infection do not produce clinical lesions and have minimal clinical symptoms. Because the virus is neurotropic, it infects the peripheral nerves and migrates to a regional ganglion where it remains dormant (latent).

In this location it is undetected by the immune system, protected from therapeutic agents, and undiagnosed until activated. Activation results in migration along the nerve axon to surface epithelial cells. This migration can be triggered by a number of factors that may include emotional stress, trauma, cold, sunlight, gastric upset, fever, menstrual cycle, and any number of other factors that result in suppression of the immune system.

Whether patients have primary or secondary occurrences, the incubation period before the emergence of visible lesions ranges between 1 and 26 days; however, it is most commonly 7 to 8 days. Patients usually notice altered sensation in the affected tissue, usually characterized by fullness or a lack of tactile or sensory perception. At this stage and during the vesicular stage that follows, the patient's saliva and genital secretions are highly contagious.

ACUTE PRIMARY HERPETIC GINGIVOSTOMATITIS:

An uncommon clinical presentation of an initial herpes simplex infection in which multiple shallow ulcers are present throughout both the keratinized and gland-bearing intraoral surfaces; accompanied by systemic symptoms of fever, lymphadenopathy, and myalgia. These infections usually occur in young children, although they also occur in adults. The initial oral infection can vary and is termed acute primary herpetic gingivostomatitis.

Mild forms exhibit multiple small, punctate, shallow ulcers involving both keratinizing and nonkeratinizing oral mucosal surfaces. The ulcers may be confined to the gingiva, or they may involve various sites from the lips and perioral skin to the nasopharynx .

Severe forms may present as large, diffuse, whitish ulcers that exhibit scalloped borders and erythematous halos. These lesions lack the characteristic distinct individual punctate appearance of lesions seen in the milder form.The different appearance results from the coalescence of many small ulcers into single, large superficial ulcers.

In both the mild and severe forms of primary herpetic gingivostomatitis, the patient experiences fever and lymphadenopathy that lasts from 2 to 10 days. Muscle soreness (myalgia) and inability to masticate and swallow food are common problems. If patients are healthy, the signs and symptoms may only last from 2 to 4 days.

In immunocompromised patients a prolonged form of acute primary herpetic gingivostomatitis may develop.

Commonly, these patients are receiving chemotherapy for a malignancy, are organ transplant recipients, or have a congenital or acquired immunodeficiency syndrome

(AIDS).

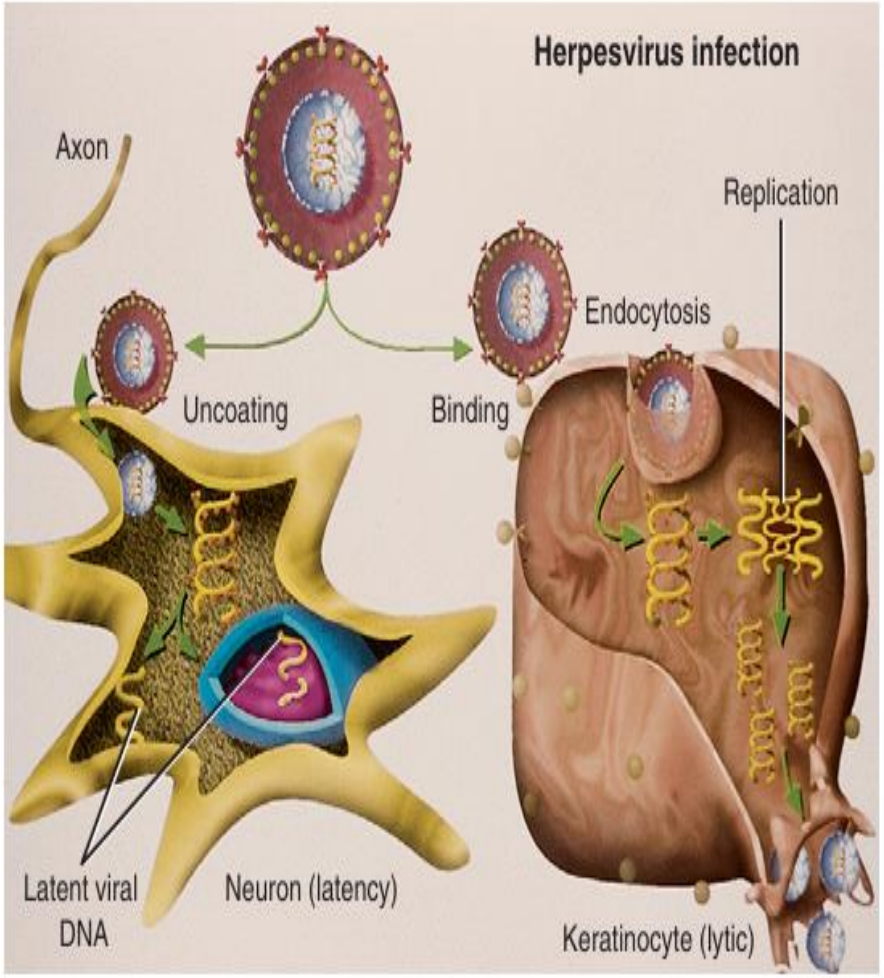


FIGURE 7-2

Two basic types of herpes simplex infection. Lytic infections *(right)* commonly occur after endocytosis of herpesvirus into keratinocyte. Replication and reassembly ensues that overwhelms host cell and causes it to burst, which releases large numbers of viruses. Latent infections *(left)* commonly occur in the cell body of neurons, where viral DNA remains dormant within the cytoplasm or nucleus until activated to replicate and migrate along a neural axis to an epithelial surface.

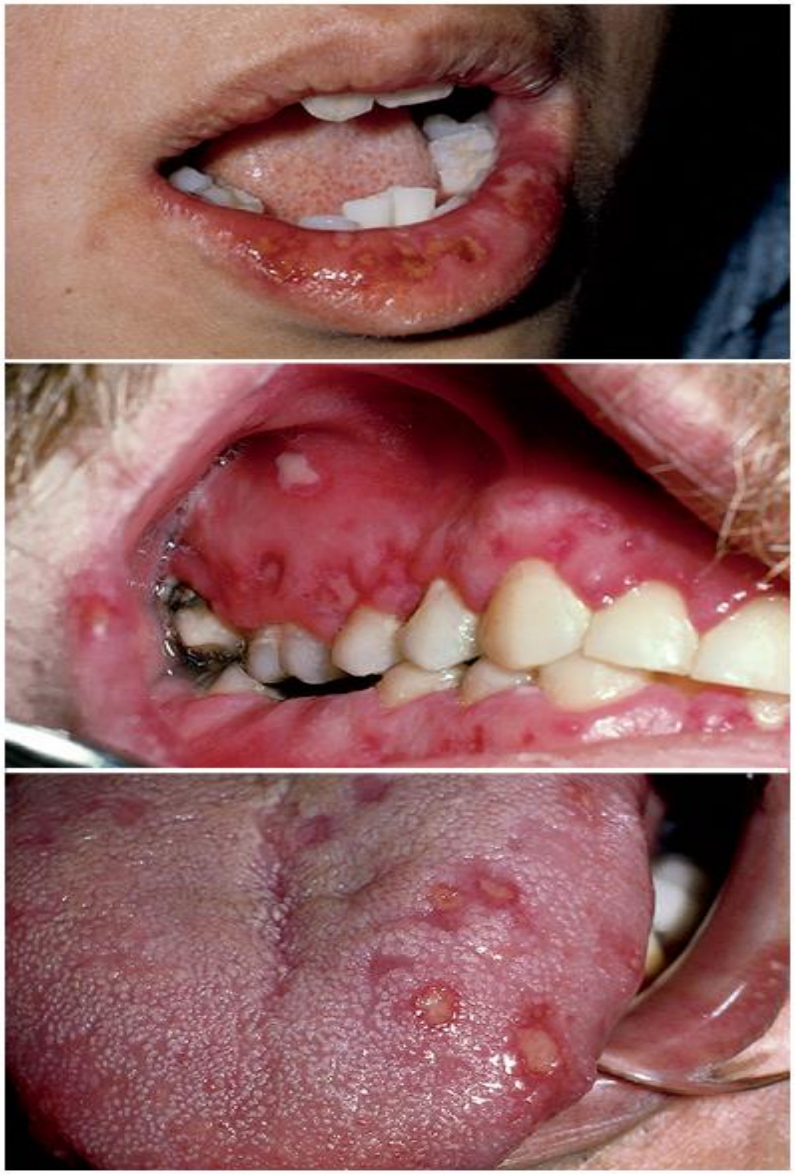


FIGURE 7-3

Acute primary herpetic gingivostomatitis. Multiple shallow punctate lesions on both keratinizing and gland-bearing mucosa. **A,** Lower lip; **B,** gingiva; and **C,** tongue.

Secondary Oral Herpes Simplex

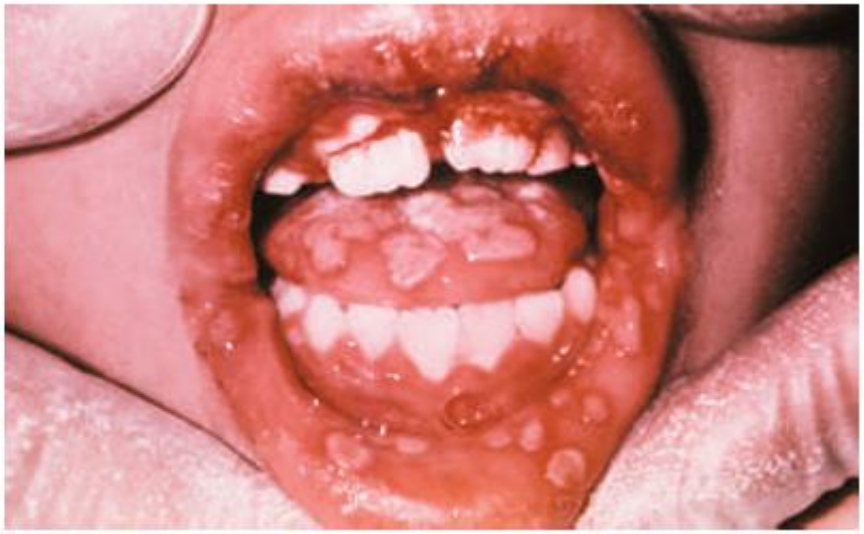
RECURRENT ORAL HERPES SIMPLEX.

The two main clinical types of recurrent oral herpes simplex infections based on the location of the lesions are:

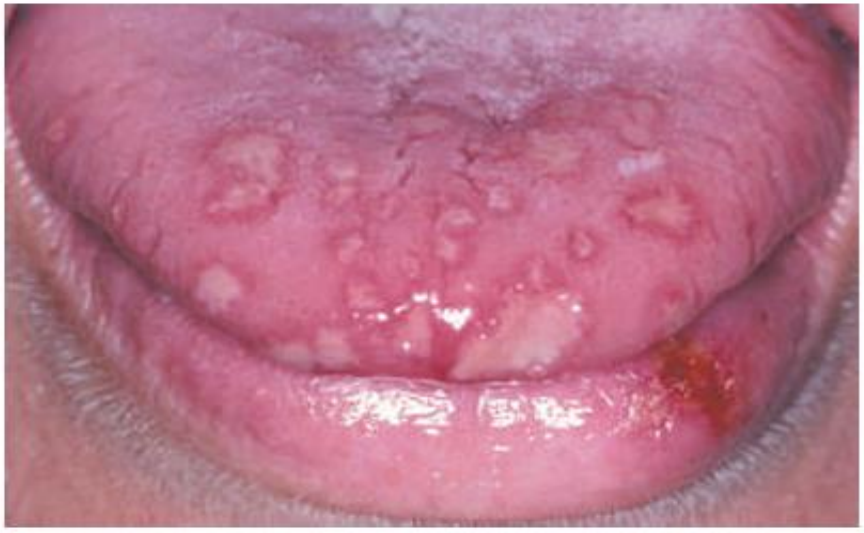
(1) recurrent herpes labialis and

(2) recurrent intraoral herpes.

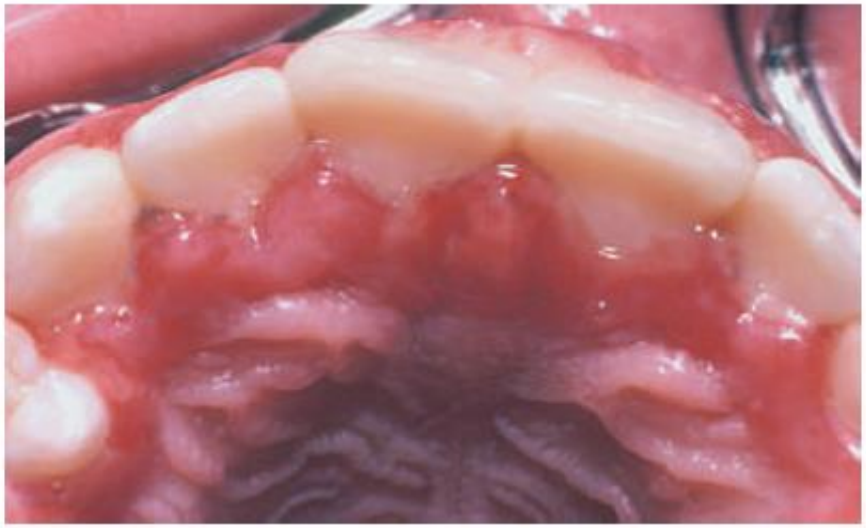
Recurrent herpes labialis affects the lips, whereas recurrent intraoral herpes involves the palate or maxillary gingiva. Both are commonly associated with recent dental treatment and present as a cluster of small vesicular or punctate lesions.The clinical appearance of the lesions found in the two types differs. Because the labial lesions often involve dry mucosa or skin, they will form identifiable fluid-filled vesicles that rupture, ulcerate, and resolve as crusted brownish lesions. Intraoral lesions are found on the wet and fragile mucous membranes and seldom form a clinically visible vesicle. Lesions are punctate with red or white bases that slowly disappear .



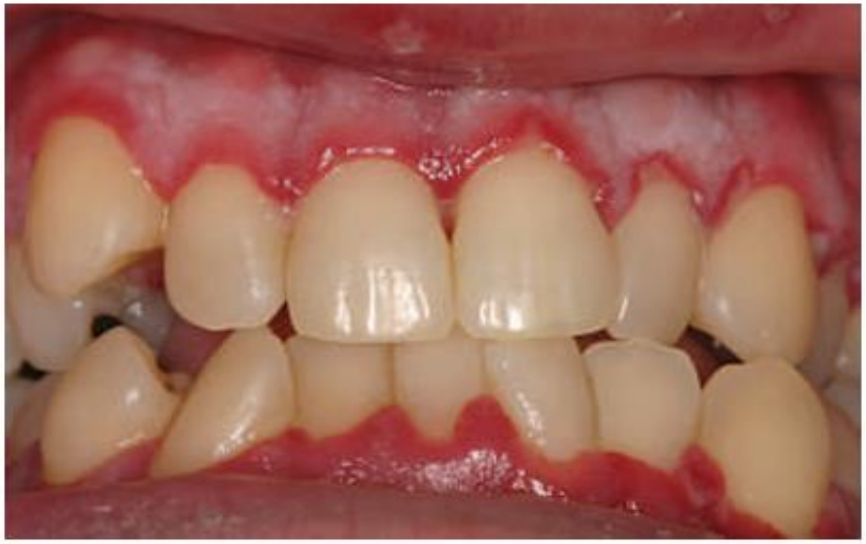
• **Fig. 7-1 Acute Herpetic Gingivostomatitis.** Widespread yellowish mucosal ulcerations. (Courtesy of Dr. David Johnsen.)



• **Fig. 7-2 Acute Herpetic Gingivostomatitis.** Numerous coalescing, irregular, and yellowish ulcerations of the dorsal surface of the tongue.



• **Fig. 7-3 Acute Herpetic Gingivostomatitis.** Painful, enlarged, and erythematous palatal gingiva.



• **Fig. 7-4 Acute Herpetic Gingivostomatitis.** Painful, enlarged, and erythematous facial gingiva. Note erosions of the free gingival margin. (Courtesy of Dr. Gina Liford.)

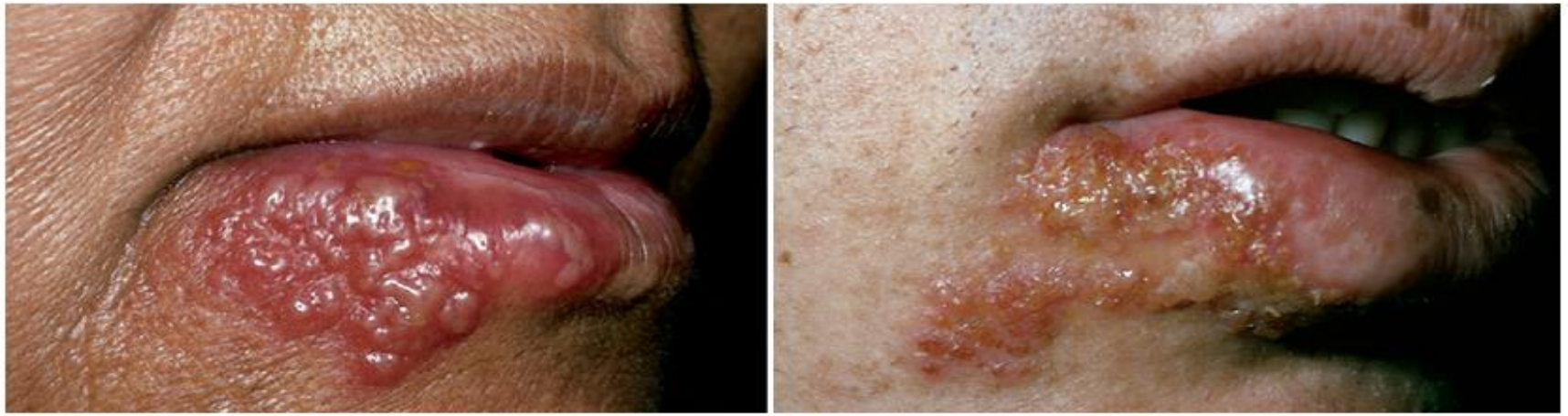


FIGURE 7-4
Recurrent herpes labialis. A, Early stages consisting of fluid-filled viral vesicles. **B,** Late stage demonstrating brownish crusted lesions.

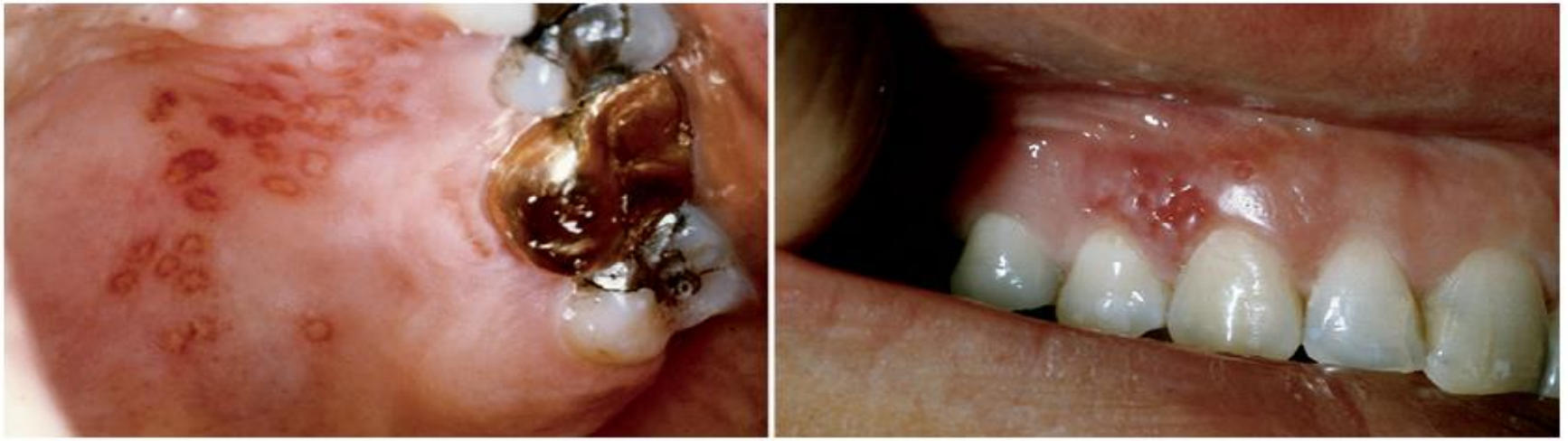


FIGURE 7-5
Recurrent intraoral herpes. A, Common intraoral site on posterior palate over greater palatine foramina. **B,** Occasionally encountered gingival lesions.

RECURRENT HERPES LABIALIS:

Episodic occurrences of a cluster of vesicles and shallow ulcers localized to the lateral aspects of the lips in patients with latent herpes simplex infections; viruses dormant in ganglia that innervate the lips are triggered by a variety of internal and external factors. It is commonly termed a cold sore, because it often occurs after an upper respiratory viral infection. Reactivation of a latent HSV residing in the trigeminal ganglion can be triggered by prolonged exposure to sunlight, trauma and manipulation of the lips, fever, immunosuppression, menstruation, and periods of stress and anxiety.

few definitive treatments are presently available for herpes labialis. Empiric treatments include keeping the lesions soft and covered with an ointment to prevent further spreading and secondary bacterial infection. Although patients experience significant discomfort in the area, they do not exhibit elevated temperatures and seldom exhibit lymphadenopathy.

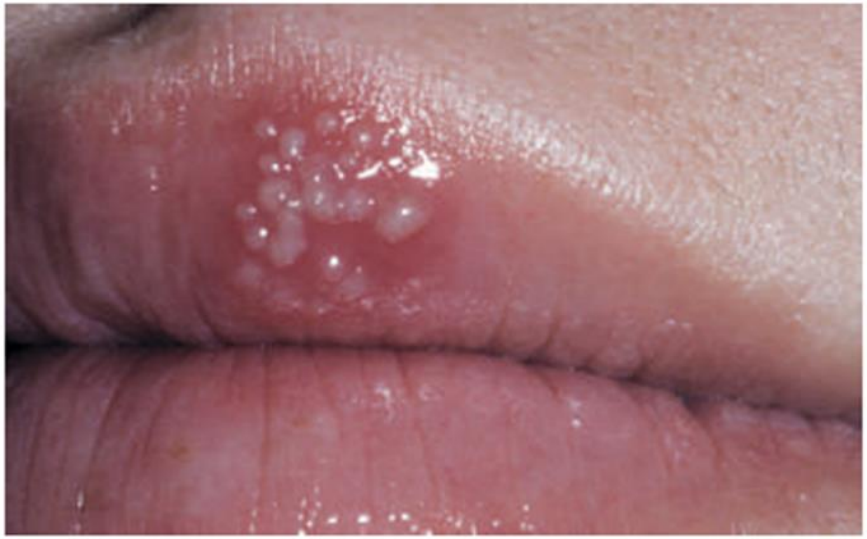
RECURRENT INTRAORAL HERPES:

Episodic occurrences of an intraoral cluster of symptomatic shallow punctate ulcers, commonly but not exclusively on the mucosa overlying the greater palatine foramina and often occurs after dental treatment or injection of a local anesthetic into the area.

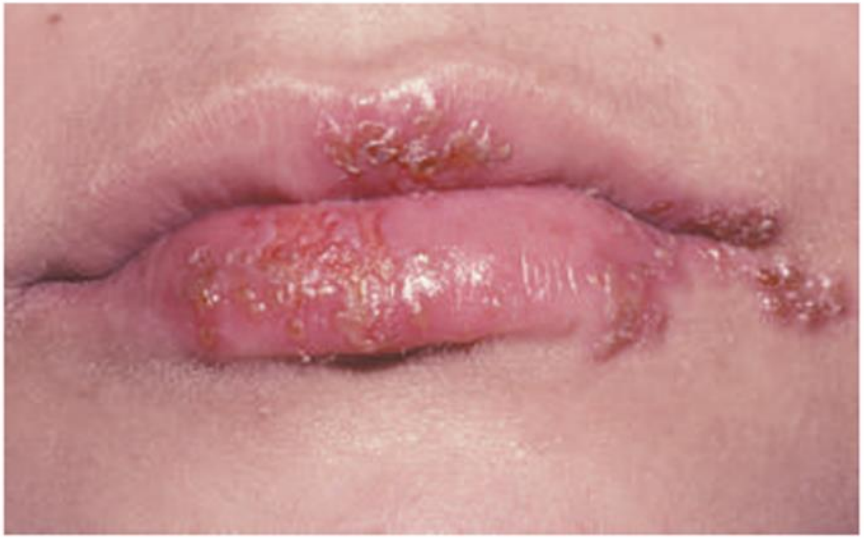
The most common site is the hard palate over the greater palatine foramina. Other intraoral sites include the free and attached gingiva, especially the maxillary gingiva, and the lateral aspects of the tongue.

In patients who are immunosuppressed, the intraoral recurrent lesions are often substantially larger, deeper, and accompanied by fever and lymphadenopathy.

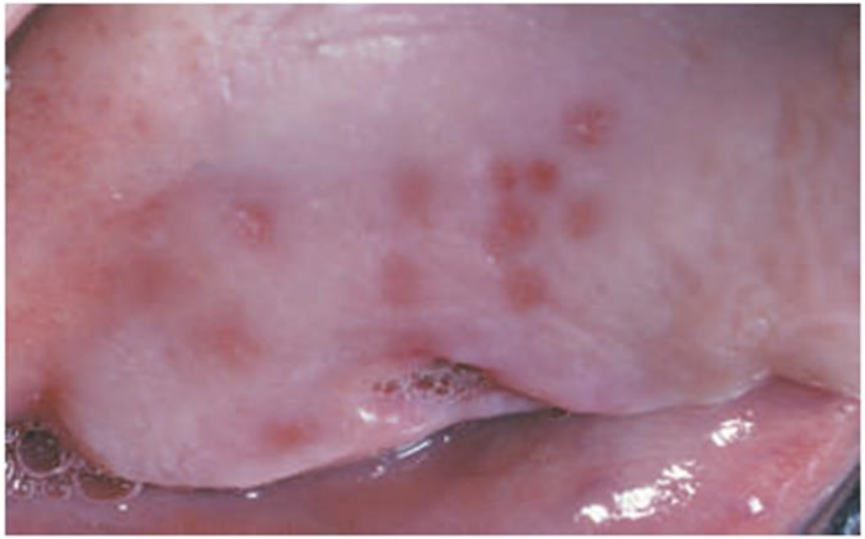
No known treatment exists for recurrent intraoral herpes simplex.



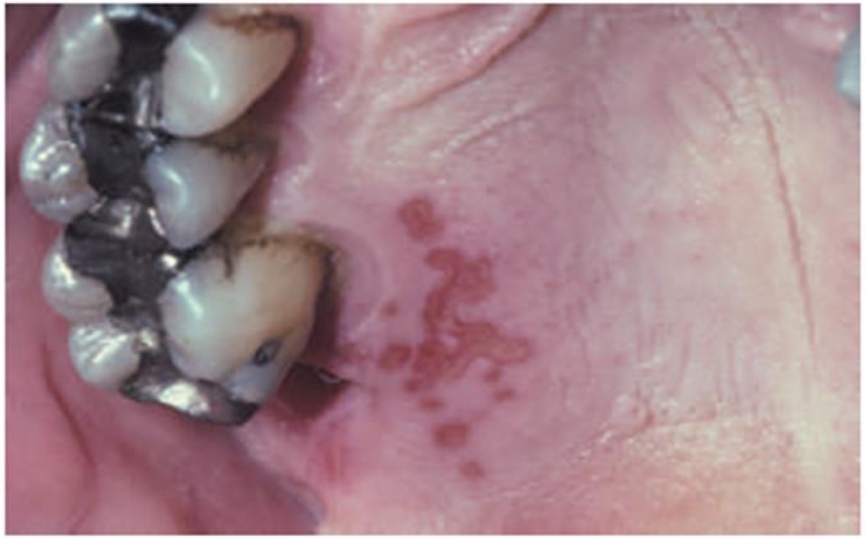
• **Fig. 7-5 Herpes Labialis.** Multiple fluid-filled vesicles on the lip vermilion.



• **Fig. 7-6 Herpes Labialis.** Multiple sites of recurrent herpetic infection secondary to spread of viral fluid over cracked lips.



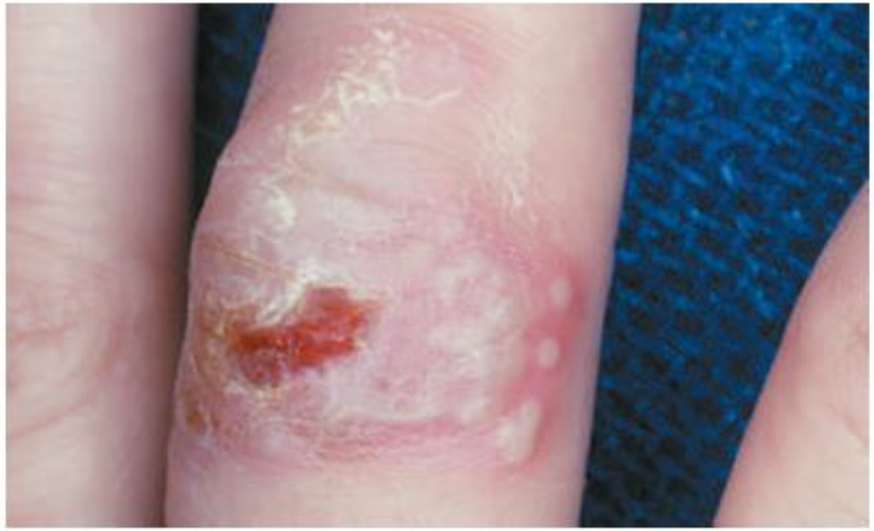
• **Fig. 7-7 Intraoral Recurrent Herpetic Infection.** Early lesions exhibiting as multiple erythematous macules on the hard palate. Lesions appeared a few days after extraction of a tooth.



• **Fig. 7-8 Intraoral Recurrent Herpetic Infection.** Multiple coalescing ulcerations on the hard palate.

HERPETIC WHITLOW:

A primary or secondary herpes simplex infection localized to the hands or fingers and acquired by direct contact with an active lesion. Before the time when gloves were required for all clinical procedures, herpetic whitlow was a common occurrence on the hands of health care workers. In addition to infection by direct contact with oral lesions, herpetic whitlow can occur by autoinoculation from oral or genital lesions. Lesions are usually vesicular or pustular and surrounded by a wide zone of erythema. Throbbing pain, high fever, and regional lymphadenopathy of the arm or axilla are common. The symptoms are often of sufficient severity to incapacitate the patient for 1 or more weeks. Restricting contact with others is usually advisable, because lesions on the fingers are highly contagious. Immediate treatment with oral famciclovir has been shown to be effective in reducing the symptoms and duration of the lesions.



• **Fig. 7-9 Herpetic Whitlow.** Recurrent herpetic infection of the finger.

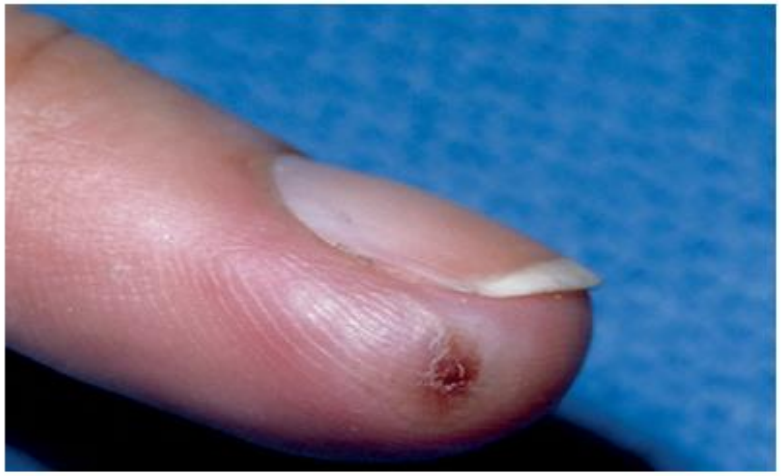


FIGURE 7-6
Herpetic whitlow. Painful, inflamed herpetic lesion on finger.

HISTOPATHOLOGY

During the prodromic stage before vesicle formation,the infected individual keratinocytes initially accumulate fluid and swell, giving the cytoplasm a vacuolated appearance termed ballooning degeneration. Some cells exhibit nuclear changes consisting of margination of the chromatin and the presence of large eosinophilic intranuclear inclusion bodies; many will undergo syncytial changes resulting in multinucleated epithelial giant cells .

Clinically visible papules and vesicles develop when the accumulation of intracellular and intercellular edema results in lysis of a number of adjacent cells. In addition to the numerous ballooned cells and virus particles, multinucleated epithelial giant cells are present within the fluid . Although the content of most mucosal vesicles will clinically appear as a clear transudate, purulent exudate is occasionally present on the skin and pustules will develop. Pustules or vesicles are seldom seen on mucosal surfaces, because the epithelial layer is fragile and readily ruptures, leaving a punctate and shallow erosive lesion.

Microscopic examination of the contents of an intact vesicle reveals a fluid-containing fibrin, ballooning degenerated and multinucleated epithelial cells, and some acute inflammatory cells . The base of the lesion may exhibit an intact basal cell layer or, more commonly, a thin inflamed zone of connective or granulation tissue (or both).

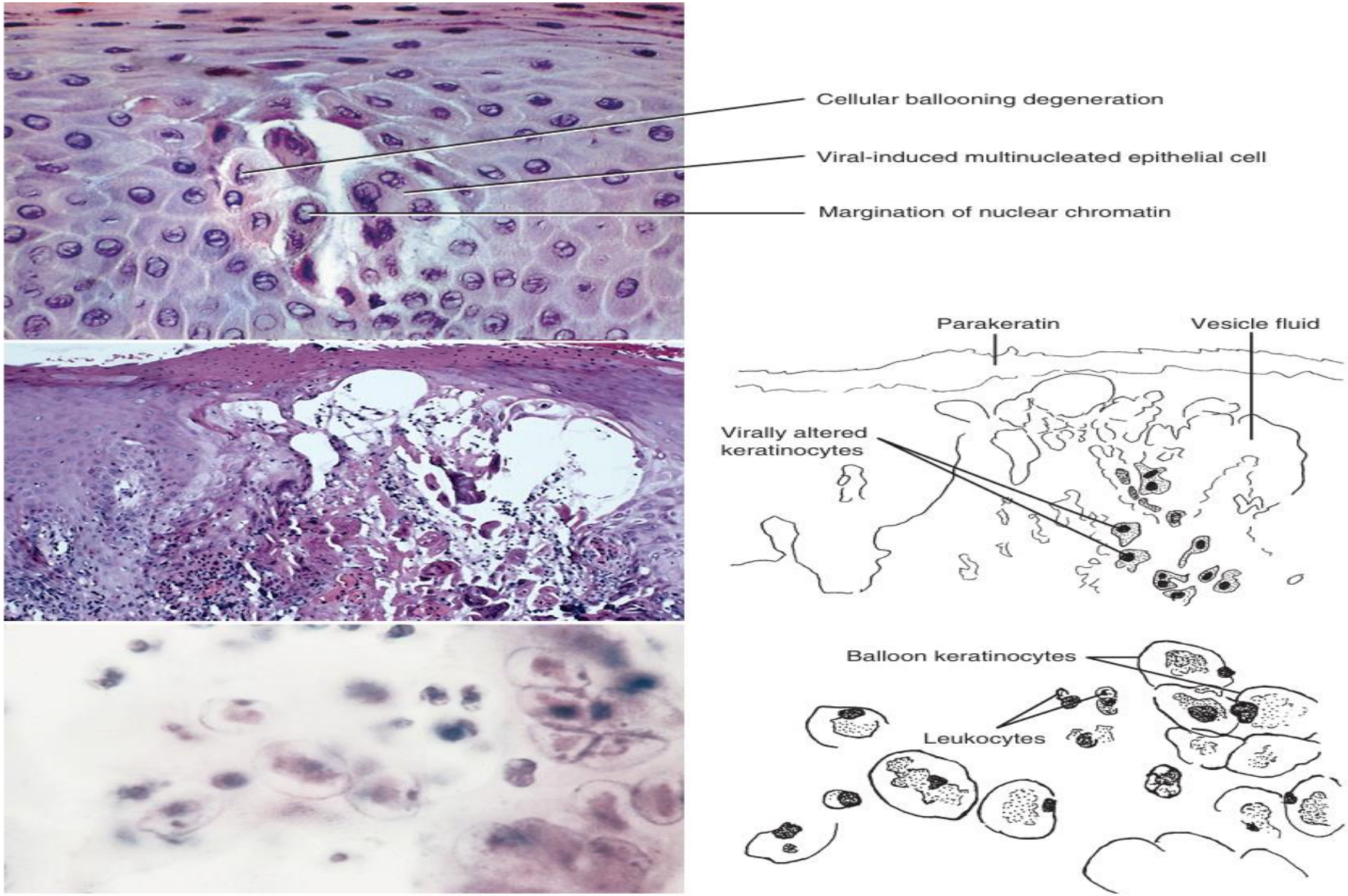
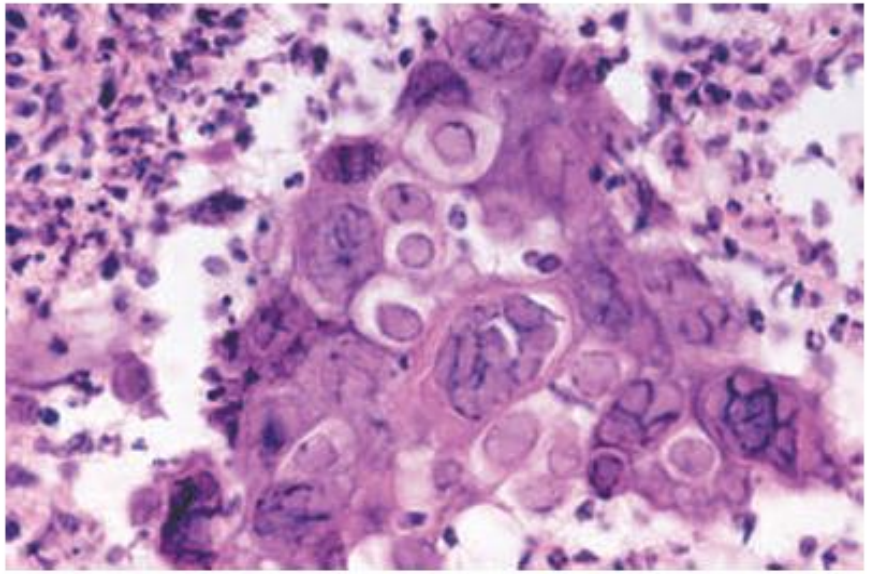
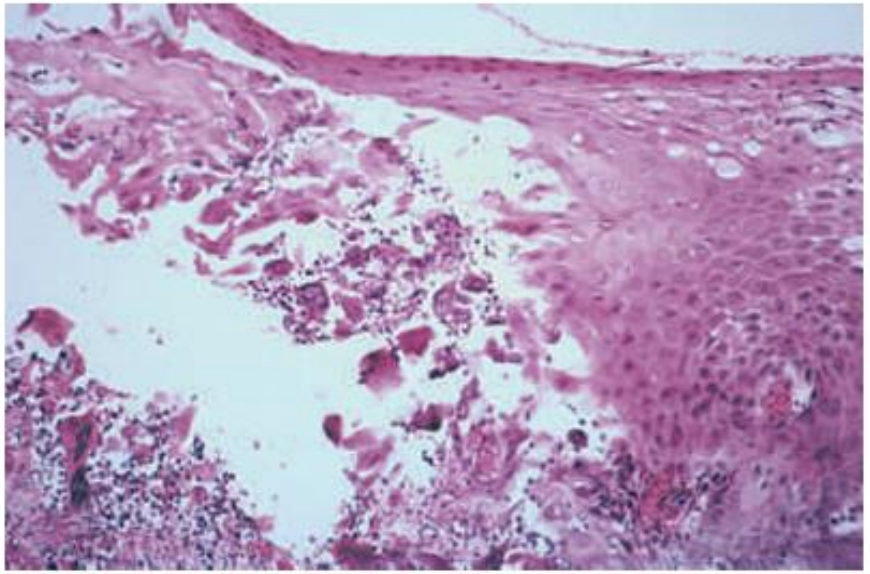


FIGURE 7-7

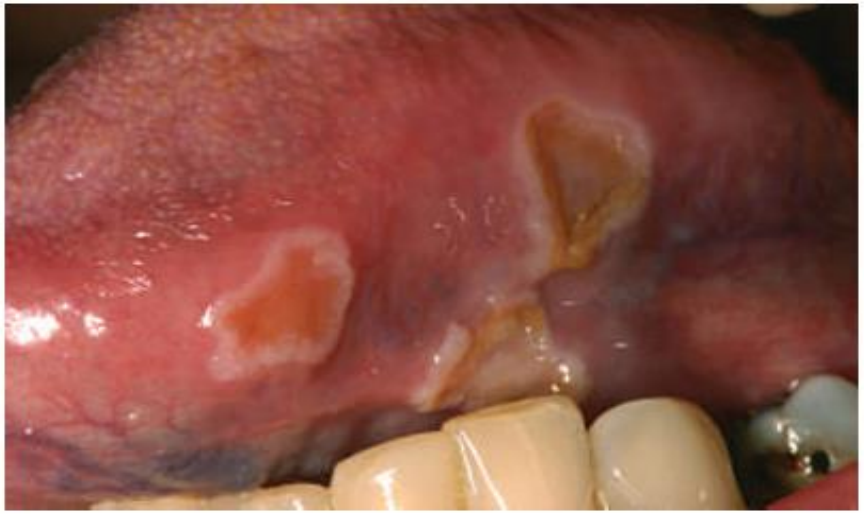
Herpes simplex. Early and late stages of intraepithelial viral vesicle formation. **A,** Incipient vesicle formation early in prodromal stage before presence of a clinically visible vesicle exhibiting ballooning degeneration, nuclear margination, and multinucleation of the spinous layer of keratinocytes (viral cytopathic changes). **B,** Fully developed but intact intraepithelial viral vesicle that contains fluid, virally altered keratinocytes, large numbers of viruses, and necrotic debris. **C,** Photomicrograph of cytologic smear of viral vesicle contents that reveals enlarged and ballooned keratinocytes and associated leukocytes.



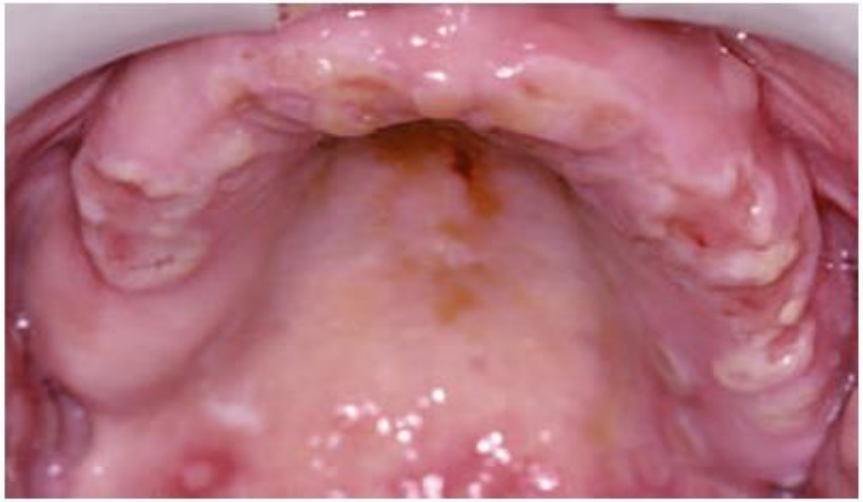
• **Fig. 7-12 Herpes Simplex.** Altered epithelial cells exhibiting ballooning degeneration, margination of chromatin, and multinucleation.



• **Fig. 7-13 Herpes Simplex.** Intraepithelial vesicle demonstrating acantholytic and virally altered epithelial cells.



• **Fig. 7-10 Chronic Herpetic Infection.** Numerous mucosal erosions, each of which is surrounded by a slightly raised, yellow-white border, in a patient receiving systemic corticosteroid therapy for systemic sclerosis and rheumatoid arthritis.



• **Fig. 7-11 Chronic Herpetic Infection.** Numerous shallow herpetic erosions with raised, yellow and circinate borders on the maxillary alveolar ridge in an immunocompromised patient.

DIAGNOSIS

Diagnosis of a herpes simplex infection is usually based on the clinical findings. When the diagnosis is not readily apparent, one or more of the following laboratory procedures may be useful.

1) Biopsy. Ideally, an excisional biopsy of an intact vesicle is obtained. The viral cytopathic effects (CPE), including cellular ballooning degeneration, multi-nu cleated epithelial cells, and nuclear inclusions, can be observed in routine hematoxylin and eosin (H&E) stained tissue slides.

2) Cytologic smear. The clinician obtains the specimen by puncturing an intact vesicle and expressing the vesicular (blister) fluid onto a glass slide or by mechanically removing cells from the base or edges of a lesion and smearing them onto microscopic slides. The smears are stained and examined for the CPE of the virus on the epithelial cells. The test is not specific for HSV, because similar CPE are found in the epithelium of VZV lesions.

3) Culture. The culture specimen is best obtained from intact vesicles or pustules. Contents of a needle aspiration are optimal, but a cotton swab may also be used to directly inoculate a tissue culture. The cultured cells are examined for CPE on epithelial cells. High concentrations of the virus will produce changes in the cultured cells after 24 hours; the mean time for a positive test is 1 to 3 days.

4) Fluorescent antibody. The specimen consists of smears or suspensions of cells stained with antibodies against HSV-1 and HSV-2 antigens. This method is not as sensitive as the culture method.

5) Serology. This is an indirect test in which blood samples are tested to detect antibody levels in the serum against specific viral antigens. Serology is sensitive only for primary infections, because levels of circulating antibody in recurrent disease are usually too low to be detected.

TREATMENT

Treatment of HSV infections varies with the type and location of the infection and the systemic condition of the patient(competency of the patient's immune system). When taken systemically, therapeutic antiviral agents such as acyclovir, famciclovir (penciclovir), and valacyclovir can be of help, particularly in immuno compromised patients.

Treatment of the more generalized oral lesions of primary infections is mostly palliative, using soothing oral rinses and analgesics. Antibiotics are often prescribed for the prevention of secondary infections.

Of the systemic antiviral agents available for recurrent HSV, only acyclovir and famciclovir (penciclovir) appear to have some effect. The use of topical 1%penciclovir in a cream base during early prodromal stage was shown to be slightly more effective than 5% acyclovir in reducing the healing time, viral shedding, and the duration of the painful phase.

Varicella-Zoster Virus

VZV is a member of the herpes family of viruses and shares many features with the HSV. The primary infection of VZV is known as varicella or chicken pox; the recurrent disease is termed herpes zoster or shingles. Primary infections are followed by a period of latency during which the neurotropic virus resides in the regional ganglia. Later, if the host's immune system is suppressed, the virus may emerge to produce recurrent disease along a specific dermatome.

Varicella (Chicken Pox)

Primary infection of the VZV acquired during childhood that produces a generalized symptomatic maculopapular rash of the skin, malaise, fever, and minor lesions throughout the oral cavity.

CLINICAL FEATURES

Varicella is the initial infection of VZV and is usually acquired in childhood. Unlike HSV infections, the primary infection is usually symptomatic and includes fever, headache, malaise, sore throat, and lung congestion. Over 50% of those initially affected will be children between the ages of 5 and 9. After an incubation period of approximately 2 weeks, patients develop a cutaneous hemorrhagic maculopapular rash accompanied by malaise and a low-grade fever. Lesions quickly progress to vesicles and pustules that rupture and become crusted. For approximately 1 week, new lesions will continue to appear so that a mixture of lesions at various stages of development and resolution is always present. The oral vesicles rupture early and are usually seen as small ulcers that closely resemble aphthous ulcerations. The oral lesions are not particularly painful. Occasional pustular skin lesions become secondarily infected and may heal as a small, depressed scar (pock). When acquired in adulthood the disease may be severe and progress to interstitial pneumonia.

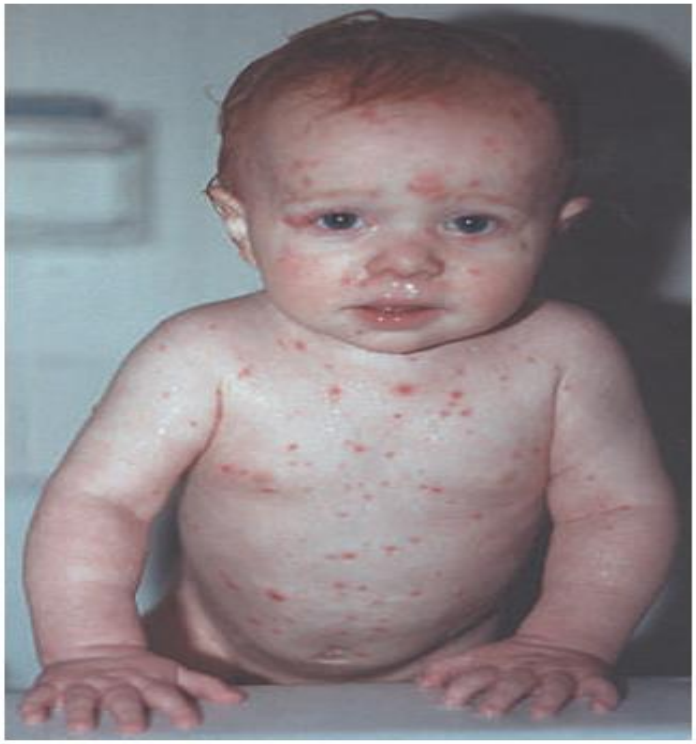
Herpes Zoster (Shingles):

A regional occurrence of VZV that appears as vesicular eruptions of the skin or mucosa in a distinctive unilateral pattern; pain persists for prolonged periods after lesions heal. Herpes zoster is the recurrent form of a varicella infection. It affects 10% to 20% of the population and can occur at any age, but it is more common in the elderly and the immunocompromised. Factors that decrease immune function, such as human immunodeficiency virus (HIV) infection, chemotherapy, malignancies, and chronic corticosteroid use, increase the risk of developing herpes zoster.

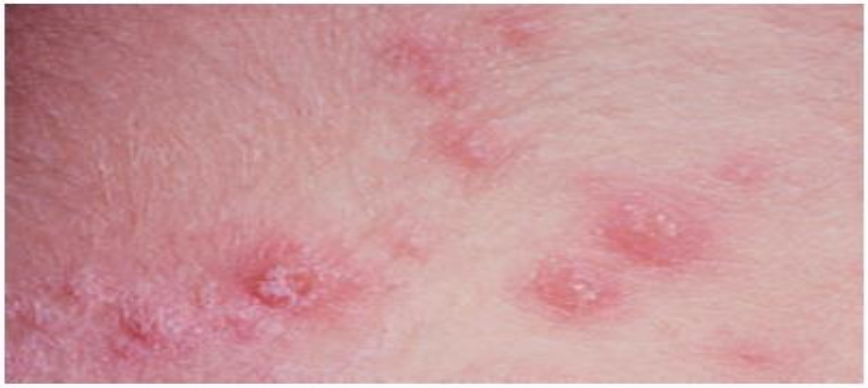
The virus is believed to infect the dorsal root ganglia during the primary infection, where it remains latent until reactivated. The frequency and severity of herpes zoster in older people appears to be the result of an age-related decline in VZV-specific T cell–mediated immunity. On the skin the predominant clinical feature is a unilateral linear vesicular rash outlining the cutaneous distribution of the affected peripheral nerves.

Coalescence of the vesicles, followed by crusting, occurs quickly. When herpes zoster involves the trigeminal nerve, unilateral facial and oral lesions may develop along the ophthalmic, maxillary, and mandibular distribution of the nerve .

Lesions on the intraoral mucosal surfaces are sharply and distinctively unilateral along the nerve distribution . The mucosal lesions develop as fragile vesicles that rupture easily and are usually seen as crateriform ulcers that may persist from 2 to 3 weeks, usually healing within 1 month. . In older patients the pain may persist for 1 month or more after the lesions have healed. This condition is termed postherpetic neuralgia and is characterized by burning and severe pain. The healed area may remain hypersensitive for months or years and can be highly debilitating. In Ramsey Hunt syndrome, patients develop a triad of conditions consisting of ipsilateral facial palsy, external auditory canal lesions, and loss of taste in the anterior two thirds of their tongue.



• **Fig. 7-14 Varicella.** Infant with diffuse erythematous and vesicular rash. (Courtesy of Dr. Sherry Parlanti.)



• **Fig. 7-15 Varicella.** Numerous vesicles with surrounding erythema and early crusting.

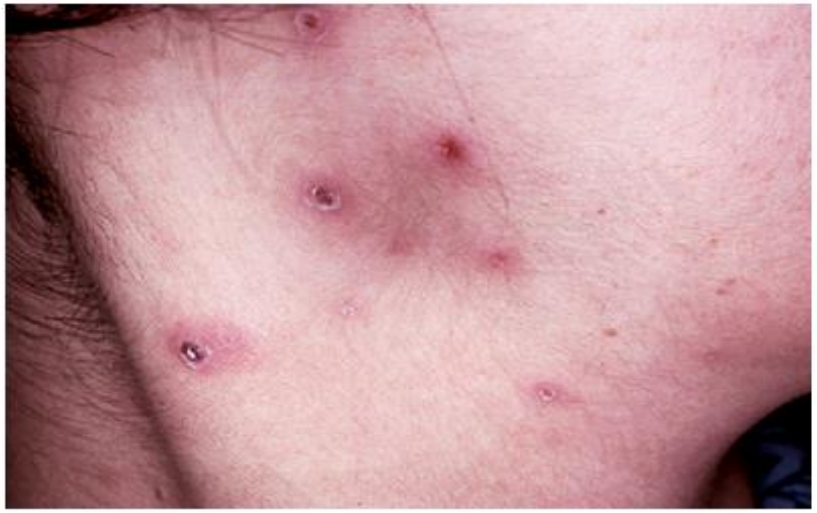
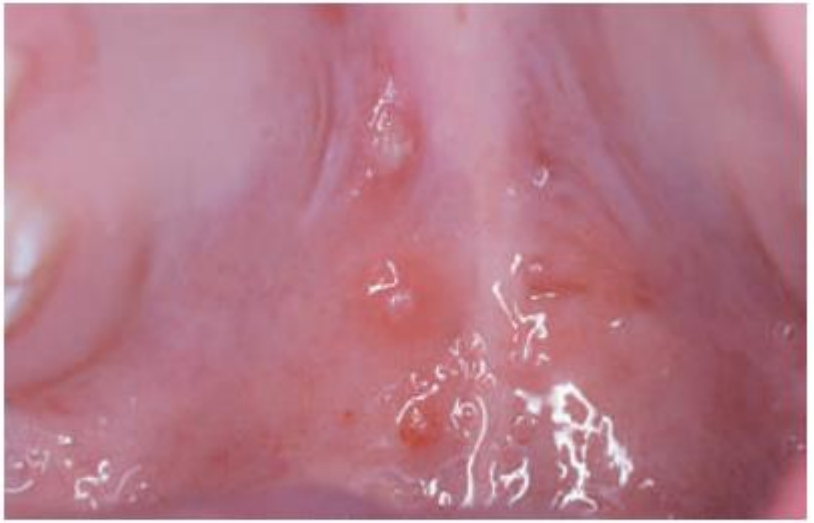


FIGURE 7-8

Varicella (chicken pox). Crusted lesions (pox) of skin of the late stage of a primary infection of the varicella-zoster virus (VZV) in a young patient.



• **Fig. 7-16 Varicella.** White opaque vesicles on the hard palate. (Courtesy of Tristan Neville.)

HISTOPATHOLOGY

The tissue changes in lesions of varicella and herpes zoster are essentially the same as in those of HSV. During the prodromal period epithelial cells containing replicating viruses exhibit cytoplasmic swelling because of intracellular edema (ballooning degeneration), margination of nuclear chromatin, and the formation of intranuclear inclusion bodies. Multinucleation of epithelial cells will also be seen when intraepithelial vesicles have formed. The postvesicular ulcer is similar to any other shallow ulcer characterized by a fibrino-purulent exudate covering a zone of granulation tissue.

DIAGNOSIS

The presence of unilateral lesions along dermatomes of the peripheral nerves is pathognomonic for herpes zoster. In varicella or herpes zoster when the classic distribution of lesions is not present, as often occurs in immunocompromised patients, and when involvement is more diffuse, one or more of the following laboratory techniques may be diagnostically helpful.

Cytologic smear. The specimen consists of fluid obtained from vesicles and smeared on slides. The presence of epithelial cells that exhibit cytopathic changes including ballooning degeneration, intranuclear inclusions, and multinucleation of epithelial cells are positive findings of a viral infection. Unfortunately,HSV infection will give a similar result.

Culture. Swabs of vesicle fluid or lesional tissue are cultured in the same manner as for HSV.

Direct immunofluorescent antibody. Microscopic examination of a sample of lesional tissue is reacted with an antibody to the VZV, labeled with fluorescein dye, and viewed with ultraviolet (UV) light.

Serology.

The most frequently used are the fluorescent antibody to VZV membrane antigen (FAMA) and the enzyme-linked immunosorbent assay (ELISA) tests that measure the level of VZV antibody circulating in the patient's blood. They are mainly used to document the presence of the virus and the severity of the infection and are most effective in primary infections of varicella when antibody levels are high.

TREATMENT

Herpes zoster is usually treated with orally administered acyclovir. Other antiviral medications include famciclovir and valacyclovir. The antiviral medications are most effective when started within 72 hours after the onset of the rash. The addition of an orally administered corticosteroid can provide modest benefits in reducing the pain of herpes zoster and the incidence of postherpetic neuralgia.

Ocular involvement in herpes zoster can lead to rare but serious complications and generally merits referral to an ophthalmologist. Patients with postherpetic neuralgia may require narcotics for adequate pain control.

Tricyclic antidepressants or anticonvulsants, often given in low doses, may help to control neuropathic pain. Capsaicin, lidocaine patches, and nerve blocks can be used in selected patients

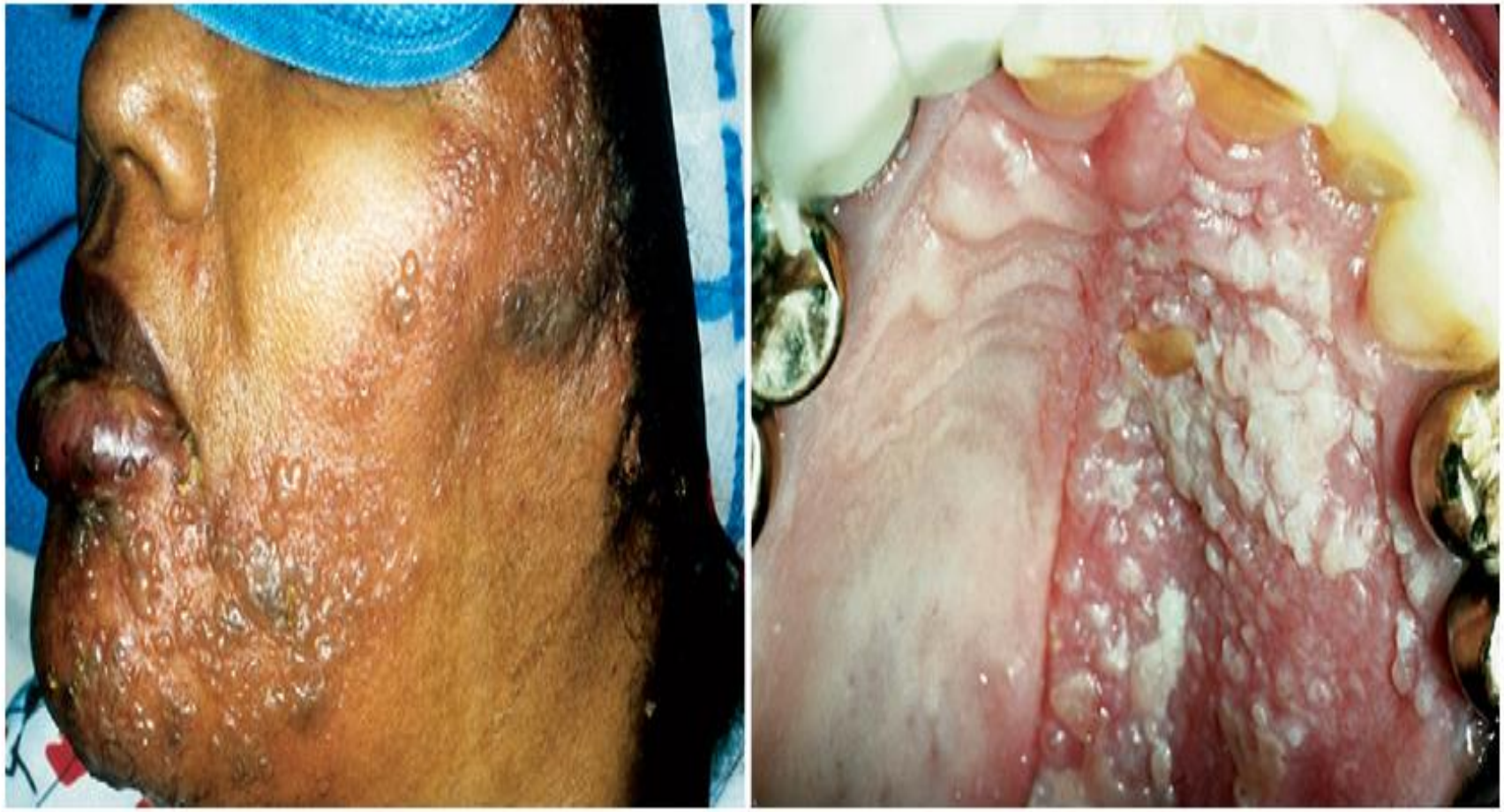


FIGURE 7-9

Herpes zoster (shingles). A, Multiple unilateral painful vesicles follow the mandibular branch of the trigeminal nerve. **B,** Multiple vesicles on an erythematous base with a unilateral, sharp line of demarcation that corresponds to the nerve distribution of the palate.

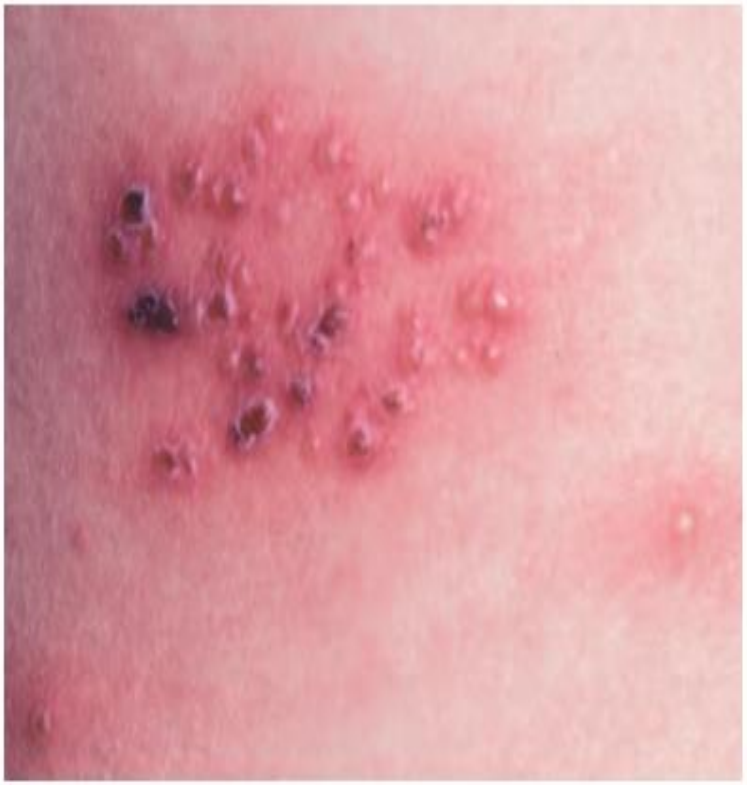


Fig. 7-17 **Herpes zoster.** Cluster of vesicles with surrounding erythema of the skin.

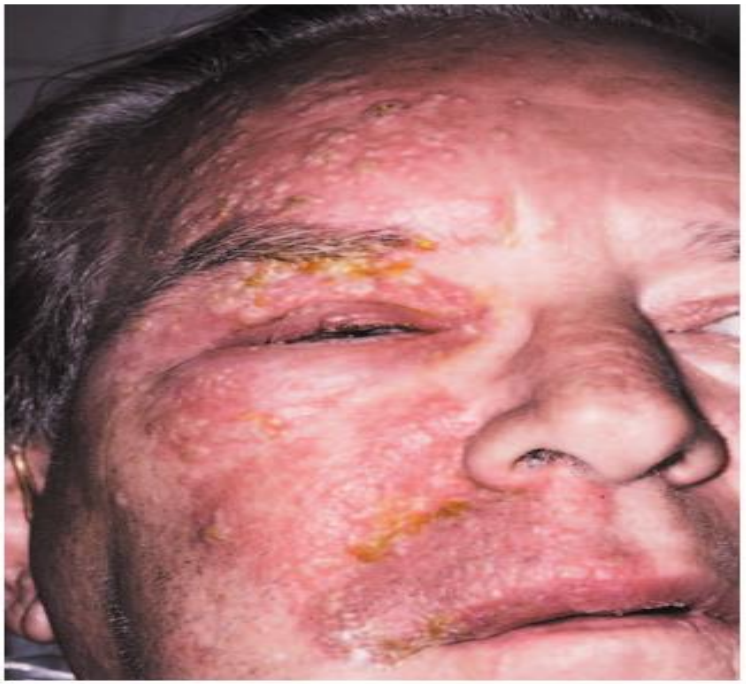


Fig. 7-18 **Herpes zoster.** Numerous crusting facial vesicles that extend to the midline.

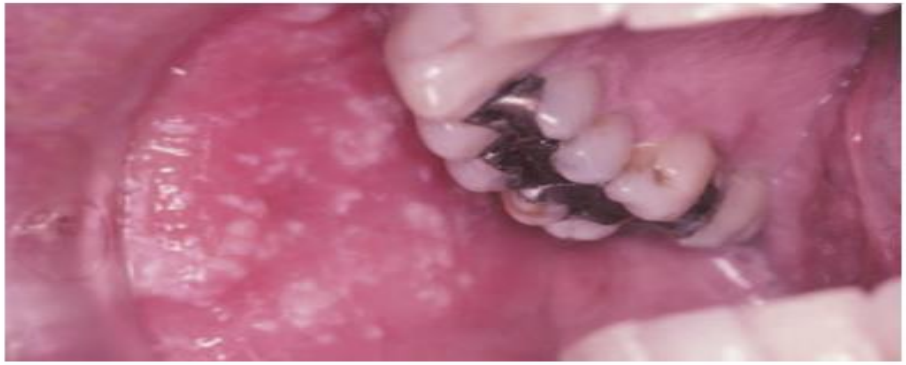


Fig. 7-19 **Herpes zoster.** Numerous white opaque vesicles on the right buccal mucosa of the same patient depicted in Fig. 7-18.

COXSACKIE VIRUSES

The coxsackie viruses are part of the picorna-virus family, one of the largest and most prevalent of the RNA viruses. This family also includes the rhinoviruses of the common cold.

Coxsackie viruses have a wide range of tissues for which they exhibit tropism. Included among the tissues is the epithelium of the oropharynx. There are two types coxsackie-virus A and coxsackie-virus B, each with multiple subtypes (A1 to A23 and B1 to B6). The diseases affecting the oral region are of the coxsackie-virus A group. The major ones are herpangina (most subtypes); hand, foot, and mouth disease (A9, A16); and lymphonodular pharyngitis (A10).

HERPANGINA:

A nontreatable mild infection caused by a mixture of coxsackie-virus A localized to the posterior soft palate and nasopharynx that consist of multiple small shallow ulcers resembling a herpetic infection that lasts for approximately 1 week. Herpangina is a misnomer because it is not caused by a herpes virus as the name implies. It is transmitted by inhalation of airborne droplets or by contacts with saliva containing coxsackievirus A. The virus can survive outside the body for 2 to 4 hours. Herpangina frequently occurs in outbreaks, particularly among school children. Nearly all of the subtypes can be isolated from oral lesions. Patients usually develop a permanent immunity to a particular member of a subgroup but not to other members.

CLINICAL FEATURES

Symptoms are usually mild and of short duration, lasting no more than 1 week. Patients complain of a sorethroat and difficulty swallowing. There may be a mild fever and some malaise. Small vesicular or punctate lesions with a white base will be present on the posterior soft palate near the uvula and anterior fauces of the tonsils . The lesions rarely appear anterior to this region. This is of particular help in distinguishing this entity from other viral diseases and herpetiform aphthous ulcers.

TREATMENT

Because the symptoms are mild and of short duration, no specific treatment is necessary.

HAND, FOOT, AND MOUTH DISEASE:

A highly contagious systemic infection of coxsackie-virus A subtypes (usually 9 and 16) of limited duration in which vesicular eruptions occur on the palms of hands, soles of feet, and mucosa of the anterior part of the mouth.

Hand, foot, and mouth disease is usually caused by subtypes 9 and 16 of coxsackie-virus A, but others have also been isolated. It is highly contagious and occurs in local outbreaks, mostly among children in the 1- to 5year age group.

CLINICAL FEATURES

During the short incubation period the patient experiences malaise, low-grade fever, nausea, and an eruption of small vesicles on an erythematous base on the palms of the hands and the feet . Within1 to 2 days oral vesicles and ulcers appear on the mucous membranes and are usually confined to the anterior part of the mouth . Lesions are uncommon in the oropharyngeal area, which differs from herpangina.

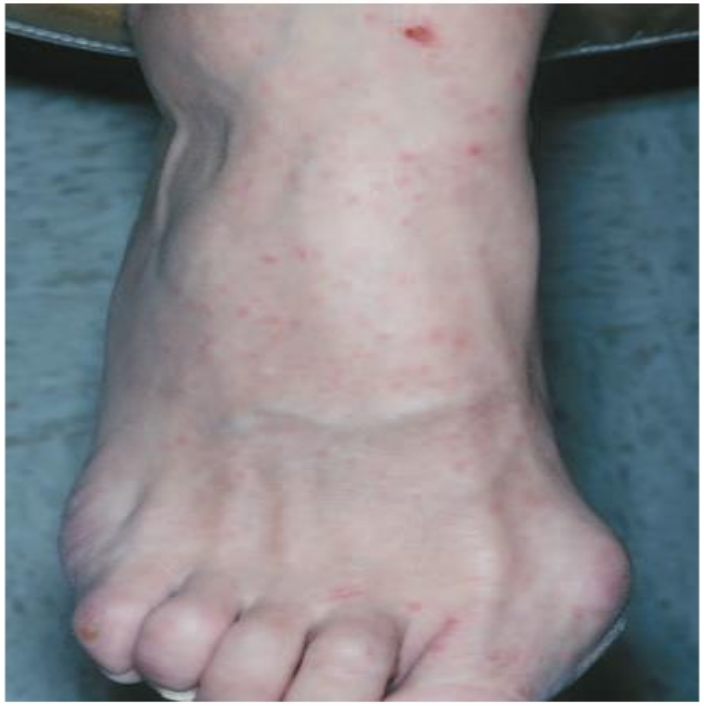


Fig. 7-25 Hand-foot-and-mouth disease. Numerous erythematous macules of the foot.

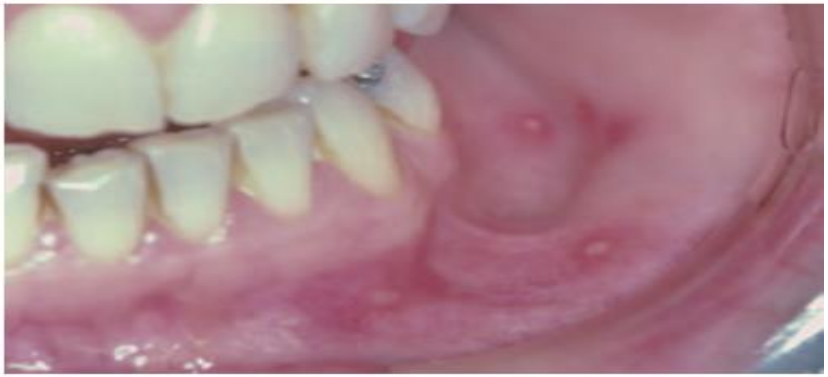


Fig. 7-26 Hand-foot-and-mouth disease. Multiple aphthouslike ulcerations of the mucobuccal fold.

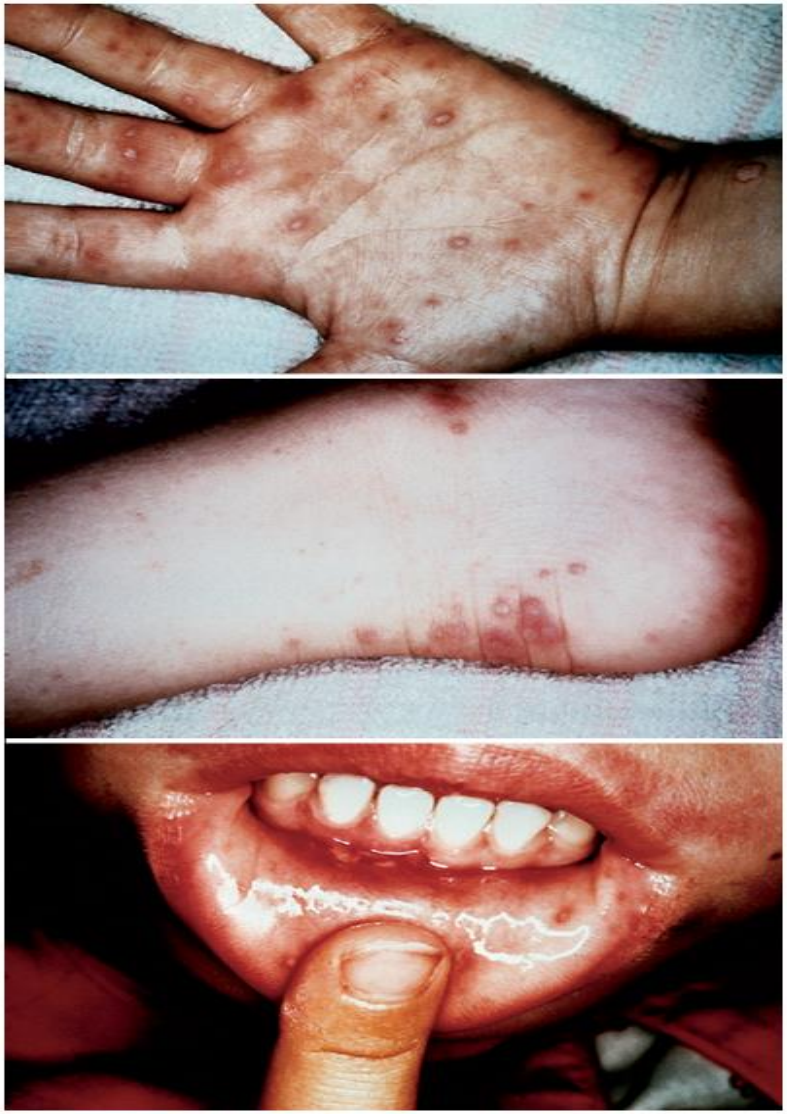


FIGURE 7-13
Hand, foot, and mouth disease. Eruption of small vesicles on the palms of the hands **(A),** feet **(B),** and lower lip **(C)** of a young patient. (Courtesy Dr. W. Goebel.)

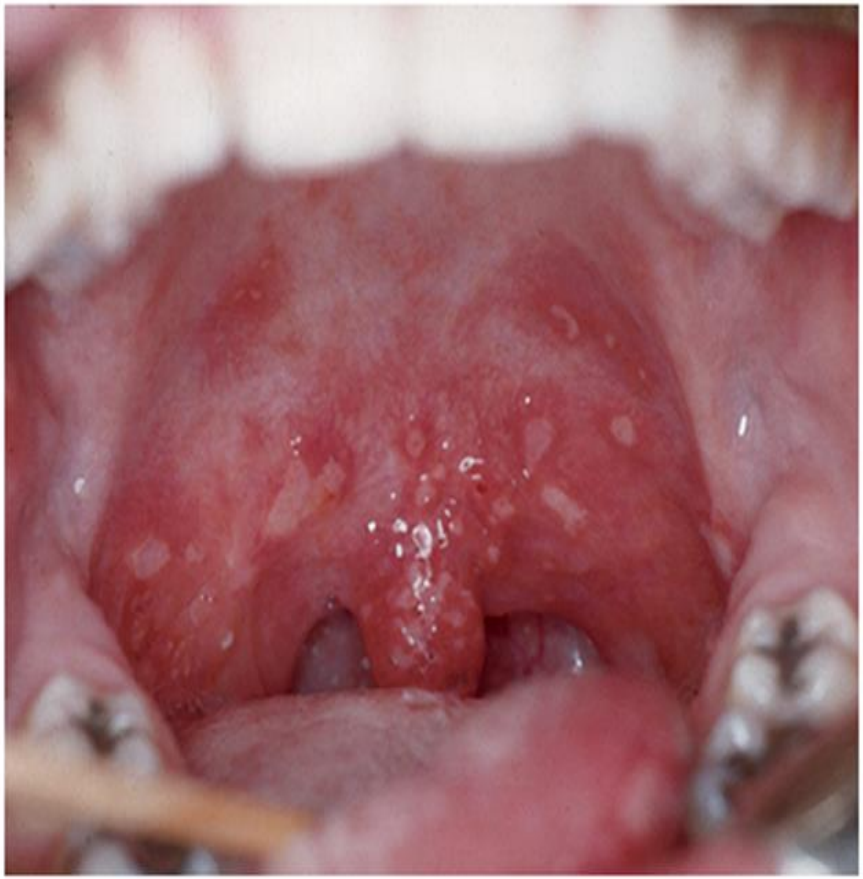


FIGURE 7-12

Herpangina. Multiple small vesicular and punctate lesions of the posterior soft palate and nasopharynx.

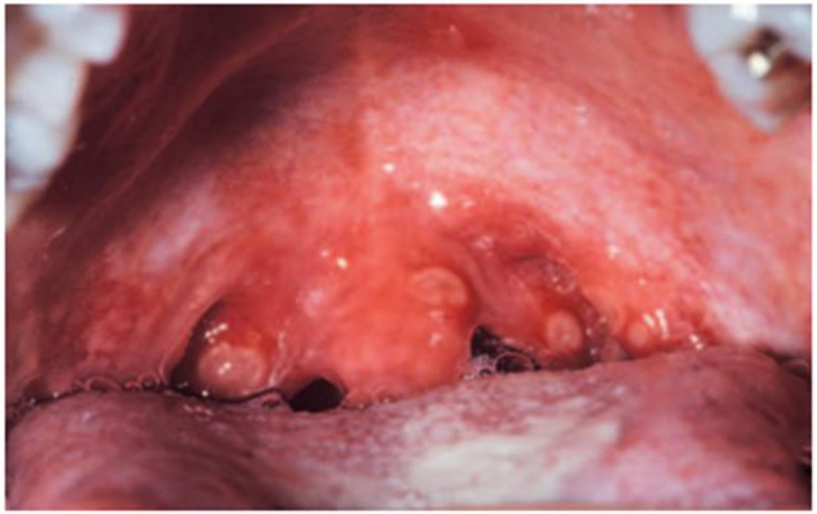


Fig. 7-23 **Herpangina.** Numerous aphthouslike ulcerations of the soft palate.

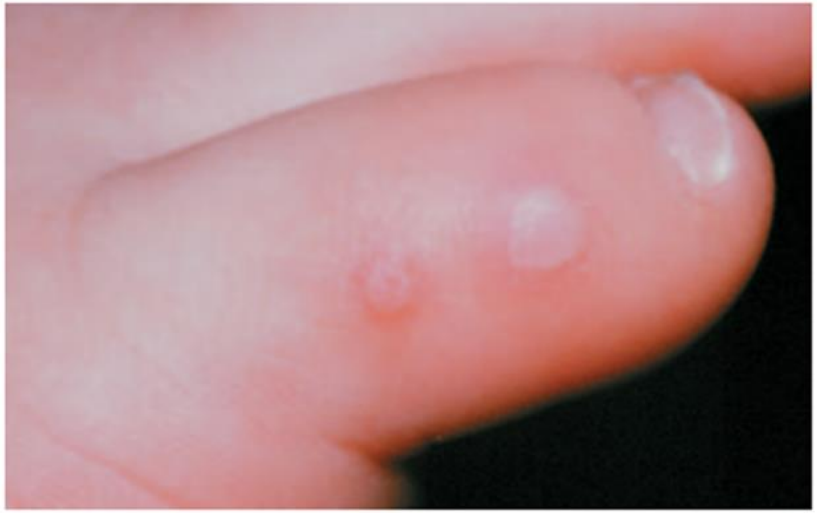


Fig. 7-24 **Hand-foot-and-mouth disease.** Multiple vesicles of the skin of the toe. *(Courtesy of Dr. Samuel J. Jasper.)*

PARAMYXO-VIRUSES

The paramyxo-viruses are large RNA viruses. The two most prominent members are (1) measles and (2) mumps viruses. Both viruses are transmitted through saliva and therefore have implication to health care workers who must recognize the presence of these diseases in their patients to prevent transmission. The viruses are easily and rapidly transmitted.

MEASLES:

A highly contagious systemic viral infection contracted through the respiratory system and spread through the circulatory system, with a predilection for skin blood vessels that produce a skin rash and sometimes pneumonia and encephalitis.

Measles is one of the most severe and widespread of the childhood exanthematous diseases. The virus enters the body through the respiratory system and undergoes rapid replication within the respiratory epithelium before extending to the regional lymph nodes, invading white blood cells and spreading throughout the body via the circulatory system. The virus has a predilection for blood vessel walls, particularly those of the skin, and produces the characteristic erythematous rash.

CLINICAL FEATURES

Excruciating headaches, a rash, photophobia, high fever, and a cough are the hallmarks of a pre-rash measles infection. After an incubation period of 2 to 4 days in which the lungs are infected, the virus spreads to the brain, superficial blood vessels, conjunctiva, urinary tract, GI tract, and oral mucosa. Symptoms emanate from all sites during the next week. Lesions referred to as Koplik spots infrequently occur on the oral mucous membranes, usually before the development of a skin rash.

They are usually asymptomatic, transient in nature, and often overlooked, appearing as small white papules on an erythematous base on the buccal mucosa. Palatal petechiae and generally inflamed mucous membranes and gingiva are also present during the peak of the infection. Patients become contagious approximately 4 days before they feel ill, making intervention to prevent spread of the virus difficult. A skin rash eventually appears, indicating the presence of the disease.

TREATMENT

Measles is treated symptomatically with analgesics, fluids, and rest. Patients who develop otitis media and pneumonia may be given antibiotics.

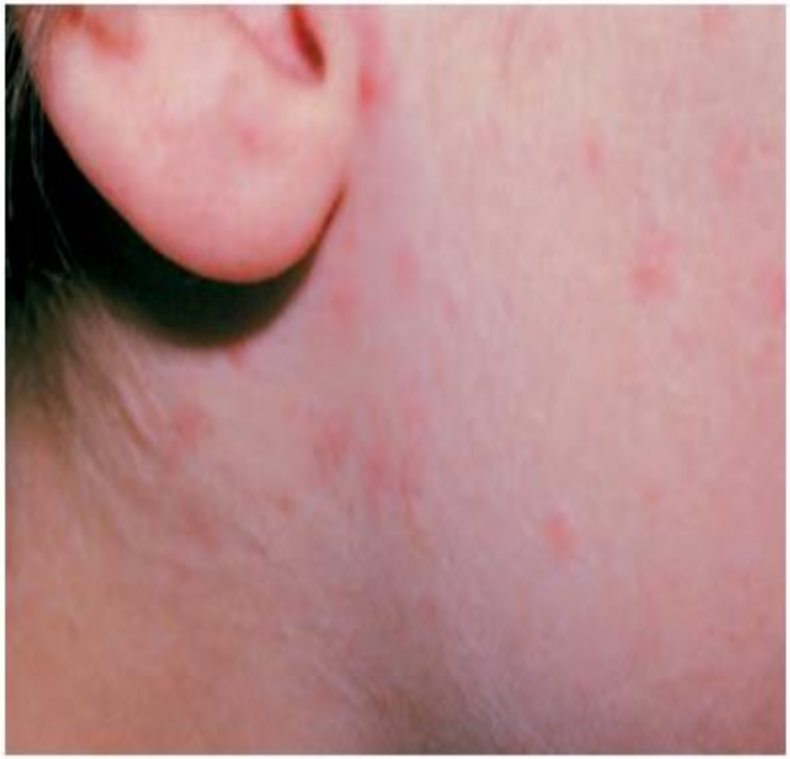


Fig. 7-29 Rubeola. Erythematous maculopapular rash of the face. *(Courtesy of Dr. Robert J. Achterberg.)*

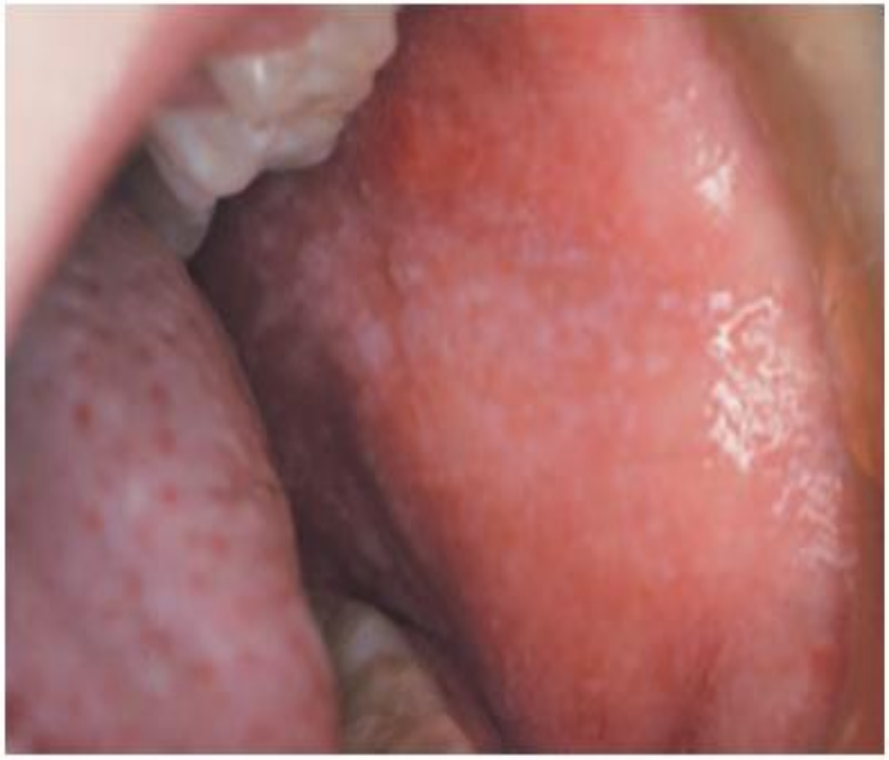


Fig. 7-28 Rubeola. Numerous blue-white Koplik's spots of buccal mucosa. *(Courtesy of Dr. Robert J. Achterberg.)*

MUMPS:

A viral infection contracted through the respiratory system that primarily affects one or more major salivary glands with swelling and pain; occasionally affects other organs and produces fever and malaise.

The mumps virus is a paramyxovirus that has only one subtype. Evidence of infection is present in age of 15, although not all will have obvious symptoms. The virus is spread through saliva and nasal droplets and is communicable during the prodromal period 2 weeks before the onset of clinical signs and symptoms. It infects and replicates in the respiratory mucosa before disseminating to the salivary glands, CNS, testes, ovaries, pancreas, and occasionally the eyes and middle ear.

CLINICAL FEATURES

Patients with classic mumps manifest swelling of one or both parotid glands in addition to the usual signs and symptoms of viral infections such as headache, fever, and malaise. In some patients the submandibular glands will also be involved. The enlarged glands are very painful, especially at mealtime. The clinical sign of the elevation of the earlobe on one or both of the affected sides when it is viewed from behind the patient. This is indicative of involvement of the tail of the parotid gland. This sign helps to differentiate mumps from non parotid causes of facial swelling (dental abscess, associated cellulitis). Intraorally the papilla over the opening of Stensen duct on the buccal mucosa

may be red and enlarged. Symptoms may last as long as 4 to 5 weeks. In some patients, involvement of the major salivary glands does not occur, making diagnosis more difficult. In these cases the diagnosis is made by detecting viral-specific antibodies in the blood or by recovering the mumps virus from the urine.

TREATMENT

No antiviral agents are available for the treatment of mumps. Patients are treated symptomatically with analgesics, bed rest, and a bland diet.

Fig. 7-31 Mumps. Bilateral parotid enlargement. *(From Neville BW, Damm DD, White DK: Color atlas of clinical oral pathology, ed 2, Hamilton, 1999, BC Decker.)*

FOCAL EPITHELIAL HYPERPLASIA:

Multiple papillary or sessile areas of epithelial hyperplasia of the oral mucosa in young patients that frequently regress spontaneously; the epithelium is extensively thickened and contains koilocytes, HPV-13, and HPV-32.

Focal epithelial hyperplasia, commonly known as Heck disease, is a condition found primarily in isolated groups of native Indians of North and Central America and Brazil, northern native peoples, and other groups in Europe and Africa. The lesions are usually multiple and often involve the gingiva and buccal and labial mucosa of the mouth . Lesions are sessile and may be pink or white. Although most lesions occur in children, they can also be found in older patients. Recently they have been found in HIV-positive or otherwise immunosuppressed patients. In children most of the lesions regress spontaneously. If lesions persist they can be surgically excised. The lesions contain abundant HPV-13 and HPV-32.

HISTOPATHOLOGY

Greatly thickened layers of parakeratin and extensive acanthosis characterize the surface of focal epithelial hyperplasia. Epithelial cells of the upper spinous layer display enlarged nuclei and vacuolated clear cytoplasm (koilocytes) indicative of an HPV infection. The basal cell layer exhibits increased mitotic activity. Cells with an unusual arrangement of the nuclear material resembling abnormal mitotic figures are a frequent finding within the spinous cell layer. These have been referred to as mitosoid cells or bodies . The underlying connective tissue is usually loose and well vascularized, exhibiting a variable infiltrate of lymphocytes.

TREATMENT

Those lesions that do not regress spontaneously can be surgically excised. Until the diagnosis has been firmly established for individual patients, lesions should be surgically excised and submitted to a laboratory for a definitive diagnosis. Topical treatment with beta interferon has been found to be an effective alternative for some patients.

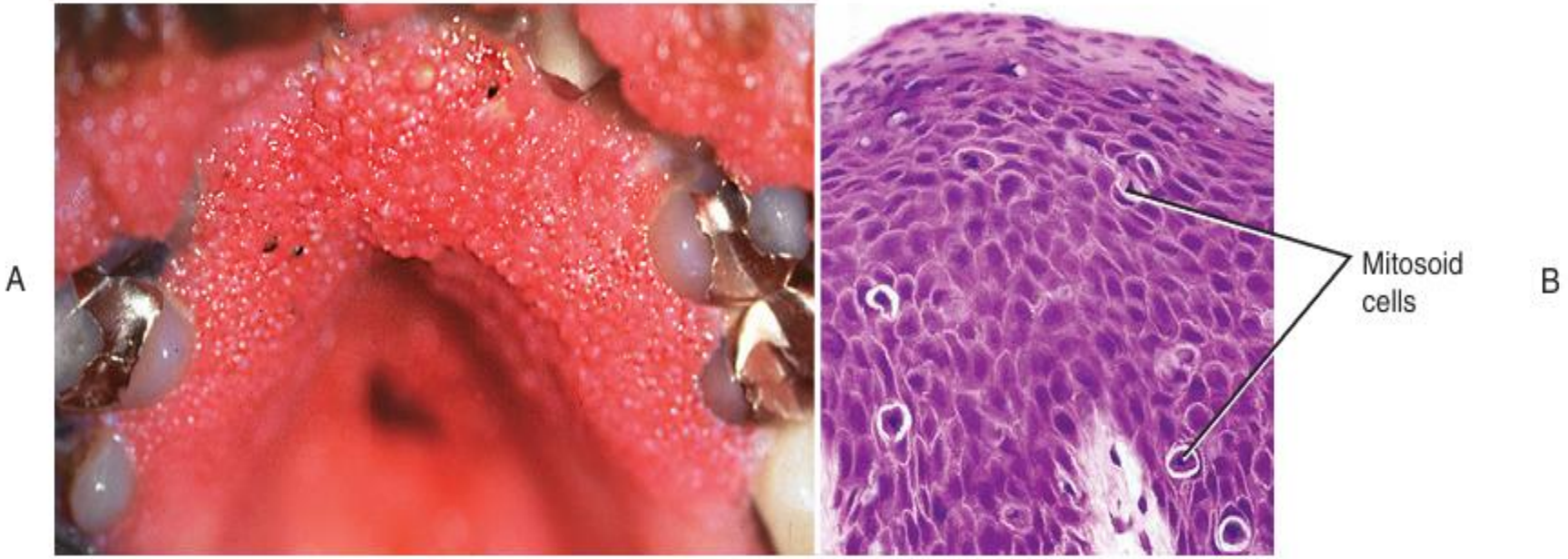


FIGURE 7-17

Focal epithelial hyperplasia. A, Multiple sessile and papillary lesions of the anterior gingiva and labial mucosa of an adult. **B,** Spinous layer epithelial cells with unusual arrangement of the nuclear material resembling abnormal mitotic figures (mitosoid cells).

Human Immunodeficiency Virus

HIV exhibits tropism for T lymphocytes, macrophages, and certain nerve cells. The viral envelope contains specific surface glycoproteins, notably gp120 and gp41, which bind with both the primary CD4 receptor and the CCRS or CXCR4 co-receptors on the surface of T-lymphocyte helper cells or macrophages. Successful binding allows the contents of the viral core to enter the cytoplasm of the host cell, leaving the viral envelope behind.

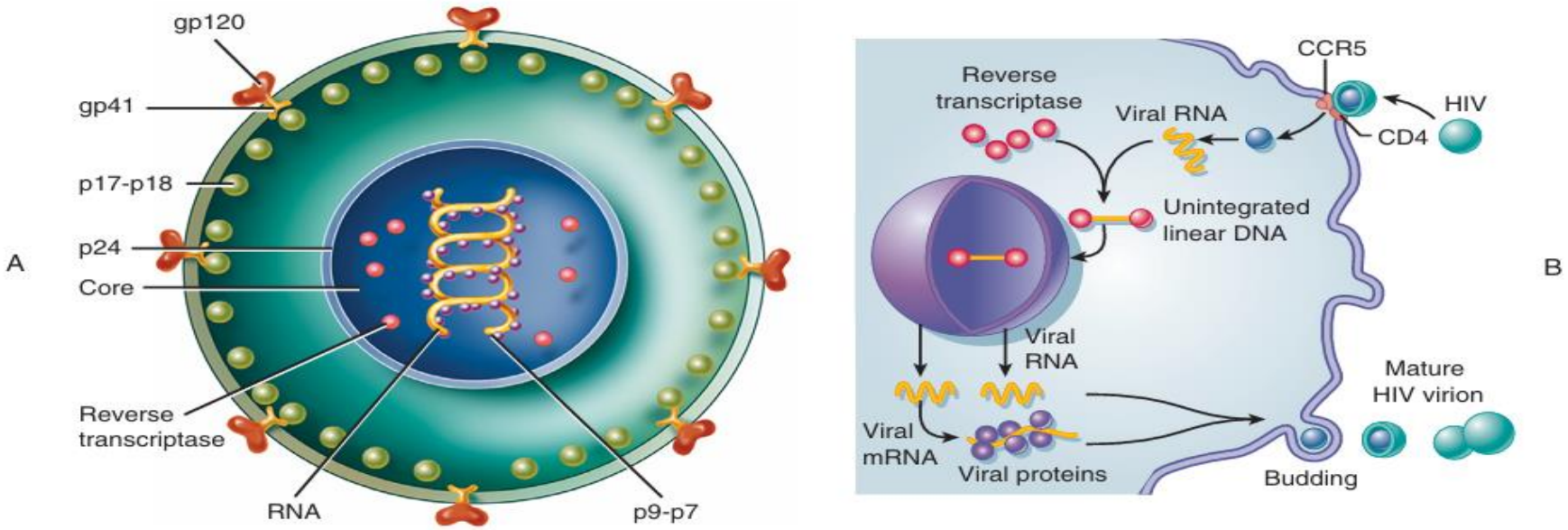


FIGURE 7-18

Human immunodeficiency virus. A, A retrovirus with essential envelope glycoproteins, core enzymatic proteins, and RNA chromatin. **B,** Process of replication of human immunodeficiency virus (HIV) retrovirus. The virus attaches to a target cell, usually a lymphocyte with a surface CD4 receptor and either a CCR5 or a CXCR4 co-receptor. Cytoplasmic reverse transcriptase changes virus' RNA to DNA that becomes integrated into the nuclear genome directing the cell to produce cytoplasmic viral RNA and other viral proteins sufficient to replicate HIV.

Patients with HIV infection progress through clinical stages that vary extensively among individuals. During this time the viral load (measured as antibodies to the virus) increases while the CD4 count decreases . Five stages can be identified: (1) window, (2) seroconversion, (3) asymptomatic, (4) symptomatic, and (5) AIDS.

Window Stage

After initial contact with HIV, commonly a 2 to 12 week delay is seen before antibodies to the virus are detectable in the blood using the ELISA technique. During this period, patients are unaware of their status; testing will often yield a false negative. If suspicion is high that an infection has taken place, a more specific test that targets actual specific HIV antigens, known as the Western blot technique, is usually confirmatory of the patient's status if sufficient viral particles are present in the blood.

Seroconversion Stage

Over the ensuing weeks as antibodies and virus appear in the blood in greater numbers, patients will experience noticeable malaise, lethargy, mild temperature elevation, headache, arthralgia, myalgia, chronic cough, and possibly a skin rash. These symptoms are similar to those of flu or a mild form of infectious mononucleosis. This period usually lasts between 2 and 4 weeks.

Asymptomatic Stage

This phase consists of a prolonged period of latency, with few if any symptoms that may last for 6 months in infants and 10 to 20 years in adults. Although the level of HIV viremia achieved during the first year after initial infection does not correlate with the rate of progression to clinical AIDS and survival, the level of viremia present at the 1 year mark ("set point") and during the following

prolonged latency period are significant. The lower the levels of the viral load during this period, the longer the survival rate. Viral loads less than 4500/ml at the "set point" and during the latest period have resulted in survival well beyond 10 years, whereas loads greater than 36,000/ml have greatly shortened survival. With the advent of numerous drugs or combinations of drugs, such as the highly active antiretroviral therapy (HAART) protocol, to inhibit viral reverse transcriptase and enzyme proteases, viral loads or viremia during latency have been significantly reduced. With the continued use of these intervention therapies, pre-AIDS states and eventual survival rates are expected to become significantly prolonged for patients who are able to tolerate the considerable drug side effects and complications.

Symptomatic Stage.

Progression to the symptomatic stage varies extensively and is dependent on an individual decline in CD4 T cell count. Some or all of the following insidious symptoms of pre-AIDS gradually appear:

- **Night sweats, malaise, fever • Weight loss • Memory loss, mild dementia**
- **Chronic infections • Generalized lymphadenopathy**
- **Diarrhea**

AIDS Stage

Once an HIV-positive patient's CD4 lymphocyte count falls below 200/ l, one or more of the following severe and disabling symptoms appear, or both happen, the patient is classified as having AIDS:

- **Pneumocystis**
- **Bacterial pneumonia**
- **Cryptosporidiosis**
- **Toxoplasmosis**
- **Cerebral meningitis**
- **Kaposi sarcoma**
- **Non-Hodgkin lymphoma (NHL)**
- **Generalized herpes simplex, varicella-zoster infections**
- **CMV retinitis, pneumonia, colitis**
- **Candidiasis, cryptococcosis, histoplasmosis, or other deep mycotic infections**
- **Mycobacterium**

BOX 7-1

Oral Lesions of HIV-Positive Pre-AIDS Patients

Hairy leukoplakia
Acute pseudomembranous candidiasis
Diffuse herpes simplex gingivostomatitis
Gingivitis/periodontitis
Acute nonspecific ulcers
Diffuse varicella-zoster lesions

BOX 7-2

Common Oral Lesions in Patients with AIDS

Candidiasis
- Intraoral
- Esophageal

Hairy leukoplakia
Diffuse herpes simplex gingivostomatitis
Diffuse varicella-zoster lesions
Kaposi sarcoma
Non-Hodgkin lymphoma
HIV gingivitis/periodontitis
Acute nonspecific ulcers
Chronic ulcers
Cryptococcosis
Histoplasmosis
Cytomegalovirus ulcer
Herpes simplex infection

BOX 7-3

Infrequent Oral Conditions Found in Patients with AIDS

Atypical tuberculosis
Coccidioidomycosis
Molluscum contagiosum infection
Toxoplasmosis
Bacillary angiomatosis
Condyloma acuminatum
Enlarged parotid glands
Xerostomia
Squamous cell carcinoma

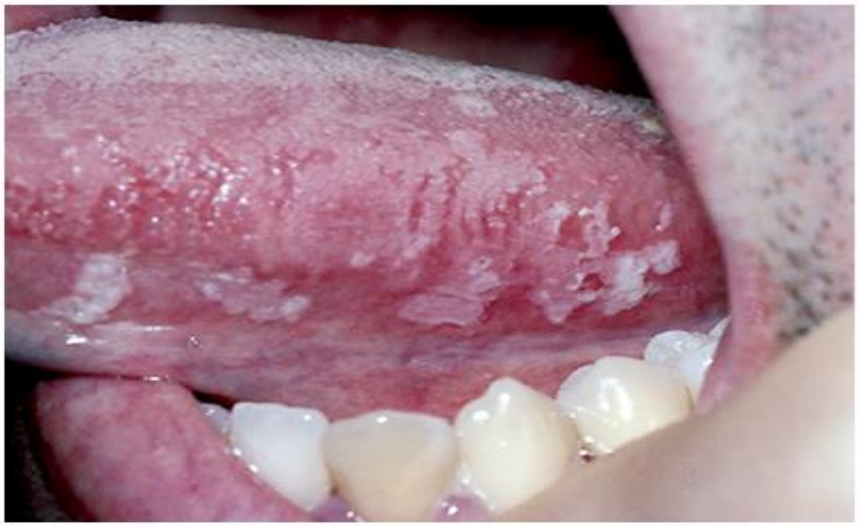


FIGURE 7-20
Hairy leukoplakia. White lesions with vertical striations on the lateral surface of the tongue; common in human immunodeficiency virus–positive patients but occasionally found in patients with other causes of immunosuppression.

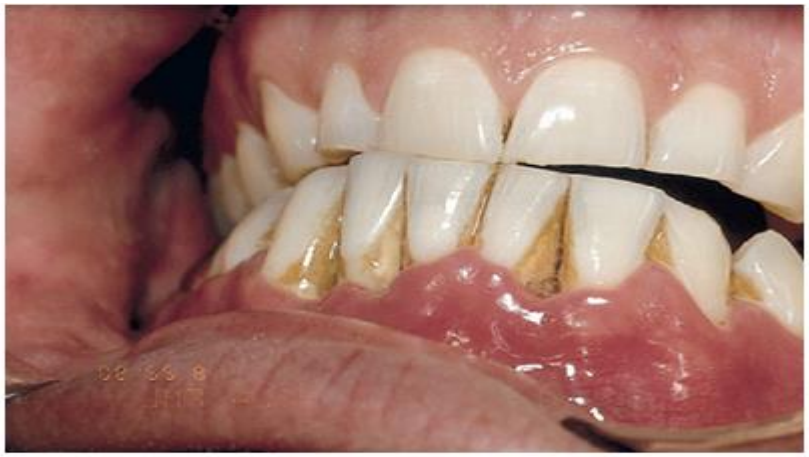


FIGURE 7-24
HIV necrotizing ulcerative periodontitis. Focal areas of an advanced gingival recession and an erythematous gingiva, with features suggestive of a superimposed acute necrotizing ulcerative gingivitis.

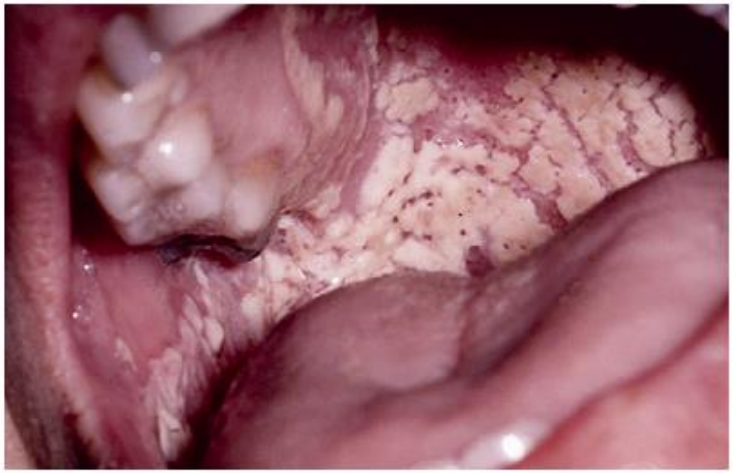


FIGURE 7-22
HIV candidiasis. Persistent acute pseudomembranous candidiasis on the palate.

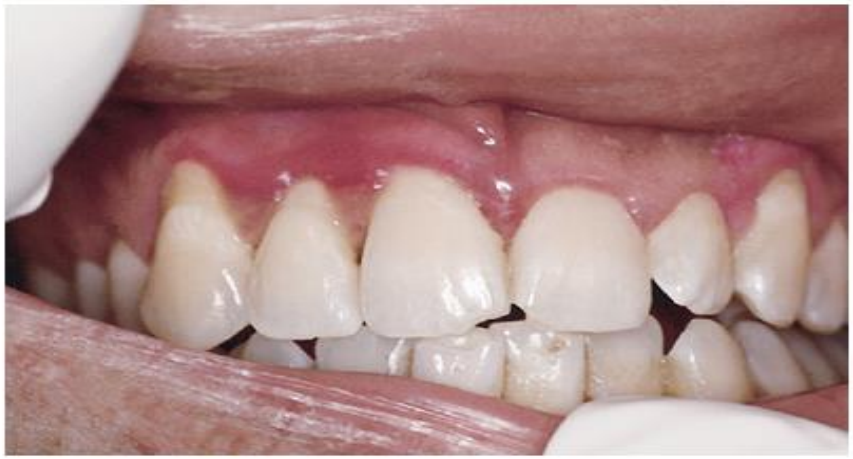
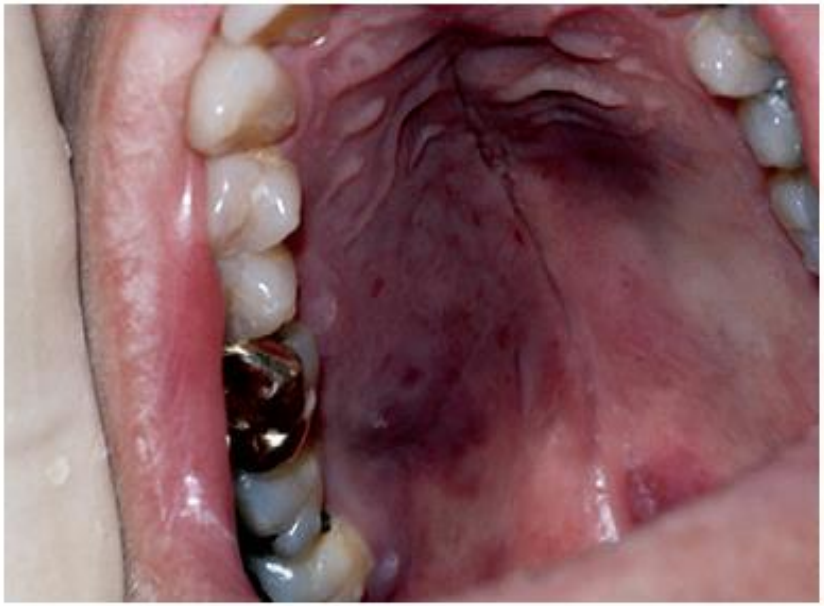
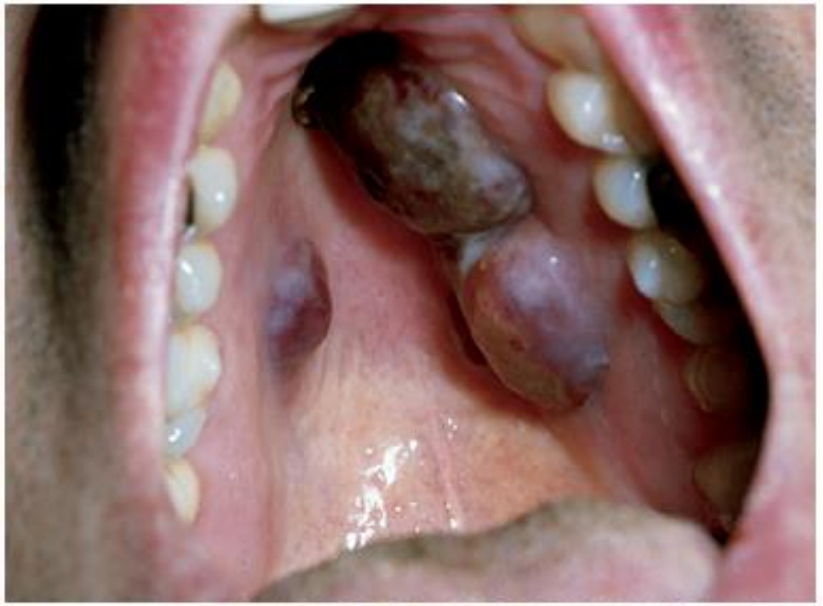


FIGURE 7-23
HIV linear gingival erythema. Atypical, intensely erythematous gingival inflammation involving several teeth with uninvolved adjacent gingiva.

FIGURE 7-25
Acute nonspecific ulcer. Deep crateriform ulcer with rolled borders and no identifiable causative factor that is penetrating the underlying muscle in a patient who is HIV positive.



A



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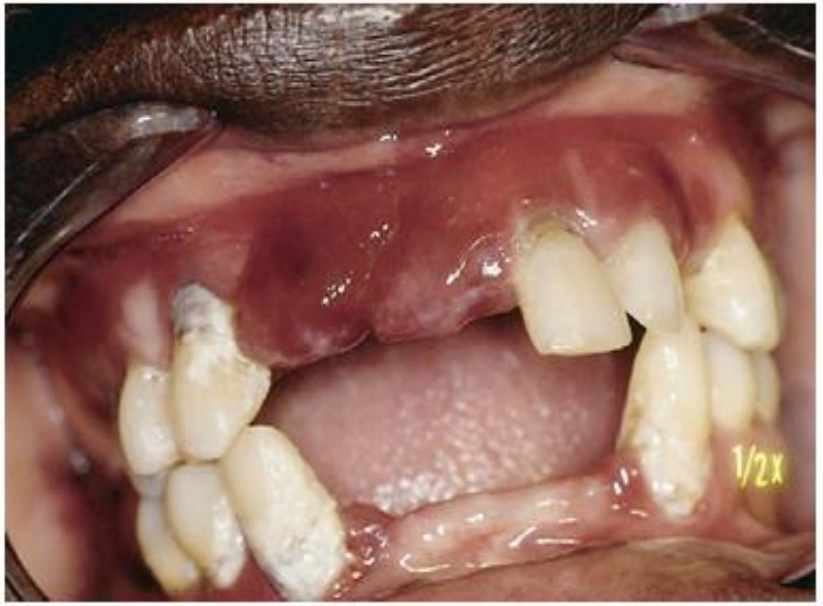

C

FIGURE 7-26

Kaposi sarcoma. A, Diffuse purplish macular lesion on the right side of the hard palate. **B,** Nodular form of Kaposi sarcoma involving both the right and left sides of the palate. **C,** Combined macular and nodular lesions of the anterior maxillary gingiva.

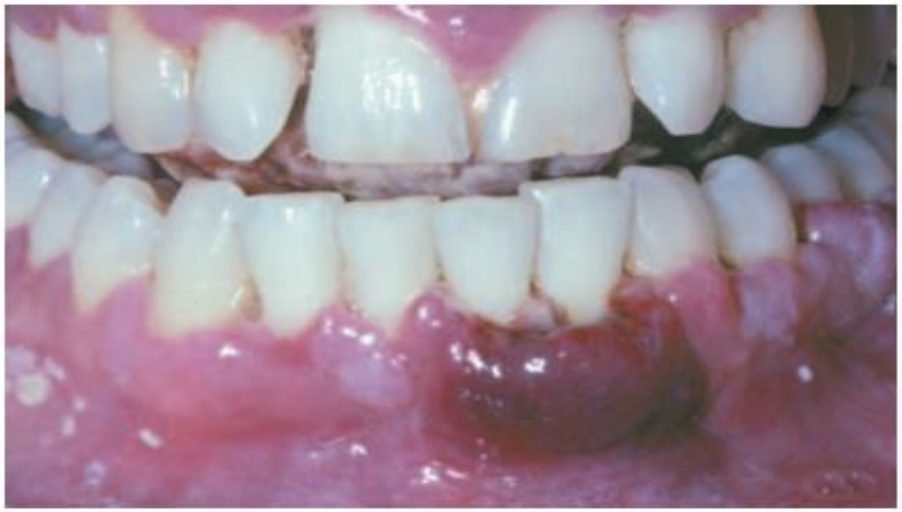

Fig. 7-40 HIV-associated Kaposi's sarcoma (KS). Raised, dark-red enlargement of the mandibular anterior facial gingiva on the left side.

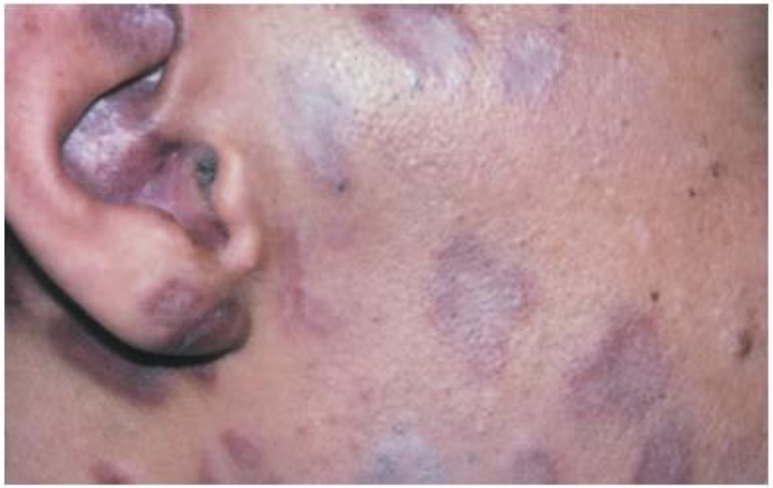

Fig. 7-38 HIV-associated Kaposi's sarcoma (KS). Multiple purple macules on the right side of the face.

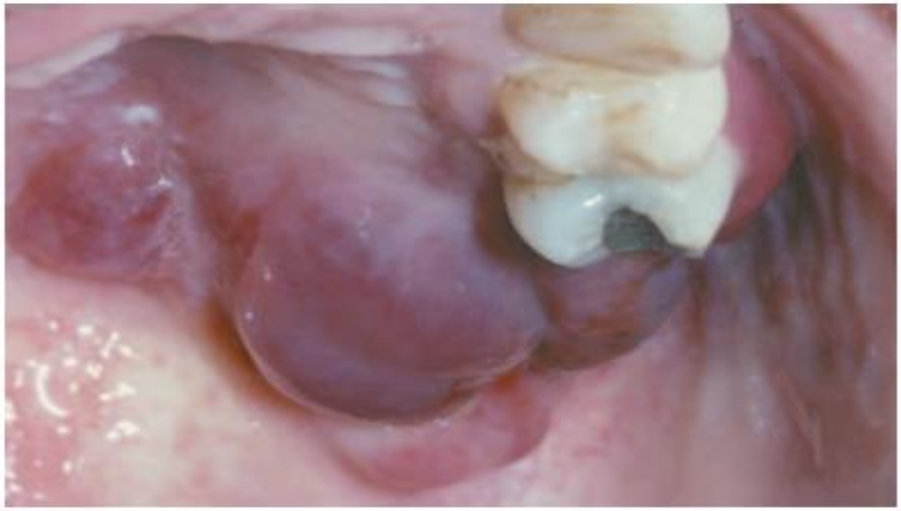

Fig. 7-41 HIV-associated Kaposi's sarcoma (KS). Diffuse, red-blue nodular enlargement of the left hard palate.

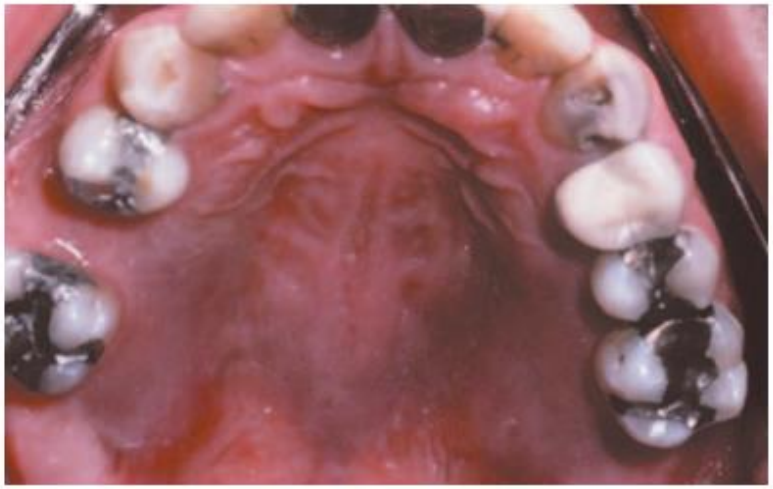

Fig. 7-39 HIV-associated Kaposi's sarcoma (KS). Large zones of KS exhibiting as a flat, brownish, and M-shaped discoloration of the hard palate.

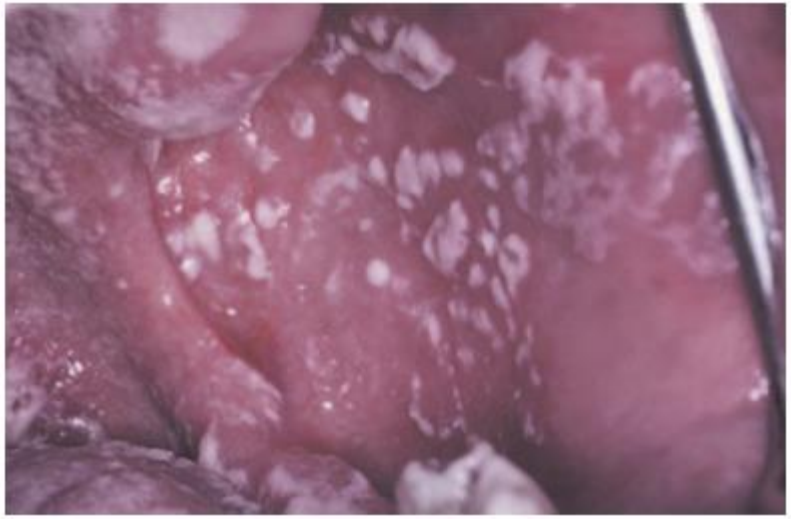

Fig. 7-32 HIV-associated candidiasis. Extensive removable white plaques of the left buccal mucosa.

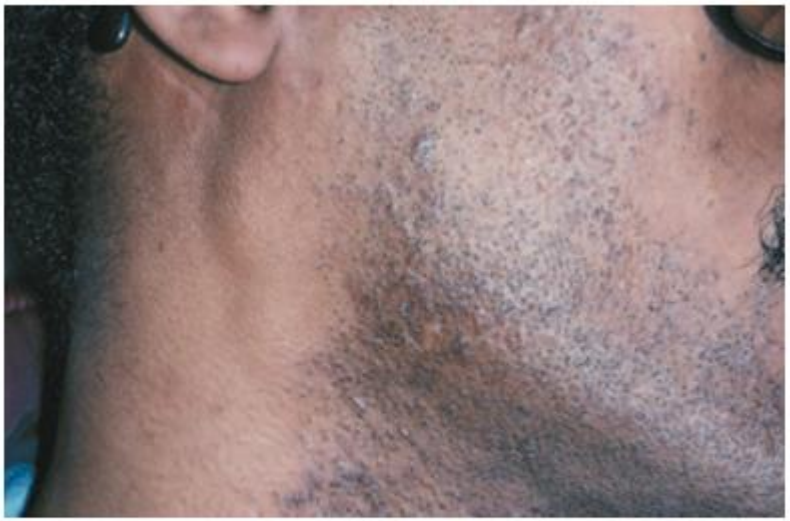

Fig. 7-43 HIV-associated lymphadenopathy. Enlarged cervical lymph nodes in a patient with persistent generalized lymphadenopathy (PGL).

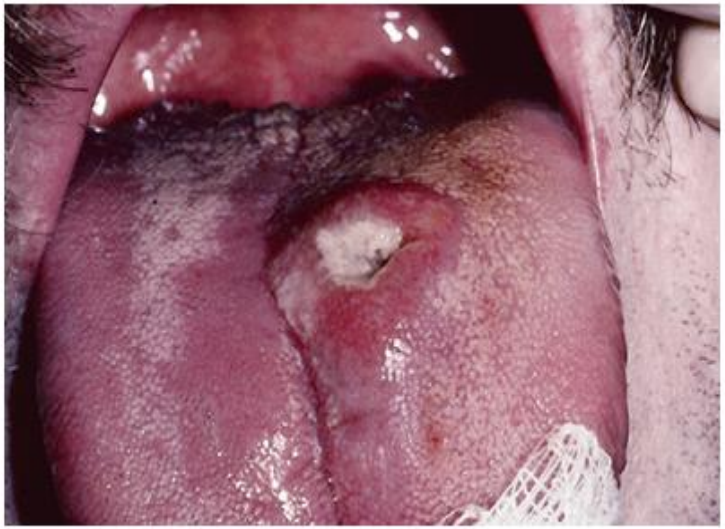

FIGURE 7-28

Non-Hodgkin lymphoma. Rapidly enlarging lesion with central ulceration on the dorsal side of the tongue.

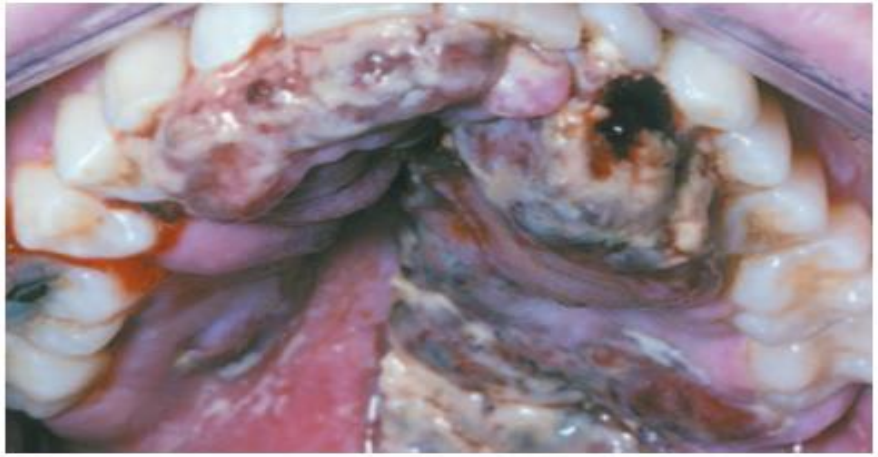

Fig. 7-42 HIV-associated Kaposi's sarcoma (KS). Diffuse, red-blue gingival enlargement that demonstrates widespread necrosis.

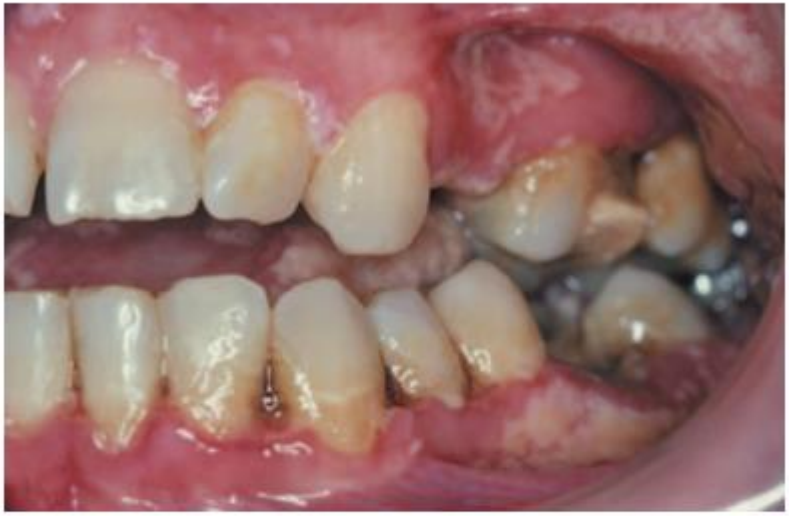

Fig. 7-46 HIV-associated necrotizing ulcerative gingivitis (NUG). Multiple punched-out interdental papillae of the mandibular gingiva. Note diffuse pseudomembranous candidiasis of the surrounding mucosa.

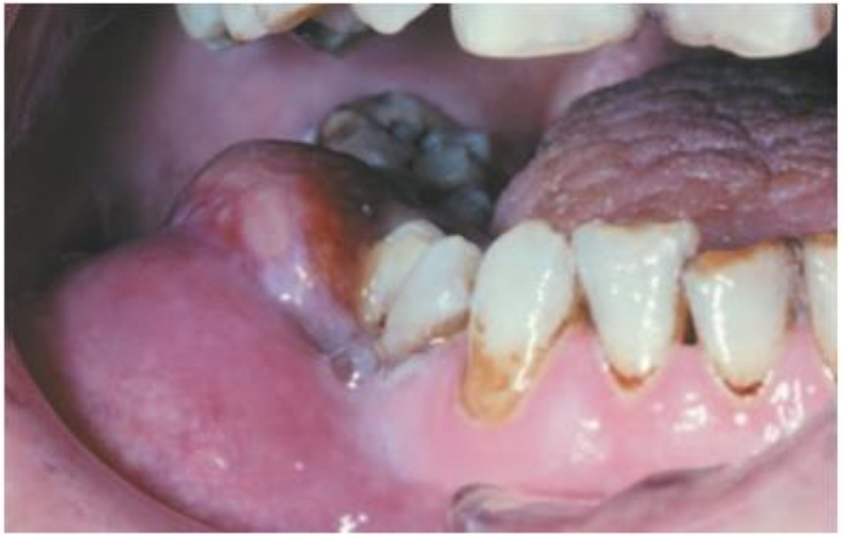

Fig. 7-44 HIV-associated lymphoma. Erythematous and ulcerated soft tissue enlargement of the posterior mandibular gingiva and mucobuccal fold on the right side.

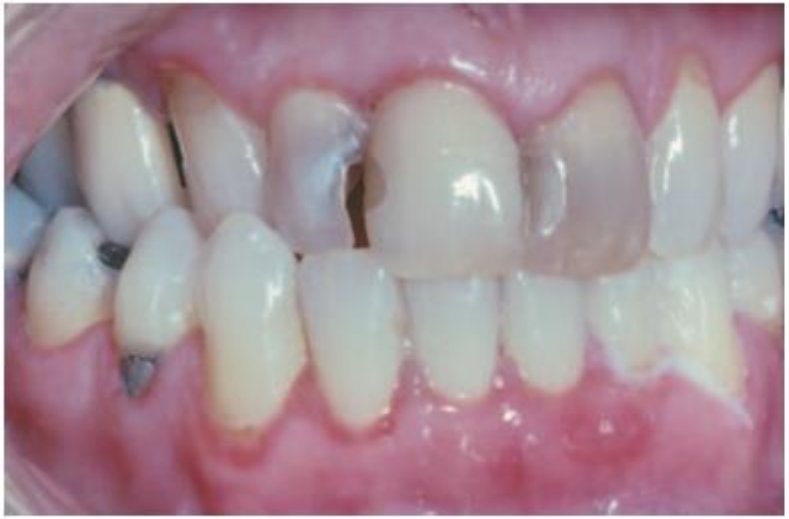

Fig. 7-45 HIV-associated gingivitis. Band of erythema involving the free gingival margin.

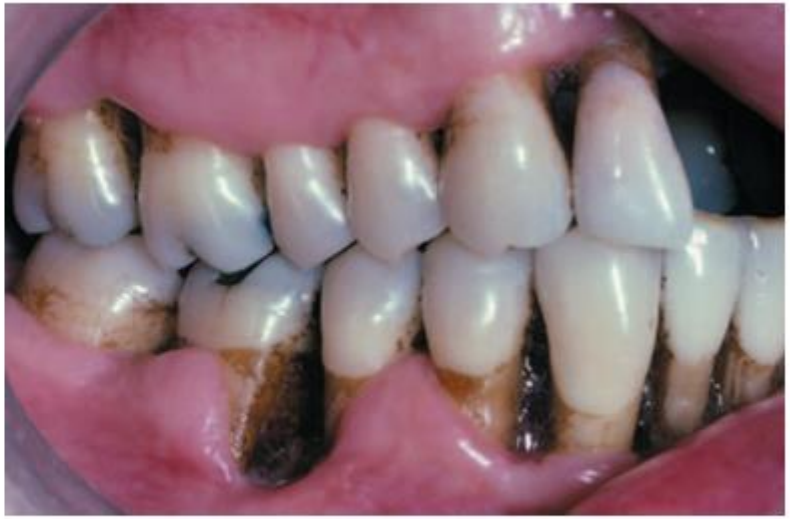

Fig. 7-47 HIV-associated periodontitis. Extensive loss of periodontal support without deep pocketing.

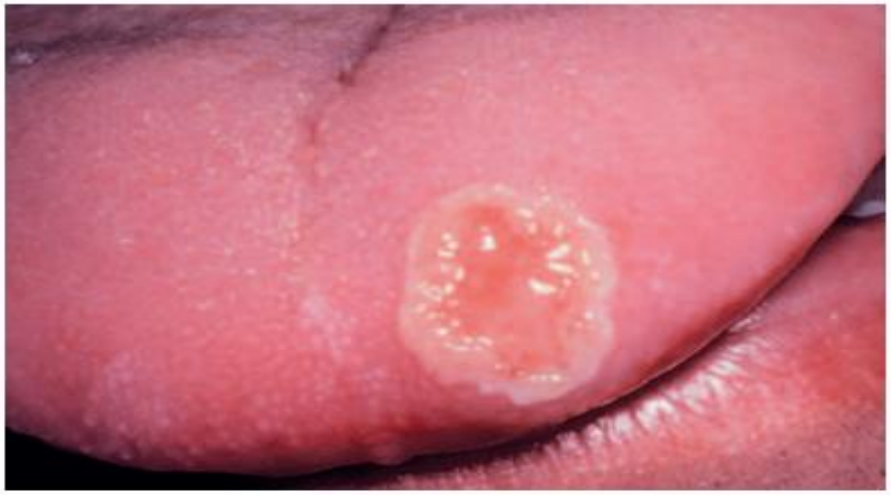

Fig. 7-50 HIV-associated recurrent herpetic infection. Mucosal erosion of the anterior dorsal surface of the tongue on the left side. Note the yellowish circinate border.

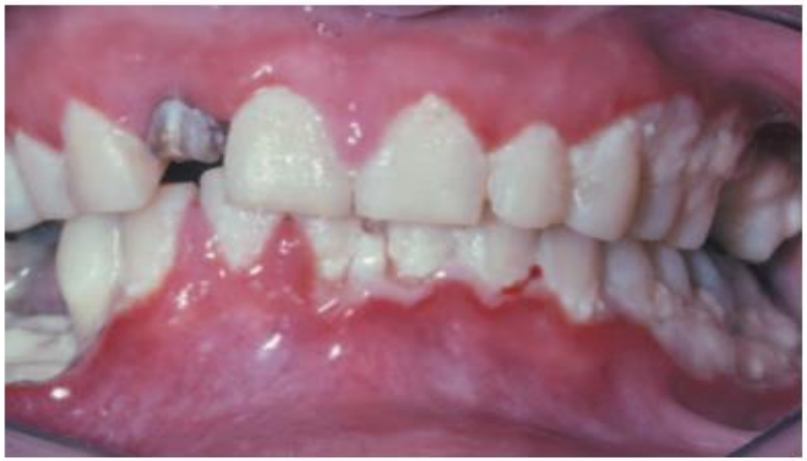

Fig. 7-48 HIV-associated periodontitis with necrotizing stomatitis. Diffuse gingival necrosis with extension onto alveolar mucosa.

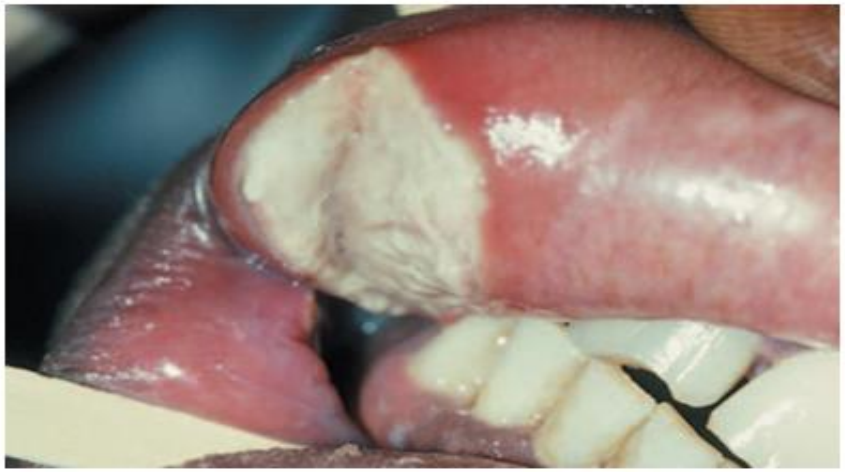

Fig. 7-58 HIV-associated ulceration. Atypical mucosal ulceration that mandates biopsy and may be attributable to a variety of causes.

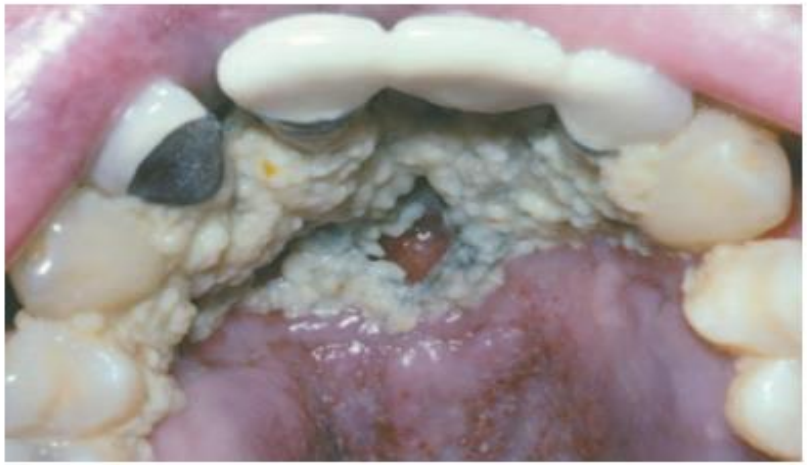

Fig. 7-49 HIV-associated necrotizing stomatitis. Massive necrosis of soft tissue and bone of the anterior maxilla.

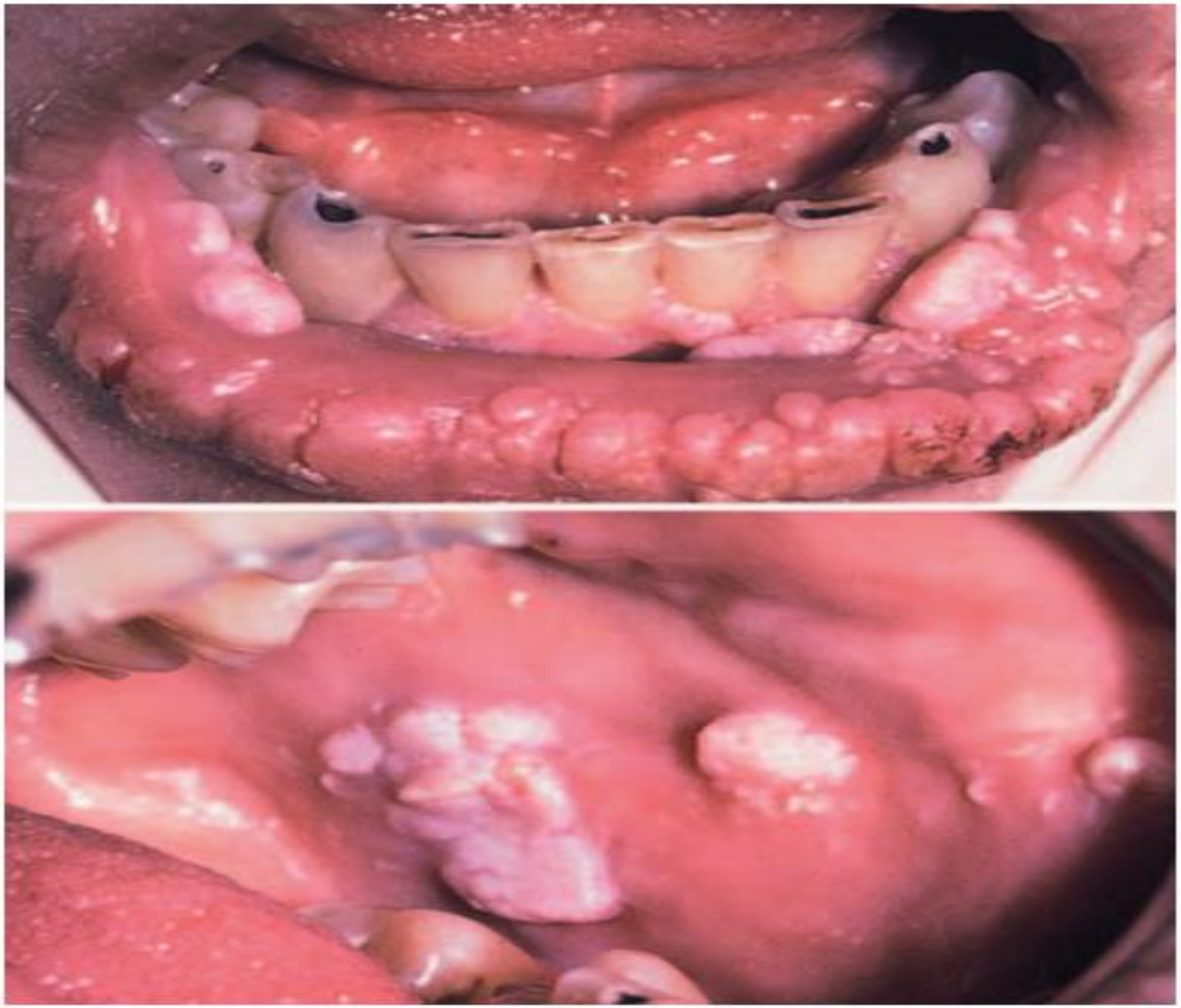

Fig. 7-51 HIV-associated human papillomavirus (HPV) infection. Multiple exophytic and somewhat papillary nodules of the lip, buccal mucosa, and gingiva.


Thank
you