Jurnal Eduhealth
Volume 15, Number 04, 2024, DOI 10.54209/eduhealth.v15i04
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

Insights Into Oral Manifestations As Diagnostic Indicators Of Viral Infections : A Literature Review

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Article Info
Keywords:
infectious diseases,
oral manifestations,
oral lesions,
viral infections.

ABSTRACT
Background: Infectious diseases, particularly viral infections, represent a major global health concern, with significant implications for oral health. Despite their clinical relevance, oral manifestations of viral infections are often underdiagnosed due to their complex and varied presentations. Early recognition of these manifestations can aid in timely diagnosis and management, improving overall patient outcomes. Objective: This study aims to systematically review the oral manifestations associated with viral infections to provide a comprehensive reference for healthcare professionals in diagnosing and managing such conditions. Methods: A systematic review was conducted using five databases, including PubMed and Scopus, to identify relevant studies published between 2014 and 2024. Keywords such as "oral manifestation" and "viral infection" were used. Eligible studies were selected based on predefined inclusion and exclusion criteria, focusing on articles in English with clinical relevance to oral health. Data were extracted independently by multiple authors and analyzed to identify patterns and significant findings regarding oral manifestations of viral infections. Results: The review identified 133 articles, with 24 studies meeting the inclusion criteria. Key findings revealed that human herpesviruses, including HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, and HHV-8, frequently present with distinct oral lesions. These lesions range from vesicles and ulcers to gingival overgrowth and vascular tumors. The study highlights the diagnostic importance of oral findings, particularly in immunocompromised patients. Conclusion: Oral manifestations are critical diagnostic indicators of viral infections and provide an opportunity for early disease recognition. A thorough understanding of these manifestations can enhance clinical diagnosis, reduce healthcare costs, and improve patient outcomes. Future research should focus on developing diagnostic algorithms incorporating oral and systemic findings for better clinical utility.

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INTRODUCTION

Infectious diseases are one of the main health problems in developing countries, including Indonesia (Aniq Noor Mutsaqof et al., 2015). Infectious diseases include various types of diseases caused by viral, bacterial, and parasitic infections (Stein, 2014). Viral infections of the oral cavity are one type of infectious pathology that affects the tissues of the oral cavity

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(Santosh & Muddana, 2020). Viral diseases can arise due to cell damage or as a response of the immune system to proteins in viruses (Burrell et al., 2017). Viral infections generally appear suddenly, characterized by the appearance of single or multiple vesicles or ulcers. Some viral conditions can also be accompanied by general symptoms, such as fever, fatigue, and swollen lymph nodes (Santosh & Muddana, 2020). In addition, viral infections are also associated with the development and progression of periodontal disease. In dental practice, viral diseases that affect the tissues of the oral cavity are often found, but often receive less attention in terms of diagnosis and treatment due to the complexity of their diagnostics (Burrell et al., 2017). Oral health affects overall health and quality of life. Some viruses show specific manifestations on the oral mucosa or characteristic features that can help dentists, oral pathologists, or oral medicine specialists in making a clinical diagnosis (Sarasati et al., 2023). Oral manifestations of viral infections can appear as (1) the initial indication of disease, (2) significant additional symptoms accompanying viral disease, or (3) the only visible sign of viral disease (Sarasati et al., 2023). This article aims to review the various oral manifestations of viral infectious diseases, as a guide for medical personnel in diagnosing diseases caused by viral infections.

RESEARCH METHODS

Search Strategy and Selection Criteria

The search strategy and selection criteria for this study were based on the PICO framework, with the research question: “What are the oral manifestations of viral infections?”. The researchers used five databases, including PubMed and Scopus. The last search was conducted on June 1, 2024. The researchers used the following combinations of search terms: [“oral manifestations” and “viral infections”], [“viral diseases” and “oral manifestations”], and [“oral manifestations” and “infectious diseases”]. In addition, a manual search was conducted for relevant articles and reviews that may not have been captured through the primary search strategy. This systematic review focused on articles published in the last ten years to ensure relevance and accuracy in understanding current patterns of viral infections affecting oral health. Only English-language articles were included. Eligible articles were selected based on interauthor consensus. In addition, new eligible studies were identified through careful examination of relevant references cited in included articles and other reviews. The primary search outcome determined through summary estimation was the percentage of oral manifestations observed in patients with confirmed viral infections. Articles are stored in Mendeley Desktop V1.19.5 software to manage citations, remove duplications, and coordinate the review process.

Data Extraction and Management

The authors assessed the titles and abstracts of the studies obtained through the systematic search described previously. Next, the lead author and co-authors re-evaluated the titles and abstracts to make a final decision regarding article inclusion. Eligible articles were then reviewed in depth for the data extraction process. The authors independently performed data extraction, and any discrepancies in the data extraction process were resolved by discussion with the co-authors. Furthermore, a final data extraction table was

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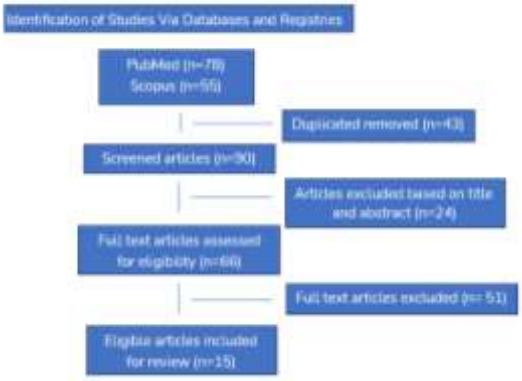
created using Microsoft Excel for further analysis. This table includes important information obtained from each eligible article, such as author names, year of publication, study design, with a special emphasis on data collection regarding oral manifestations of viral infections.

RESULTS AND DISCUSSION

The initial systematic search yielded 133 articles, of which 43 were identified as duplicates and removed. After title and abstract screening of the remaining 90 articles, 24 articles were deemed ineligible and excluded. Further, full-text article screening was performed on 66 articles, resulting in the elimination of 42 articles due to not meeting the eligibility criteria. Finally, 15 studies were deemed eligible and included in the systematic review. The review and selection process for these articles is illustrated in the PRISMA flow diagram (Figure 1).



Picture1. PRISMA Flowchart

Oral Lesions Associated with Herpesvirus

The Herpesviridae family consists of eight species of human herpesviruses, namely Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Human Herpesvirus type 6 (HHV-6), type 7 (HHV-7), and type 8 (HHV-8) (Van Heerden, 2006).

HSV-1 and HSV-2 (Herpes Simplex Infection)

HSV is part of the Herpesviridae family and is known as a pathogenic virus that causes mucocutaneous conditions in the oral cavity and genital area. HSV-1 and HSV-2 are the two main types of herpesviruses that are distinguished by specific antibodies. HSV-1 is commonly associated with pharyngeal infections, meningoencephalitis, and dermatitis above the waistline, while HSV-2 is more commonly associated with infections in the genital and anal areas (Santosh & Muddana, 2020; Van Heerden, 2006). HSV-1 and HSV-2 can cause primary and/or recurrent infections in both the oral and genital areas. Herpetic infection due to contamination of fingers with saliva is called herpetic whitlow (Santosh & Muddana, 2020). Transmission occurs primarily through infected saliva or direct contact with mucocutaneous lesions, with most infections occurring without obvious symptoms (Santosh & Muddana, 2020).

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Primary Herpes Simplex Infection In The Oral Cavity

Infections commonly associated with primary herpetic gingivostomatitis tend to be subclinical in early childhood, with only a small proportion of patients experiencing acute primary infection (Harmiyati & Dewi, 2022). This infection generally causes painful lesions on the skin or mucosa, although it can also occur without symptoms. HSV replicates primarily at the portal of infection, which is usually the oral or genital mucosal tissue, thereby infecting sensory nerve endings. After that, HSV is transported to regional ganglia via sensory nerve endings and remains latent (Santosh & Muddana, 2020). This infection usually occurs in older children and is characterized by symptoms such as fever, malaise, headache, cervical lymphadenopathy, and vesiculo-ulcer eruptions on the peri-oral skin, vermilion, or intra-oral mucosal surfaces. The vesicles, which are usually 2 to 3 mm in diameter, rupture leaving painful ulcers, which generally heal without scarring within seven to ten days. Swelling and redness of the gingiva occurs due to general inflammation. After that, the virus migrates to the trigeminal ganglion, where it remains in a latent state (Drago et al., 2021; Van Heerden, 2016).

Secondary Labial Herpes

Various factors, such as colds, influenza, fever, UV exposure, menstruation, emotional disturbances, stress, and anxiety, can increase susceptibility to recurrent infections. These factors can trigger reactivation of the virus, which then migrates along one of the sensory divisions of the trigeminal nerve. Lesions are usually found on the mucocutaneous border of the lips or peri-oral skin. A burning sensation often precedes the appearance of a small group of vesicles. These vesicles then enlarge, merge, ulcerate, and form crusts before finally healing in about 10 days (Santosh & Muddana, 2020; Van Heerden, 2016).

Varicella-Zoster Virus: Chicken Pox (Varicella)

Varicella-zoster virus(VZV) is a member of the Herpesviridae family and is a pathogenic virus known for its ability to cause mucocutaneous conditions affecting the oropharyngeal mucosa and skin (Van Heerden, 2006). Chickenpox is a primary infection caused by the Varicella-zoster virus (VZV), which is commonly spread in children through direct contact or airborne droplets. After an incubation period of 2 to 3 weeks, the infection usually begins with a prodromal phase characterized by symptoms such as malaise, mild fever, headache, anorexia, and pharyngitis. The lesions that form are small erythematous vesicles on the buccal mucosa that quickly develop into shallow ulcers. These lesions can appear 1 to 3 days before or at the same time as the appearance of exanthema. Mucosal lesions can also affect other areas, such as the nose, conjunctiva, larynx, trachea, gastrointestinal tract, urinary tract, and genitals. However, oropharyngeal lesions are usually fewer in number and less severe than primary HSV infections, and are generally not accompanied by gingival swelling. The typical manifestation is pruritic erythematous macules and papules, initially appearing on the scalp and face before spreading to the trunk and extremities. These lesions rapidly progress from maculopapular to elliptical vesicles on an erythematous base, giving a characteristic “dewdrop on rose petal” appearance. The lesions then crust over, a process that typically lasts for 1 to 2 weeks. After the lesions resolve, areas of residual hypopigmentation may be seen. In addition, new lesions usually appear gradually over a period of 2 to 4 days. One of the

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hallmarks of chickenpox is the presence of lesions at various stages of development within each affected area (Drago et al., 2021; Santosh & Muddana, 2020).

Epstein-Barr Virus (EBV) Infection

Epstein-Barr virus (EBV) is a member of the Herpesviridae family and is known as a pathogenic virus that infects B cells in the oropharyngeal epithelium (Huang et al., 2023; Kikuchi et al., 2017; Santosh & Muddana, 2020). EBV is a very common herpesvirus and is usually transmitted through contact with saliva. EBV infection in children is generally asymptomatic, but often causes infectious mononucleosis (IM) in adolescents and adults. Skin lesions have been reported in approximately 2% to 3% of patients with acute IM, usually in the form of a maculopapular (morbilliform) rash that lasts for several days, although some patients may show atypical forms (Guidry et al., 2018). In addition, a maculopapular rash that often affects the palms and soles usually appears approximately 7 to 10 days after therapy with ampicillin or other beta-lactam antibiotics. Petechiae of the eyelids, periorbital edema (usually without conjunctivitis, known as “Hoagland Sign”), and urticarial lesions have been reported during IM. Some patients may also present with maculopapular enanthema and petechiae localized between the hard and soft palates, which often merge. EBV infection in infants and children is generally asymptomatic, while in adolescents and adults it often causes infectious mononucleosis (Hong & Ko, 2015; Huang et al., 2023; Kikuchi et al., 2017). The classic triad of symptoms associated with EBV infection includes fever, lymphadenopathy, and pharyngitis. Other symptoms that often occur include hepatosplenomegaly, oral ulceration, rhinitis, or cough. However, hepatomegaly, rhinitis, and cough are less common in children younger than 4 years of age. Complications of EBV infection can include myocarditis, hepatitis, hemolytic anemia, thrombocytopenia, aplastic anemia, splenic rupture, encephalitis, and seizures (Drago et al., 2021; Guidry et al., 2018; Hong & Ko, 2015; Kikuchi et al., 2017).

Cytomegalovirus (CMV) infection

Cytomegalovirus(CMV) is a member of the Herpesviridae family and is a common cause of asymptomatic infections in humans. However, CMV can also cause significant clinical manifestations in immunocompetent individuals (Burrell et al., 2017; Harmiyati & Dewi, 2022). Ulcers due to CMV infection are often nonspecific and are more common in patients with AIDS, who usually show keratotic skin lesions and ulcerations on the mucosa or skin. In addition, CMV infection can be associated with gingival enlargement and periodontal disease. In immunosuppressed individuals, oral ulcerative lesions can occur due to concurrent infection with CMV and other herpesviruses, such as EBV, HHV-6, and HHV-8. Coinfection between EBV and CMV can trigger the development of macular and papular rashes accompanied by petechiae on the palate (Harmiyati & Dewi, 2022; Santosh & Muddana, 2020).

HHV-6 and HHV-7 infections

HHV-6 and HHV-7 are primarily transmitted through saliva and usually remain latent for life. Primary infection with HHV-6, and less commonly HHV-7, can cause exanthema subitum (roseola infantum), which is the most common exanthematous fever in children under 3 years of age. In patients with exanthema subitum due to HHV-6, the presence of an ulcer at the uvula-palate-glossa junction is the hallmark of symptomatic primary HHV-6 infection.

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Nagayama Spot, a type of enanthema associated with primary HHV-6 infection, appears as erythematous macules and papules located on the soft palate and uvula. These patches are found in approximately two-thirds of patients with exanthema subitum. In addition, during endogenous systemic reactivation, HHV-6 and HHV-7 can contribute to other diseases, especially pityriasis rosea (PR) (Drago et al., 2021; Eliassen et al., 2018; Hamada et al., 2023; Santosh & Muddana, 2020).

Pityriasis rosea(PR) typically begins with a single erythematous, oval, scaly plaque known as the mother patch. Within about 14 days, a secondary eruption develops, characterized by smaller, scaly macules and papules distributed along skin creases over the trunk. This distribution pattern often gives a “Christmas tree” or “theater curtain” appearance on the back. Oropharyngeal lesions have been reported in approximately 30% of patients with PR, following the course of the skin eruption. These lesions typically resolve with resolution of the skin eruption or within a few days. The most commonly observed enanthem patterns include petechial, macular, and papular lesions, with the presence of oropharyngeal lesions often associated with systemic symptoms (Drago et al., 2021; Eliassen et al., 2018; Hamada et al., 2023).

HHV-8 infection

HHV-8 is transmitted to humans through a variety of routes, including sexual contact, salivary secretions, blood transfusions, and organ transplantation. The virus is associated with the development of vascular neoplasms, angiogenesis, inflammation, and cellular proliferation. HHV-8 infection has been associated with several diseases, including Kaposi sarcoma (KS), lymphoma, and multicentric Castleman disease (Burrell et al., 2017). The hallmarks of Kaposi sarcoma (KS) include hyperpigmented purple-black, compressible nodules on the skin, with an asymmetrical linear distribution, typically found on the legs, soles, back, face, or genitalia. In oral involvement, clinical features typically include maculopapular (75%) or nodular (14%) lesions, as well as tumor-like proliferative lesions (11%) that primarily affect the hard palate before spreading to the oropharynx. The tongue, gingiva, and oral mucosa may also be involved, although rarely. These lesions are prone to bleeding, especially after feeding. More aggressive types of KS, such as AIDS-related KS and transplant/iatrogenic KS, often involve the oropharyngeal mucosa and can cause gingival hyperplasia (Burrell et al., 2017; Dai et al., 2020; Drago et al., 2021).

Oral Lesions Associated with Human Papillomavirus (HPV)

Human Papillomavirus (HPV) is a group of viruses with more than 200 types, of which about 40 can infect the anogenital and oropharyngeal areas. HPV is classified into low-risk types, which generally cause warts, and high-risk types, which have the potential to cause cancer.(Chung et al., 2014). Types 16 and 18 are the leading causes of cervical cancer and are also associated with oropharyngeal cancer, including in the oral cavity. HPV is transmitted through skin-to-skin contact. Oropharyngeal infection can occur through oral-genital contact, kissing, or autoinoculation. The risk of infection is increased in individuals with multiple sexual partners and those who engage in oral sex. HPV infects squamous epithelial cells in the oral cavity and oropharynx.(Candotto et al., 2017). The virus integrates its DNA into the host cell genome, causing dysplasia or precancerous changes. The oncogenic proteins E6 and E7

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produced by high-risk HPV types inactivate tumor suppressor proteins such as p53 and pRb, leading to uncontrolled cell proliferation and potential transformation into cancer.(Candotto et al., 2017; Chung et al., 2014).

Oral Manifestations of HPV

a. Oral Warts (Oral Papilloma):Low-risk HPV types, such as types 6 and 11, can cause benign lesions in the oral cavity known as squamous papillomas. These lesions usually appear as small, white or pink growths with a ridged surface.(Candotto et al., 2017; Chung et al., 2014).
b. Condyloma Acuminata:Caused by low-risk types of HPV, these lesions are larger in shape with a cauliflower-like surface, often found on the oral mucosa.
c. Precancerous Lesions and Oropharyngeal Cancer:High-risk HPV types, especially type 16, are associated with oropharyngeal cancer. Early symptoms may be vague, but may include persistent sore throat, difficulty swallowing, a lump in the neck, or a non-healing ulcer in the mouth. These lesions can occur on the base of the tongue, tonsils, and the back of the throat.(Candotto et al., 2017).

Hand, Foot And Mouth Disease (HFMD)

Hand, Foot, and Mouth Disease(HFMD) is a viral infection that is common in children, but can also affect adults. This disease is characterized by fever, the appearance of vesicular lesions on the hands, feet, and ulceration in the oral cavity. HFMD is most often caused by the Coxsackie A16 virus and Enterovirus 71 (EV-A71). This virus belongs to the Picornaviridae family, which is a single-stranded RNA virus without an envelope. Clinical manifestations in the form of fever are often the initial symptoms that appear before skin and oral lesions. Then the appearance of vesicular rashes on the palms of the hands, soles of the feet, and sometimes on the buttocks. And lesions in the oral cavity usually begin as erythematous macules which then develop into painful vesicles and ulcerations. These lesions are often found on the buccal mucosa, tongue, and gums, causing discomfort when eating and swallowing.(Amanda et al., 2023; Zhu et al., 2023).

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus (HIV) is a virus that attacks the immune system, specifically CD4 cells, which play a vital role in the body's defense against infection. Over time, HIV can weaken the immune system, leading to Acquired Immunodeficiency Syndrome (AIDS). Oral manifestations are often an early indicator of HIV infection and can predict disease progression.(Astuti & Komala, 2023).

Oral Manifestations of HIV/AIDS:

1. Oral Candidiasis: A Candida fungal infection of the oral cavity, often appearing as a white plaque on the oral mucosa that can be removed. Oropharyngeal candidiasis is the most common opportunistic infection in people with HIV/AIDS.
2. *Oral Hairy Leukoplakia*: White lesions on the lateral sides of the tongue with a folded or hairy surface, caused by reactivation of the Epstein-Barr virus. These lesions are often found in patients with HIV/AIDS.

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3. Kaposi's sarcoma: A vascular tumor lesion that appears as a purplish red patch or nodule on the oral mucosa, especially on the palate. Kaposi's sarcoma is one of the common oral manifestations in HIV/AIDS patients.
4. Periodontal Disease: Including erythematous linear gingivitis and necrotizing periodontitis, characterized by severe gingival inflammation, pain, and bleeding. These periodontal lesions are closely associated with HIV infection and have implications for both oral and systemic health.
5. Oral Ulcers: Painful open sores on the oral mucosa, often recurring and difficult to heal in individuals with HIV. These ulcers can be an indicator of HIV infection.
6. Esophageal Candidiasis: Candida infection extending to the esophagus, causing pain on swallowing and can be a sign of significant immunodeficiency. Esophageal candidiasis is common in HIV patients with CD4 counts below 200 cells/mm³(Astuti & Komala, 2023; Masuku et al., 2021; Ramayanti, 2017).

Mumps

Mumps, also known as mumps, is a contagious viral disease caused by the mumps virus, a member of the Paramyxoviridae family. The disease is characterized by swelling of the parotid glands, which are salivary glands located in front of and below the ears. Although vaccination has significantly reduced the incidence of mumps, outbreaks still occur in various parts of the world.(Su et al., 2020a; Tesini, 2023). Mumps is caused by the mumps virus which is transmitted through respiratory droplets or direct contact with the saliva of an infected person. The virus can be spread through coughing, sneezing, or sharing eating utensils with an infected person. The average incubation period is 16 to 18 days, with a range of 12 to 25 days.(Gouma et al., 2016; Su et al., 2020). Early symptoms of mumps are often nonspecific, including fever, headache, muscle aches, fatigue, and loss of appetite. The most common symptom is swelling of the parotid glands (parotitis), which causes puffy cheeks and a painful jaw. This swelling can occur on one or both sides of the face.(Su et al., 2020). In addition to parotitis, mumps can cause other oral manifestations, such as swelling of the submandibular and sublingual glands located under the jaw, the tongue can also experience swelling although less frequently, then there is pain when chewing or swallowing due to swelling of the salivary glands, and dysfunction of the salivary glands due to infection can reduce saliva production, causing dry mouth.(Gouma et al., 2016; Stein Zamir et al., 2015).

CONCLUSION

The most common cause of oral ulceration and blistering is a viral infection. However, the diagnosis of oral viral infections is often challenging, not because of the complex clinical presentation, but because of the many types of viral infections that affect the oral tissues and the low frequency of such cases in daily dental practice. Early recognition of oral viral infections is essential because it can reduce morbidity, comorbidities, and costs of clinical care. Oral lesions offer a unique advantage in visual examination, with symptoms such as blisters, ulcerations, discoloration, and surface/texture changes easily identifiable to differentiate them from other conditions. Although it is not always possible to directly relate oral findings to medical symptoms in the diagnosis, a deeper understanding of oral findings can improve the

diagnostic ability of the family physician. Therefore, the development of a diagnostic algorithm for oral lesions taking into account systemic manifestations can be a valuable tool in clinical practice.

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Jurnal Eduhealth
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