Review Article

Viral infections of oral cavity

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Abstract

Viral infections of the oral cavity usually manifest as either ulceration or blistering presentation of oral tissues. Oral viral infections are encountered in dental practice but received less clinical interest due to the lesser frequency of patients and diagnostic challenges. The clinical presentation, pathogenic mechanism, investigations, and management of oral viral infections are integrated into the article which will enable general dentists to develop critical thinking processes on differential diagnosis and management through a multidisciplinary approach with specialist dentists.

Keywords: Acyclovir, blister, herpes, oral cavity, zoster

Introduction

A viral disease of the oral cavity is the infectious type of pathology affecting oral tissues. Viral diseases may either occur due to cellular destruction or consequence of immune reaction following viral proteins. Viral infections typically present with abrupt onset and association of solitary or multiple blister or ulcerations. Concomitant general symptoms such as fever, malaise, and lymphadenopathy are observed in a few viral conditions. Viral infections are also linked to the development and progression of periodontal diseases. A viral disease of oral tissues is often encountered in dental practice, however, limited attention is given in diagnosis and management due to diagnostic challenges. Certain viral infections are associated with tumor formation and, hence, early reporting and referral to oral disease management are essential in dental practice.

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Relevance of Oral Health in Family Medicine and Primary Care Practice

Oral health influences overall health and quality of life.[1] The majority of viral infections tend to have oral manifestations, and general dentists majorly focus on the management of dental and periodontal diseases. Oral manifestations of viral infections may present as (1) preliminary sign of disease, (2) important co-symptom of viral disease, or (3) only sign observed in such viral disease. Although special dentists, for example, oral medicine, oral surgeon, and oral pathologist, may play a significant role in diagnosing and management of oral infections, the specialist dentist usually embraces a multidisciplinary route in such situations.[2] Thus, dental surgeons, specialist dentists, and primary care/family physicians need to be updated with common conditions/emerging oral viral infections in relation to diagnosis and management. Thus, primary care and family physicians have a greater role in managing oral conditions that require multidisciplinary action from dental team.[3] Hence, family physicians are emphasized to incorporate oral health into routine practice through examination of oral cavity and its findings, counseling on dietary and hygiene practice will support in achieving better oral health, and by extension overall health. Primary care and family physicians provide integrated accessible

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health care services and who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community. The discussion of entire list of oral viral infections is beyond the scope of this article, instead of common and/or important conditions are presented. This article aims to address clinical features, diagnostic concepts, and management of herpes simplex virus (HSV-1), herpes zoster, Epstein-Barr virus, cytomegalovirus, human herpesvirus (HHV) 7 and 8 infections of oral cavity.

Herpes Simplex Infection

HSV belongs to herpes viridae group and is a significant pathogenic virus that is known to cause mucocutaneous conditions in the oral cavity and genital region. HSV-1 and 2 are the two major types of herpes viruses that can be distinguished by the distinct antibodies. HSV-1 is known to have a significant association with pharyngeal infection, meningoencephalitis, and dermatitis above the waistline; whereas HSV-2 is associated with genital and anal region infections. However, depending on the sexual practices, HSV-1 and 2 can cause primary and/or recurrent infections in the oral and/or genital region. Herpetic infections that develop secondary to salivary contamination over the finger are termed as herpetic whitlow.[4,5]

Primary Herpes Simplex Infection of Oral Cavity: Pathogenesis and Latency

The incidence of primary HSV-1 infections usually occurs at an early age, often results in painful skin or mucosal lesions, but can also be asymptomatic. HSV replicates at the portal of entry, often at oral or genital mucosal tissue, leading to infection of sensory nerve endings. Following to portal into sensory nerve endings, HSV is then transported to regional ganglia and establishes latency.[6]

Clinical Features

The incidence of primary HSV 1 infection is higher between 2 and 3 years of life, however, HSV-1 may still occur in adolescents and adults and occasionally in individuals older than 60 years.[7,8] Recurrence is directly related to the severity of primary infection, as reflected by the size, number, and spread of lesions.[9] Primary herpes infections are usually accompanied by prodromal symptoms or systemic symptoms that include fever, headache, malaise, nausea, vomiting, and lymphadenopathy.[10,11] HSV-1 infection of oral cavity included are vesicles as well as ulcerations that appear on the oral mucosa and generalized acute marginal gingivitis, often follows prodromal symptoms.[12,13]

Management

Primary HSV infections are usually treated with palliative care. Symptomatic and milder patients are managed by supportive care that includes maintenance of fluids, acetaminophen to reduce fever, and use of topical anesthetics such as lidocaine, liquid Benadryl, milk of magnesia, or Carafate to relieve oral burning sensation and/or pain. In patients with prolonged symptoms (more than 24–48 h) with vesicle eruption, anti-HSV medications are employed to accelerate healing by inhibiting DNA replication in HSV-infected oral epithelial cells.[14]

Current drug on antiviral mechanism includes three classes of drugs which target viral DNA replication: acyclic guanosine analogs (licensed drugs: acyclovir, ganciclovir, penciclovir, valacyclovir, valganciclovir, and famciclovir), acyclic nucleotide analogs (licensed drugs: cidofovir, adefovir dipivoxil), and pyrophosphate analogs (licensed drugs: foscarnet). Routinely used drugs from the abovementioned list include acyclovir, valacyclovir, cidofovir, and foscarnet. Acyclovir is a gold standard for prophylactic and treatment of HSV infection[12] [Table 1]. Acyclovir drug-resistant is rising rapidly with the increasing number of transplant and cancer patients.[7]

Recurrent Herpes Simplex Infection

Pathogenesis and latency

Recurrent herpes simplex infection occurs with reactivation of HSV to trigeminal nerve ganglion. Reactivation virus may be a resultant of numerous conditions such as age, exposure to sunlight or cold, trauma, physical or emotional stress, fatigue, pregnancy, immunosuppressive state, fever, respiratory illness, menstruation, systemic illness, or malignancy and lead recurrent herpes simplex infection. The usual incubation period is 3–9 days.[12]

Clinical features

Recurrent herpes lesions are directly related to the severity, size, and a number of lesions in primary infection. Recurrent lesions may occur at primary inoculation site or in the adjacent areas of surface epithelium that is supplied by involved nerve ganglion. Recurrent herpes labialis (RHL) is the most common type of recurrent herpes simplex infection. RHL often appears on the vermillion border or skin of upper and/or lower lip and is commonly referred as cold sore, fever blister, or night fever.

Recurrent HSV infections occur on the lips and keratinized oral mucosal areas such as palate and gingiva. However, a recurrent intraoral herpetic lesion can occur on any oral mucosal site and is usually observed in immunocompromised individuals. Recurrent HSV infections can trigger episodes of erythema multiforme.

Table 1: Medication management of primary herpes simplex virus (HSV) infection in adults

Antiviral drug	Prescription
Acyclovir	Oral route, 200 mg five times a day for 7-10 days or oral route, 400 mg three times a day for 7-10 days.
Valacyclovir	Oral route, 1000 mg two times a day for 7-10 days.
Famciclovir	Oral route, 250 mg three times a day for 7-10 days.

Antiviral medications are usually administered as prophylactic doses for the patients who have a history of recurrent episodes of erythema multiforme.[10] Recurrent intraoral herpetic lesions are more common in advanced AIDS, transplant patients, and cancer patients receiving chemotherapy or immunosuppressive drugs. Recurrent HSV lesions in immunocompetent patients may appear as large ulcers, which may involve labial, genital, or rectal mucosa if left untreated. These lesions have the potential to disseminate and cause generalized infection. Therefore, it is important for clinicians to rule out HSV as a cause of oral vesicles or ulcerations in patients with immunocompromised conditions.[15]

Management

Recurrent herpetic lesions are usually treated with topical antiviral medications. Topical penciclovir reduces the duration and pain of recurrent lesions by 1–2 days. Patients are recommended to apply topical penciclovir over the affected site for every 2 h for 4 days while awake.[15,16] Topical acyclovir is also available for topical use and reduces the duration of recurrent herpes lesions by 12 h. Topically acyclovir is also recommended in recurrent herpes infections and is usually effective when the lesions commenced during prodromal symptoms. Vander *et al.* mentioned that the benefit of applying acyclovir is limited when compared with topical penciclovir.[17] Oral or intravenous administration of acyclovir is usually effective in immunocompetent patients. However, cases of acyclovir-resistant HSV have been reported,[18] and foscarnet has been an effective therapy for acyclovir-resistant patients. Valacyclovir should be used with caution for immunocompetent patients due to the potential risk of hemolytic uremic syndrome. Recommended drug dosage and regimens used to treat recurrent oral HSV infections[11] are given in Table 2.

Herpes Simplex virus-1 (HSV-1) and Bell's Palsy

Bell's palsy occurs with the reactivation of the HSV-1 virus from latency in the geniculate ganglion rather than primary infection. The mechanism through which the virus damages the facial nerve is unclear.[19] Bell's palsy appears to be more common in adult life where HSV-1 is well-established.[20]

Varicella Zoster Infection

Varicella-zoster virus (VZV) belongs to herpes viridae group, is a significant pathogenic virus that is known to cause mucocutaneous conditions in oropharyngeal mucosa and skin.[11]

Pathogenesis and Latency

VZV causes both primary and recurrent infections and remains latent in neurons present in sensory ganglia. The incubation period is approximately 2 weeks. VZV is responsible for two major clinical infections: the primary type is chickenpox and the recurrent type is shingles (herpes zoster [HV]).

Chicken Pox Infection

Clinical features

Chickenpox usually begins with prodromal symptoms such as headache, pharyngitis, rhinitis, and anorexia. The prodromal symptoms are followed by maculopapular rash that are intensely pruritic or vesicular eruptions of the skin and low-grade fever. The eruptions are noted on the trunk and spread to involve the face and extremities. Chickenpox spread from nasopharyngeal secretions or by coming in direct contact with skin lesions of the infected patients. Oral lesions are characterized by small blister-like manifestations that involve various areas of oral mucosa. Oral lesions resemble vesicles of primary HSV, but these lesions are not particularly an important symptomatic, diagnostic, or management problem. Complications of chickenpox include encephalitis, pneumonitis, Reye's syndrome, and Guillain-Barre syndrome.[21]

Herpes Zoster Infection

Pathogenesis and latency

Following the primary infection of varicella-zoster, virus becomes reactivated from the latency at dorsal root of cranial nerve ganglia. The nerves most commonly affected by HZV infection are C-3, T-5, L-1, and L-2. Serious ophthalmic symptoms are observed, when HZ involves the trigeminal ganglion, the first division (ophthalmic or V_1).

Table 2: Medication management of recurrent oral HSV infection in adults

Diagnosis	Drug	Route of administration	Dose	Frequency	Duration
Recurrent herpes labialis in an immunocompetent host	Acyclovir	Oral route	400 mg	Three times a day	5-7 days
Prophylaxis of recurrent herpes labialis in an immunocompetent host	Acyclovir	Oral route	400 mg	2-3 times a day	
	Valacyclovir	Oral route	500 mg-2000 mg	Twice a day	
Recurrent HSV infections in an immunocompromised host	Acyclovir	Oral route	400 mg	Three times a day	10 days or longer as necessary
	Valacyclovir	Oral route	500-100 mg	Twice a day	10 days or longer as necessary
	Famciclovir	Oral route	500 mg	Twice a day	Up to 1 year
Prophylaxis of recurrent HSV infection in an immunocompromised patient	Acyclovir	Oral route	400-800 mg	Three times a day	
	Valacyclovir	Oral route	400-800 mg	Three times a day	
	Famciclovir	Oral route	500-1000 mg	Twice a day	

Clinical features

Herpes zoster (HZ) is an acute infectious viral condition which is extremely painful and is associated with vesicular eruptions of the skin or mucous membranes in areas supplied by the affected sensory nerves. The cases of paresthesia along the course of the affected nerve have been reported. Ramsay Hunt syndrome is typically characterized by unilateral vesicles of oral mucosa and external ear, unilateral facial paralysis that appear 3–5 days later an inflamed base along the involved nerve. Unilateral vesicles are observed when geniculate ganglion of the facial nerve is involved.[22] Diagnosis of HZ is usually based on typical clinical signs and symptoms, dramatic distribution of unilateral involvement associated with this disease with extreme pain, helping to distinguish it from HSV recurrence.[23,24] VZV may also cause pain along the course of nerve with no lesions on oral mucosa or external ear; the latter is referred as zoster sine herpete or zoster sine eruption. In immunocompetent patients, HZ may cause large local lesions or disseminated infection. The cases of alveolar bone necrosis with exfoliation of teeth have been reported. Postherpetic neuralgia is a potential consequence of HZ resulting from scarring of the involved nerve during HZ infection. Postherpetic neuralgia is increasingly observed in the adult population aged 50 years and above, sometimes postherpetic neuralgia can last for months to years after the lesions are healed.[25]

Management

HZ infections are usually treated with acyclovir, valacyclovir, or famciclovir: oral acyclovir 800 mg for five times a day for 7–10 days; valacyclovir 1000 mg for three times a day for 7 days; and famciclovir 500 mg for three times a day for 7 days.

Acyclovir is usually effective in shortening the course of HZ infection for faster healing and reduces pain. Valacyclovir and famciclovir are also reported as effective drug treatment of HZ infection. Acyclovir, valacyclovir, or famciclovir have been reported to reduce the incidence as well as the duration of postherpetic neuralgia cases. Other effective therapy for the treatment of postherpetic neuralgia includes gabapentin, topical capsaicin, tricyclic antidepressants, opioids, and topical lidocaine patches.[26,27]

Epstein-Barr Virus Infection

Epstein-Barr virus (EBV) belongs to the herpes viridae group, is a significant pathogenic virus that is known to infect B cells in the oropharyngeal epithelium.

Pathogenesis and Latency

The transmission of EBV infection occurs following the contact with oral secretions, saliva on fingers, toys or other objects. EBV replicates in epithelial cells of the oropharynx and viruses are usually shed in the saliva. Cases have been reported with the genital transmission. EBV has an incubation period of 8 weeks.[28] EBV is responsible for infectious mononucleosis. EBV is also reported to be associated with several lymphoproliferative disorders, lymphomas (African Burkitt's lymphoma), and nasopharyngeal carcinoma. Other reported associated conditions are oral hairy leukoplakia, gastric carcinomas, hepatocellular carcinomas, salivary lymphoepithelial carcinomas, oral squamous cell carcinoma,[29] and smooth muscle tumors.[30,31]

Clinical Features

EBV infections of infants and children are asymptomatic, whereas the infections of adolescents and adults result in infectious mononucleosis. The classical triad of EBV includes fever, lymphadenopathy, and pharyngitis. Other symptoms of EBV infection are fever, lymphadenopathy, pharyngitis, hepatosplenomegaly, oral ulcerations, rhinitis, or cough. Hepatomegaly, rhinitis, and cough are less frequently observed in children less than 4 years of age.[32] The complications of EBV include myocarditis, hepatitis, hemolytic anemia, thrombocytopenia, aplastic anemia, splenic rupture, encephalitis, and seizures.[33]

Management

Supportive therapy is adequate in the management of EBV infection. Corticosteroid and antiviral medication are usually employed in immunocompetent patients.[34]

Cytomegalovirus infection

Cytomegalovirus (CMV) belongs to the herpes viridae group, is a frequent cause of asymptomatic infection in humans and may cause significant clinical courses in immunocompetent individuals.

Pathogenesis and latency

Transmission of CMV infection occurs through contaminated blood and body fluid secretions such as saliva, genital secretions, and breast milk. CMV can reside latently in salivary gland cells, endothelium, macrophages, and lymphocytes. Neonates may develop CMV which is also responsible for microcephaly, chorioretinitis, nerve deafness, hepatitis, hepatosplenomegaly, and thrombocytopenia. CMV chorioretinitis is significantly associated with AIDS and tends to progress rapidly. Other complications of primary CMV include myocarditis, pneumonitis, gastrointestinal disease, and aseptic meningitis.[35]

Clinical features

CMV infection often remains asymptomatic in healthy children and adults. Primary CMV infection results from either blood transfusion or sexual contact. Clinical symptoms of CMV include fever, myalgia, cervical lymphadenopathy, and mild hepatitis. The classical features of CMV include hepatosplenomegaly, thrombocytopenia, extramedullary cutaneous erythropoiesis, and petechial hemorrhages. Severe mental and motor retardation are observed in encephalitic conditions. In immunocompetent patients,[36] CMV infection may include unexplained persistent

fever and acute sialadenitis. Case reports have been published that there is a relationship between xerostomia and the presence of CMV in saliva of HIV-infected individuals.[37,38]

Management

CMV infections resolve spontaneously, medication management is usually required in immunocompetent patients. Antiviral agents such as ganciclovir, foscarnet, and cidofovir have been effective in the management of CMV infection. Newer drugs in the development of CMV infection include maribavir, CMX 001, and AIC246.[39]

Human Herpesvirus-6 (HHV-6) infection

HHV-6 infection is a common childhood exanthematous disease. HHV-6 encephalitis usually occurs in severe immunosuppressive states.

Pathogenesis and latency

HHV-6 is significantly associated with CD4 T lymphocytes. CD 45 is an essential component of the membrane receptor for HHV-6. HHV-6 becomes latent in cells of the monocyte-macrophage lineage. CD46 is an HHV-6 receptor that is expressed mostly in macrophages and cells lining blood vessels, and less often in the cells of neuronal origin. Reactivation of latent HHV-6 is significantly associated with drug-induced hypersensitivity, possibly due to a sudden decrease in serum IgG levels. HHV-6 principally targets mature CD4 T lymphocytes and has an ability to dysregulate cellular cytokine production, modulate natural killer cell function, and modify the expression of key cell surface receptors. Two variants of HHV-6 have been identified: HHV-6A and HHV-6B.

Clinical features

The virus is transmitted through the respiratory route, virus particles have been isolated from saliva. Primary infection with HHV-6 is usually asymptomatic. Cases have been reported with unspecified febrile illness and roseola. Oral lesions are not commonly associated with either HHV-6A or HHV-6B infections.[40,41]

Management

Ganciclovir and foscarnet have been used in HHV-6 infection, but their efficacy is unknown. There have been no randomized controlled trials of antiviral therapies in immunocompetent and/or immunocompromised individuals.[42]

HHV-7 infection

HHV-7 infection is ubiquitous and is acquired in childhood.[43] The genomic material of HHV-7 and both variants of HHV-6 are closely related. HHV-7 infection in children has been linked with seizures and encephalitis. The transmission of the virus is like HHV-6 infection.

Clinical features

Primary infection with HHV-7 is often asymptomatic. In symptomatic cases, it presents as a single rose-colored, scaling and herald patch. Symptoms in oral tissue are rare and if present, it may have punctuated hemorrhages, ulcers, bullae, or erythematous plaques.[44] Disseminated HHV-7 infection in immunocompromised patients may lead to multiorgan infection that includes encephalitis, pneumonitis, and hepatitis. However, there is only one case report of HHV-7 encephalitis in an immunocompetent patient. Another case presented with meningitis and optic neuritis resulting from reactivation of HHV-7 in a stem cell transplant recipient.[45,46]

HHV-8 infection

HHV-8 (HHV-8) or Kaposi's sarcoma-associated virus is the most recently identified HHV type. It is significantly associated with malignant conditions in AIDS patients.[47] HHV-8 infection is strongly associated with malignant diseases, which is Kaposi's sarcoma that involves oropharyngeal and gastrointestinal mucosal membranes.[48,49] Lesions may be solitary, multifocal, or multicentric red-purple macules, plaques, or nodules of varying size. Posterior hard palate, gingivae, and dorsum of tongue are most common sites of oral tissue involvement in Kaposi's sarcoma. To date, no neurological lesions have been associated with HHV-8 infection.[50] The treatment strategies for oral Kaposi's sarcoma range from monitoring focal, asymptomatic lesions without intervention to initiating systemic chemotherapy for widespread lesions.[51]

Conclusion

The most common reason for oral ulcerations and blisters is viral infections. A major challenge in the diagnosis of oral viral infections are not due to complex clinical presentations but the long list of viral infections that affect oral tissues and lesser frequency of oral viral infections in their routine dental practice. Early recognition of oral viral infections will reduce the morbidity, comorbidity, and the clinical care cost. Oral lesions possess an advantage for visual access for examination. The symptoms such as blisters, ulcer, color variation, surface/textural changes are easily assessable for differentiating with other conditions. Although it is not always possible to relate the oral findings with medical symptoms for arriving to clinical diagnosis, a careful understanding of oral findings will enhance the scope of Family physicians in clinical relevance for their diagnosis. Hence, formulating diagnostic algorithm of oral lesions with presence of systemic manifestations will serve as a useful tool in clinical situation.

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Conflicts of interest

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