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Role of Viruses in Periodontal Diseases: A Review

Neha Taneja, Praveen Kudva, Monika Goswamy, Geetha Bhat and Hema P. Kudva

Department of Periodontics and Oral Implantology, Jaipur Dental College, Jaipur, (Rajasthan)-302028, India
**Corresponding author*

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A B S T R A C T

Periodontitis is a multifactorial disease**.** Even though specific infectious agents are of key importance in the development of periodontitis, it is unlikely that a single agent or even a small group of pathogens are the sole cause or modulator of this heterogeneous disease. Due to the episodic nature of periodontal disease, viruses play an important role in etiology. The present review focusses on the role of viruses in periodontal diseases.

Introduction

Periodontal disease is a polymicrobial infection involving a variety of microbes that trigger inflammation, loss of connective tissue attachment and alveolar bone around the teeth. The development of human periodontitis may depend upon cooperative interactions among herpes viruses, specific pathogenic bacteria and tissue destructive inflammatory mediators.

The subgingival presence of both EBV and HCMV was reported to be associated with the major periodontopathic bacteria and the severity of periodontal disease (Brogden *et al.*, 2002; Cochran, 2008).

The hypothesis of a correlation between HCMV and EBV infection and the pathogenesis and progression of aggressive periodontitis has been proposed by various studies (Slots *et al.*, 2003; Winkler *et al.*, 1987; Winkler *et al.*, 1989). The present review article is an attempt to elaborate the role of viruses in periodontal diseases.

What are viruses?

An infective agent that typically consists of a nucleic acid molecule in a protein coat, is too small to be seen by light microscopy, and is able to multiply only within the living cells of a host.

Classification of viruses

At first, Bawden (1941) gave the hypothesis that viral nomenclature and classification should be based on the properties of viruses and not upon host responses. From the early 1950s, viruses began to be classified into

groups based on their physicochemical and structural features.

As per International Committee on Taxonomy of Viruses (2005) viruses are classified into two main divisions depending on the type of nucleic acid they possess:

Riboviruses are those containing RNA

Deoxy-riboviruses are those containing DNA.

Periodontal diseases caused by viruses

HIV

Periodontal pathology associated with the HIV-infected patient can be classified into three distinct categories:

Linear gingival erythema;

Necrotizing ulcerative periodontal diseases, including necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and necrotizing ulcerative stomatitis;

Enhanced progression of chronic adult periodontitis.

Initially, reports describing necrotic lesions of the periodontium and intense marginal gingival erythema in HIV-infected patients were published in the mid-1980s (Contreras *et al.,* 1999; 2000; Gornitsky *et al.,* 1987).

The current American Academy of Periodontology terminology for HIV-G lesions is linear gingival erythema and for HIV-P lesions is necrotizing ulcerative periodontitis (Graves, 2008; Hofbauer *et al.,* 2004).

Linear gingival erythema

Linear gingival erythema is defined as a gingival manifestation of immunosuppressed patients, which is characterized by a distinct linear erythema limited to the free gingival margin.

The lack of response of linear gingival erythema lesions to conventional periodontal therapy, including plaque control, and root planing and scaling, is a key diagnostic feature of linear gingivalerythema because it is difficult to distinguish linear gingival erythema clinically from severe gingivitis in patients with poor plaque control. Another key diagnostic feature of linear gingival erythema is its association with Candida infection. It has been reported that the extent of linear gingival erythema may be influenced by the use of tobacco (Contreras *et al.,* 2000).

Grbic et al., found that oral candidiasis was closely associated with the presence of linear gingival erythema.

Because of the evidence that Candida infection is the primary etiology of linear gingival erythema, the *American Academy of Periodontology* has classified linear gingival erythema as a gingival disease of fungal origin. The presence of Candida within the gingival tissues can explain the inability of conventional periodontal therapy to control linear gingival erythema. It can progress to necrotizing diseases in some cases.

Necrotizing diseases of the periodontium in HIV infected patients

Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis are two related periodontal lesions that have been found in both HIV-infected and non-infected patients.

The American Academy of Periodontology has classified them together as necrotizing periodontal diseases Necrotizing ulcerative gingivitis typically presents as ulceration of the interdental papilla with gingival bleeding

and severe pain (Contreras *et al.*, 1999). The lesion is commonly described as having a punched out appearance of the interproximal papilla, and the affected area typically appears to be covered with a fibrinous pseudo membrane. For a diagnosis of necrotizing ulcerative gingivitis to be made, the lesion must exhibit all three signs. Other signs and symptoms of necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis may include oral malodor, lymphadenopathy, fever, and malaise; however, these findings are inconsistent.

Cobb *et al.*, (2004) using electron microscopy, compared the microbiology of necrotizing ulcerative periodontitis in HIV-infected subjects with necrotizing ulcerative gingivitis lesions of HIV-negative subjects and found that spirochetes, zones of aggregated polymorph nuclear leukocytes, and necrotic cells typically found in necrotizing ulcerative gingivitis lesions were also found in necrotizing ulcerative periodontitis lesions, suggesting that the two lesions had a similar microbiology and pathogenesis.

Herpes virus

Classification

Human herpes viruses are classified based on details on tissue tropism, pathogenicity and behavior under conditions of culture in the laboratory.

α-Herpes viruses: Neurotropic, have rapid replication cycle and displays broad host and cell range *e.g.* HSV-1&2, Varicella zoster.

β- and γ- Herpes viruses: differ in genomic size and structure, but replicate relatively slow and in the restricted range of cells mainly of lymphatic and nodular origin *e.g.* for β- HCMV, HHV-6, HHV-7 and for γ- EBV, HHV-8.

Epstein–Barr virus

Epstein–Barr virus affects over 90% of humans (Cohen, 1997), and is usually transmitted by oral secretions or blood. The virus replicates in epithelial cells or B cells of the oropharynx. Nearly all seropositive persons actively shed virus in the saliva (Yao *et al.*, 1985). Resting memory B cells are the main site of persistence of EBV in the body (Cohen, 1997).

Pathogenesis (Winkler *et al.*, 1988; Yapar *et al.*, 2003)

The virus enters the pharyngeal epithelial cells, multiplies locally, invades the bloodstream and infects B lymphocytes in which two types of changes are produced:

The virus becomes latent inside the lymphocytes

Progeny virions (Lamster *et al.*, 2007)

Intermittent reactivation of the latent EB virus leads to clonal proliferation of infected B cells.

In immuno competent subjects, this is kept in check by activated T cells.

In the immuno deficient, B cell clones may replicate unchecked, resulting in lymphomas (Yapar *et al.*, 2003).

Infectious mononucleosis is a symptomatic disease resulting from exposure to Epstein-Barr virus (EBV, HHV-4). The infection usually occurs by intimate contact. Intrafamilial spread is common Adults usually contract the virus through direct salivary transfer, such as shared straws or kissing, hence the nickname "kissing disease." Most EBV infect ions in children are asymptomatic, in children younger than 4 years of age with symptoms.

Most have fever, lymphadenopathy, pharyngitis, hepatosplenomegaly, and rhinitis or cough. Oral lesions other than lymphoid enlargement include petechiae on the hard or soft palate, necrotizing ulcerative gingivitis (NUG).

Cytomegalo virus

Herpes viruses are found to be more frequently present in periodontal lesions and acute necrotizing ulcerative gingivitis lesions than in gingivitis or periodontally healthy sites. Most of the time, two herpes viruses are implicated in these lesions: Epstein-Barr virus (EBV) that infects periodontal B-lymphocytes and cytomegalovirus (CMV) that infects periodontal monocytes/macrophages and T-lymphocytes. Also, CMV infects salivary glands, epithelial and endothelial cells, and fibroblasts. The seroprevalence of CMV infection in the world varies widely up to 95% of population depending on the geographic area (developed/developing countries) (Neville). Very often, the infection starts early in the childhood, actually, early in gestation because placenta is pivotal in CMV transmission to the foetus (Offenbacher *et al.*, 2008) (Table 1).

Fig.1 Sites of action of various anti-viral drugs

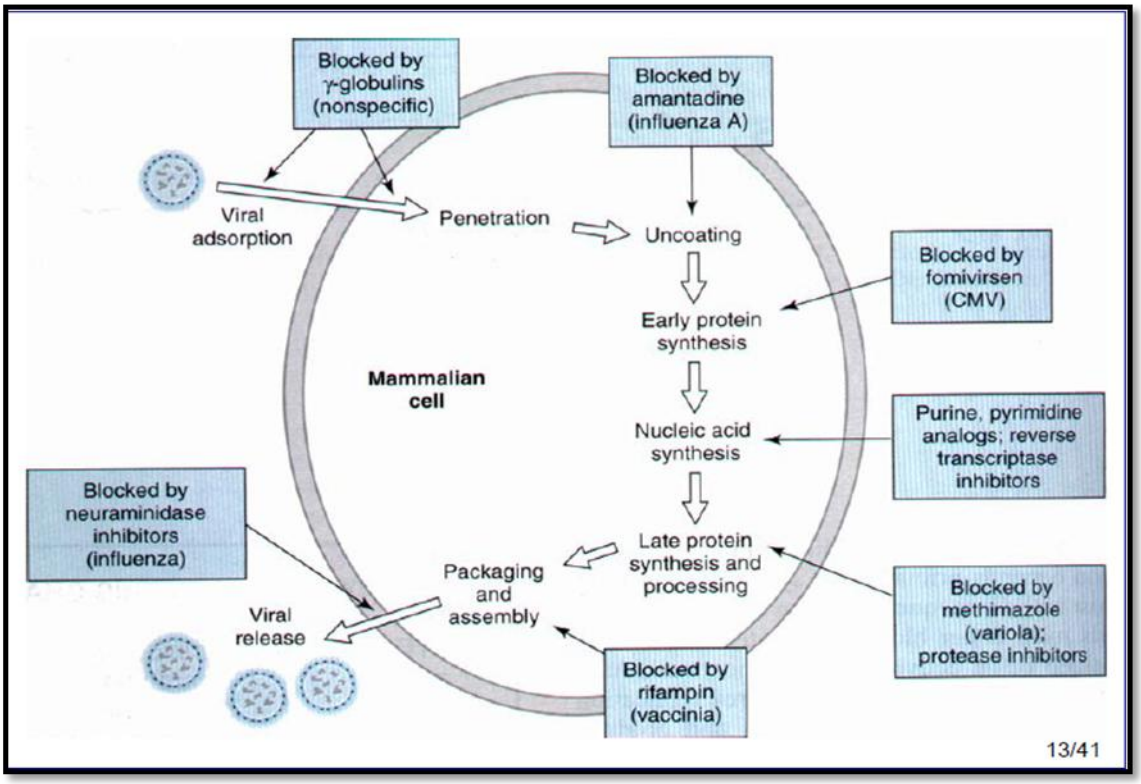

Table.1 Oral viral diseases

Disease	Virus	Systemic symptoms	Oral symptoms
Measles	Measles	cough, conjunctivitis, fever, photophobia, rhinitis	Koplik spot (Irregular red-brick maculopapular skin rash). Candidiasis, necrotizing ulcerative gingivitis and necrotizing stomatitis may be present.
Mumps	Mumps	Orchitis, aseptic meningitis, pancreatis and oophoritis.	Redness and enlargement of Wharton's and Stenson's salivary gland duct openings. involvement of the sublingual gland may produce bilateral enlargements of the floor of the mouth
Hand, foot and mouth disease	Coxsackie viruses	Ulcers on hands and feet	Square blisters on buccal mucosa, soft palate
Herpangina	Coxsackie virus	Headache, high fever, myalgia	Clustered petechiae
Squamous cell papilloma	HPV		Cauliflower like growth of oral mucosa
Verruca vulgaris	HPV		Exophytic growth on gingiva, labial mucosa,c ommissure, hard palate or tongue
Focal epithelial hyperplasia	HPV		Multiple papular lesions on oral mucosa
Oral lichen planus	HPV	Erosive lesion on skin	Erosive lesion on oral mucosa
WHIM’s syndrome	HPV	Hypogammaglobulinemia, infection, myelokathexis	Warts
Herpetic gingivostomatitis	HSV	anterior cervical lymphadenopathy, chills, fever (103' to IDS ' Fl. nausea. anorexia, irritability. and sore mouth lesions	Painful vesicular lesion on gingiva
Infectious mono nucleosis			Lymphoid enlargement, petechiae on the hard or soft palate, Necrotizing ulcerative gingivitis (NUG)
Varicella zoster virus		Fever, malaise. Advanced stages neurological complications might arise	Vesicles and ulcer in oral cavity

Table.2 Various antiviral drugs and their doses

Medication	Trade Name	Dose
Interferon alfa-2b	*Intron A*	5 million IU sq qd or 10 million IU sq 3x/week
Peginterferon alfa-2a	*Pegasys*	180 mcg subcutaneously once weekly
Lamivudine (3TC)	*Epivir-HBV (100 mg)* *Epivir*	100 mg PO qd 300 mg PO qd (or 150 mg PO bid) for HIV-coinfected
Adefovir (ADV)	*Hepsera*	10 mg PO qd
Entecavir (ETV)	*Baraclude*	0.5 mg PO qd for treatment-naïve patients 1 mg PO qd for patients with lamivudine resistance
Telbivudine (LdT)	*Tyzeka*	600 mg PO qd
Tenofovir (TDF)	*Viread*	300 mg PO qd

Abbreviations
IU = international units
sq = subcutaneously
qd = once daily
bid = twice daily

Viruses in pregenancy gingivitis

Gu¨lden Eresx, Elif Altıok, Aykut O¨zkul, and Cengiz Han Acxıkel studied that pregnancy increases the risk of the presence of sub gingival EBV in pregnant women by 3.647 times more than that of non-pregnant women.

Bacterial-viral interaction

While the role of bacterial plaque in general seems to be evident, the following observations indicate that other functions may contribute to the development of periodontal diseases.

Although all subjects with poor oral hygiene develop gingivitis, not every gingivitis lesion invariably leads to attachment loss.

There is a high prevalence of potential bacterial pathogens in certain populations despite a large variation in general levels of oral hygiene.

Global epidemiological data infers that the progression of destructive periodontitis is subject related and comparatively few individuals in the population show advanced periodontal breakdown.

The activities of periodontal sites have been demonstrated to be episodic with periods of quiescence and activation.

These uncertainties have galvanized efforts to find additional etiologic factors for periodontitis. This led to numerous researches probing to explore the possible causative factors for periodontal destruction. Important advances in understanding the infectious agents of periodontal disease have occurred in the past three decades making major inroads into the microbiology, immunology and cause related treatment of periodontal diseases. In the past decade various viruses have emerged as putative pathogens in destructive periodontal disease particularly HIV and Herpes virus.

Treatment

A prompt diagnosis of viral diseases is based upon the quantitative and qualitative

assessment of viral loads. Treatment of viral diseases is based upon administration of topical and systemic antivirals drugs in conjunction with scaling and root planning, 0.12% chlorhexidine mouthwash (Table 2 and Fig. 1).

A solid understanding of the etiology of periodontitis is critical for developing clinically relevant classification systems and therapies that can ensure long lasting disease control. Research during the past 15 years has implied that herpesviruses are involved in the etiopathogeny of destructive periodontal disease (Saygun *et al.*, 2004; Slots *et al.*, 2004). Hopefully, increased knowledge of the immunovirology of cytomegalovirus and other herpes viruses in periodontitis may lead to a greater understanding of periodontal host responses and to more effective preventive and therapeutic interventions, including future vaccination against periodontopathic Herpes viruses.

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