Review Article

Influence of Viruses in Periodontal Disease: A Review

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Abstract

The goal of this review was to assess the effect of viral infection on periodontitis development. Periodontitis is caused by a variety of factors, including pathogenic bacteria, inflammatory mediators, and viruses. In numerous clinical studies, human viruses such as HIV, HCMV, EBV, and HSV have been implicated in the pathogenesis of the periodontal disease. An association has been established between HIV infection and certain types of periodontal infection, namely, necrotizing lesions. Moreover, there are reports that chronic periodontitis is more prevalent in HIV-positive subjects, suggesting HIV infection is a risk factor for chronic periodontitis. Periodontal disease severity and the major periodontopathic bacteria were associated with subgingival EBV and HCMV. Infection with HCMV and EBV has been connected to the pathogenesis and progression of aggressive periodontitis. Periodontal destruction may be caused by HCMV and EBV in conjunction with periodontopathic bacteria.

Keywords: Gingivitis, Herpes Simplex, HIV, Periodontitis, Virus.

Introduction

Periodontal disease is the result of microbial infection, which causes inflammation and loss of connective tissue attachment as well as alveolar bone around the teeth. The primary etiologic factor of periodontitis is bacterial plaque. In most cases, the bacteria are Gram-negative that produce pathogenic factors that trigger host defense responses, causing inflammation and tissue damage.[1] Plaque contains non-bacterial microorganisms including viruses, mycoplasma, yeasts, and protozoa.[2] Numerous studies have suggested that human viruses, particularly Human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and Herpes simplex virus 1 (HSV-1) are involved in the pathogenesis of periodontal disease.[3-5] Subgingival EBV and HCMV were associated with periodontal disease severity and the major periodontopathic bacteria.[6,7] Multiple studies have implicated HCMV and EBV infection in the pathogenesis and progression of aggressive periodontitis.[8-10] As a result of the herpes virus infection, many cytokines and chemokines are released from inflammatory and non-inflammatory cells.

Human Immunodeficiency Virus (HIV)

Periodontal pathology in HIV-infected patients falls into three categories: (i) Linear gingival erythema; (ii) necrotizing ulcerative periodontal diseases, and (iii) enhanced progression of chronic adult periodontitis.[11,12]

In the mid-1980s, several reports described necrotic periodontitis and intense gingival erythema in HIV-infected patients.[11-13] HIV-associated periodontitis (HIV-P) was named after these acute necrotic lesions, which involved the destruction of the underlying bone, and HIV-associated gingivitis (HIV-G) was named after a distinct type of gingival erythema that was resistant to standard plaque control.[13] The current American Academy of Periodontology terminology for HIV-G lesions is linear gingival erythema and for HIV-P lesions is necrotizing ulcerative periodontitis.[14,15] Necrotizing ulcerative gingivitis, in addition to linear gingival erythema and necrotizing ulcerative periodontitis, was more common in HIV-infected patients.[16] Most studies have categorized necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis together as necrotizing periodontal lesions due to their similar clinical appearance and treatment.[17,18] The epidemiology of these HIV-associated periodontal lesions was initially challenging since many early studies lacked suitable

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control groups and revealed significant selection bias.[19] In addition, the lack of definitive diagnostic criteria for these lesions contributed to the wide variation in their reported prevalence across studies. For example, studies found that the prevalence of linear gingival erythema ranged from 0% to 50%.[19-23]

Linear gingival erythema is an immunosuppressed patient's gingival manifestation distinguished by unique linear erythema limited to the free gingival margin. The histology of linear gingival erythema lesions in HIV-infected patients was compared to severe gingivitis in non-HIV-infected patients by Gomez *et al.*[22] Increased numbers of polymorphonuclear leukocytes and immunoglobulin G-producing plasma cells were found in the linear gingival erythema, whereas T cells and macrophages were seen in inflammatory gingivitis in HIV-negative individuals.

Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis are two periodontal lesions that have been found in HIV-positive and HIV-negative patients both. The American Academy of Periodontology has classified them together as necrotizing periodontal diseases. Necrotizing ulcerative gingivitis is characterized by interdental papilla ulceration, gingival bleeding, and severe pain.[11] The interproximal papilla is usually described as punched out and the affected area is typically covered by a fibrinous pseudo membrane. The only difference between necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis is that necrotizing ulcerative periodontitis lesions extend into the alveolar bone. Necrotizing ulcerative periodontitis is characterized by exposed bone, gingival recession, and tooth mobility. Other symptoms of necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis include oral malodor, lymphadenopathy, fever, and malaise.

Although necrotizing ulcerative gingivitis was seen before HIV infection, cases of necrotizing ulcerative gingivitis have been strongly linked to HIV infection. A recent study analyzed the HIV serostatus of individuals who reported to a dental clinic with necrotizing ulcerative gingivitis and no prior indications or symptoms of HIV infection.[17] HIV seropositivity was detected in 69% of the individuals with necrotizing ulcerative gingivitis. It has also been demonstrated that as CD4+ cell counts decrease, the likelihood of developing necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis increases.[12] Chronic periodontitis in HIV-infected patients: Barnett *et al.*[6] found that HIV seropositive patients 35-years-old and with <200 CD4 cells per mm^3 had a considerably faster progression of periodontal disease than an HIV seronegative control group.

In HIV-infected people, the initial treatment for linear gingival erythema and necrotizing ulcerative gingivitis/necrotizing ulcerative periodontitis lesions is gross scaling and root planning to eliminate plaque and calculus deposits, as well as debridement of necrotic tissue, if present. Subgingival irrigation with either a povidone-iodine solution or a 0.12% chlorhexidine rinse, in conjunction with root planning and scaling, should be considered for the treatment of both linear gingival erythema and necrotic periodontal lesions. Furthermore, 2–3 times daily oral rinsing with 0.12% chlorhexidine rinse should be utilized as adjuvant therapy for several months. If the initial treatment fails to control the lesions, systemic antibiotics and/or antifungals should be considered.

Herpes Virus

Herpes viruses have been linked to human periodontitis in studies over the past decade. HSV, HCMV, EBV-1, EBV-2, and HHV-7 were all linked to periodontitis. It is hypothesized that an active HCMV infection in the tissue surrounding the tooth germs damages the root surface structure during the time of infection to explain the discrete nature of tissue breakdown in localized aggressive periodontitis. Infant HCMV infections have been linked to changes in tooth morphology[5,24] and teeth affected by localized aggressive periodontitis frequently exhibit cemental hypoplasia.[25] DNA virus particles found in odontogenic cells of developing teeth in hamsters have also been linked to fibrolytic and osteolytic lesions in the periodontal ligament and adjacent alveolar bone.[26] Acute necrotizing ulcerative gingivitis affects immunocompromised, malnourished, and psychosocially stressed young people and the disease can occasionally spread significantly beyond the periodontium, giving rise to the potentially fatal infection known as noma or cancrum oris.[26] Noma sequelae are thought to affect 770,000 people at the moment.[27]

Herpes virus reactivation is known to be facilitated by HIV-induced immunosuppression.[25] Herpes virus-like particles were found in 57% of biopsies taken from necrotic gingival papillae of HIV-P. Furthermore, significantly, more herpes virus species have been detected in gingival specimens from HIV-periodontitis lesions than in non-HIV patients' periodontitis lesions.[28] HCMV was found in 81% of HIV-P lesions and was the most common herpes virus species found.[28] Gingival Kaposi sarcoma lesions have been linked to severe alveolar bone loss.[29] Patients with down syndrome have a high prevalence of HCMV infection, and periodontitis lesions in these patients typically harbor multiple herpes viruses.[30] HSV maybe a significant pathogen of oral mucosal ulcers in patients with acute myeloid leukemia.[31] According to Saygun *et al.,* periodontal treatment and oral hygiene follow-up reduced periodontal as well as salivary HCMV and EBV.[4]

Varicella-Zoster Virus

Varicella is often acquired during the first 5–10 years of life. Varicella manifests itself abruptly, with or without prodromal fever and malaise.[25] Vesicles and ulcers appear first in the mouth (usually on the palate and tongue, but also the gingiva) and are followed by a cutaneous rash that spreads centrifugally from the head and trunk.[24]

EBV

The EBV infects more than 90% of humans and is typically transmitted through oral secretions or blood. The virus replicates in oropharyngeal epithelial cells or B cells. Almost all seropositive people actively shed viruses in their saliva. While EBV infection in children is typically subclinical, EBV infection in adults causes infectious mononucleosis. Fever, lymphadenopathy, and pharyngitis are the most common symptoms of infectious mononucleosis. Oral ulcers, palatal petechia, and, less commonly, gingival ulcerations can occur. The most common EBV-related lesion is oral hairy leukoplakia. Its presence usually indicates a relatively advanced stage of immunosuppression, such as in HIV infection. HIV-infected patients' T cells suppress EBV-infected B cells less effectively than immunocompetent people's T cells. Thus, HIV patients have 10–20 times the number of circulating EBV-infected B cells as healthy people (Birx *et al.*, 1986).[32] Patients with HIV have a higher EBV load in their oropharyngeal secretions. The virus enters the pharyngeal epithelial cells, multiplies locally, enters the bloodstream, and infects B lymphocytes, causing two types of changes: 1. The virus becomes latent within the lymphocytes; 2. lytic infection, with cell death and the release of mature progeny virions.[33-36]

Cytomegalo Virus (CMV)

CMV infects periodontal monocytes/macrophages and T-lymphocytes. The global seroprevalence of CMV infection ranges from 0% to 95 %, depending on the geographic area (developed/developing countries).[37] The infection usually begins in childhood, or even earlier in pregnancy, because the placenta is critical in CMV transmission to the fetus.[38] Evidence suggests that CMV has not only devised numerous strategies to evade the host immune response but has also exploited the host immune response to achieve reactivation from dormancy and disseminated infection.[39-42] Acute CMV infection is distinguished by high levels of viral replication and spread to multiple organs. Thus, the pathogenesis of acute infection demonstrates a link between viral replication levels, organ dysfunction, and disease in patients. In contrast, the pathogenesis of chronic infection is associated with a bi-directional relationship between viral gene expression and the host inflammatory response: Viral reactivation is aided by the host inflammatory response, and the presence of the virus stimulates the host inflammatory response. The disease, in this case, could be attributed to both viral and host functions.[43] As a result, CMV is reactivated regularly, causing transient immunosuppression and the overgrowth of periodontal pathogenic bacteria.[44-47] Although it has been assumed that the pathogenesis of periodontitis is based on infection caused by bacteria that colonize the tooth surface and gingival sulcus, various studies have shown that host response factors such as inflammatory response and innate immune system activation are critical to the pathogenesis of periodontal disease.[48-50] It appears that CMV infection in periodontal tissue, depending on whether the infection is latent or active, can explain some of the episodic progressive nature of periodontal disease.[34,51]

Summary

Herpes viruses may be involved in the etiopathogenesis of destructive periodontal disease, according to the research conducted over the past 15 years.[52,53] Active EBV or cytomegalovirus infection appears to be statistically associated with aggressive periodontitis, and latent Herpes virus infections are preferentially found in chronic periodontitis and gingivitis sites.[54] Herpes viruses are likely not stand-alone periodontopathic agents, but rather collaborate with specific bacteria in periodontal tissue breakdown.[55,56] Papillomaviruses and other mammalian viruses are also common inhabitants of periodontitis lesions, but their role in the disease's pathogenesis is unknown.[57-59] Repeated and long-term activation of periodontal herpes viruses, as seen in immunologically naive and immunocompromised people, may increase the frequency and severity of clinical exacerbation of periodontal disease.[60-62]

Periodontitis can develop in stages due to a combination of events, including a high herpes virus load in periodontal sites, activation of periodontal herpes viruses, an insufficient antiviral cytotoxic T-lymphocyte response, the presence of specific periodontal pathogenic bacteria, and an insufficient antibacterial antibody response.[63,64]

The development of anti-herpes virus vaccines in the not-too-distant future provides real hope for low-cost periodontitis prevention in large groups of individuals. The available evidence warrants adding human periodontitis to the list of disorders where EBV, CMV, and maybe additional human viruses are potential contributory causes.[65-67]

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