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Review Article

Inspecting Evidence between Cancer Therapy-Induced Oral Mucositis and Periodontitis: A Narrative Review

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Abstract

This narrative review aims to update the reader about the current issues surrounding central aspects implicated in the relationship between oral mucositis (OM) and periodontitis. We searched Medline/PubMed database. English language publications were included in the study. Paired reviewers selected articles for inclusion and extracted data. Forty-four studies met our inclusion criteria. The majority of the studies were review (63.8%) and clinical studies (36.2%). There is a lack of studies regarding the association of periodontal disease (PD) and OM. However, there are pathogenic similarities between them. Look for scientific evidence to confirm the relationship between PD and OM is imperative. Thus, if periodontitis can actually interfere with the occurrence and severity of OM, the establishment of strategies to reduce it may contribute to better control of OM, a serious adverse effect of cancer treatment.

Keywords: Cancer therapy, oral mucositis, periodontitis

Introduction

Oral mucositis (OM), a side effect of cytotoxic cancer therapy, is a painful condition with negative impact in daily activities and also leads economic consequences. Despite researches interest to better comprise its pathogenesis and find effective interventions, OM is still, an unmet need with a high importance for the development of a successful treatment.[1-3]

Periodontal inflammation is a prevalent condition on population, with recognized role at systemic inflammation, producing high levels circulating of cytokines (interleukin-1 [IL-1] and IL-6), prostaglandin E2 (PGE2), tumor necrosis factor (TNF), and C-reactive protein.[4-7]

Both conditions are characterized by an exuberant inflammatory reaction, regulated by an infiltration of immune cells, enzymes, and pro-inflammatory cytokines such as TNF and ILs, which outcome in both soft- and hard-tissue destructions. Further, OM and periodontal disease (PD) are two most common chronic inflammatory diseases in adults' patients receiving cancer therapy,[5,8] and despite the clear pathogenic similarities between them, its relationship is few studied.[9]

Thus, we propose careful approach for the patients under cancer therapy and that have periodontitis diagnose. The evidence indicate that these patients could suffer of a higher severity of OM. Therefore, the aim of this study is to review the physiopathological mechanisms that could explain this biological plausibility.

Review Methods

PubMed/Medline databases were searched for articles in English language focused on pathogenic mechanisms of PD and OM.

The search strategy has involved a combination of titles and relevant keywords in the medical area.

The search terms that we used were ""periodontal disease," "periodontitis pathogeneses," "oral mucositis," oral mucositis pathogeneses," "systemic disease and periodontal disease," "cytokines," "inflammation," and "infection."

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The search included the period between 1998 and 2018, which considered clinical trials, systematic reviews, and experimental animal studies.

All articles identified were full texts.

Knowledge about Periodontal Disease

PD is a complex disease in which the structures of tooth protection (classified as gingivitis) and tooth supporting (classified as periodontitis) are affected. Periodontitis is the main cause of oral infections and tooth loss. The etiology is multifactorial, with local and systemic factors enrolled. Opportunistic infections stand out among the risk factors for outset and development of PD, with a potential risk factor for bacteremia and focal infection. The clinical appearance of PDs is determined by host response against bacterial stimulus. Although specific bacteria are the major etiologic agents of PD, the host response has an important role in damage of the periodontal tissues.[10,11]

PD presents high prevalence, with about 90% of the adult population suffering from gingivitis, 60% having chronic periodontitis, and 5%–15% with aggressive periodontitis.[1,5]

The disease is initiated by certain species of subgingival Gram-negative anaerobic bacteria that coexist within dynamic communities of highly organized architecture biofilm.[12] In periodontal health, the ordered structure of the dental plaque biofilm consists predominately of Gram-positive, facultative anaerobic bacteria, although the onset of the disease is associated with a shift to Gram-negative anaerobic bacteria, which begin to colonize the subgingival pocket.[13] The high number of red complex members such as *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia* correlates strongly with periodontal tissue destruction. *Prevotella intermedia* and *Fusobacterium nucleatum*, both members of the orange complex, are also associated with diverse forms of PD.[14]

Numerous evidence strongly suggest that host inflammatory response leads tissue destruction and that the variability of host responses defines the variability in the clinical manifestation of periodontitis. Hence, although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression. The inflammatory response in a susceptible host is crucial.[4,5,15]

The destruction of soft and hard tissues, seen in periodontitis, is the result of a large number of cytokines, and the sustained presence of other effector molecules released by resident and migrating cells. Together, these inflammatory mediators of inflammation induce the cascade of molecular events associated with extracellular matrix (ECM) degradation and resultant tissue damage.[4,5,16]

The regulation of the immune response depends on inflammatory cytokine production by different subpopulations of helper T-lymphocytes (Th), which act enhancing or attenuating the inflammatory response in periodontal tissues and thus determining the activity or the latency of periodontal lesions.[6,8] These cytokines include PGE2, TNF-α, IL-1α, IL-1 β, and others.[6,7]

A biologic system model has been explored with bacterial components, environmental factors, and host genetic variations associated with disease. By this model, the microbial products active the immune system. Then, these immune responses influence the bone and connective tissue metabolism. For each individual, there are combinations of genetic variations and environmental factors. These genetic and environmental factors act on biologic mechanisms to modify the expression of genes activated by the bacterial products. Within this framework, discrete modules of genetic, environmental, and other modifying factors would define a specific expression pattern that represents the shift from health to disease.[17]

Periodontal Disease and Systemic Disease: Brief up-to-Date

Several systemic conditions are associated with a higher prevalence of PD such as diabetes mellitus. Chronic hyperglycemia due to structural changes occurs (such as a reduction in vascularization and leukodiapedesis, and increased collagenase has been the reduction of scarring) which end accelerating periodontal destruction.[18,19] Thus, people with diabetes are at increased risk for PD.

Other diseases may also predispose to PD such as autoimmune diseases. Patients with rheumatoid arthritis, dermatomyositis, lupus erythematosus, and ankylosing spondylitis have more prevalent and more severe PD than patients without these conditions.[20-22] In addition, patients with chronic orofacial pain and Alzheimer's disease also have worse gingival indexes.[23-25]

On the other hand, systemic exposure to periodontal pathogens, their toxins, and periodontal inflammatory mediators may have deleterious effects on different organs or systems. It was reported three mechanisms by which periodontal infection can influence systemic health: metastatic infection (caused by the translocation of Gram-negative bacteria of periodontal pocket into the blood flow), metastatic lesions (e.g., vascular injury caused by the effects of toxins microbial and circulating pro-inflammatory mediators), and metastatic inflammation (due to the immune response to periodontal pathogens and their toxins).[12,16]

There is increasing evidence that systemic inflammation results from the entry of oral microbial agents and their virulence factors into the circulation. Elevated serum levels of C-reactive protein and other acute-phase reactants and raised biomarkers of oxidative stress evidence this. It is, therefore, biologically plausible that nonresolving chronic inflammation derived from PD impacts on systemic health [Figure 1].[5,6]

Furthermore, periodontitis shares many common risk factors with chronic systemic diseases. These factors include smoking, diabetes, obesity, nutritional dysfunction, stress, aging, and

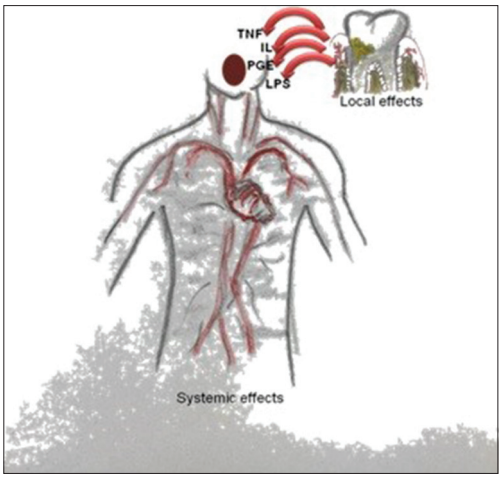

Figure 1: The destruction of tissues in periodontitis is the result of a large number of cytokines and effector molecules released by resident and migrating cells. The microbial virulence factors enter into the blood circulation and impacts on systemic health. TNF: Tumor necrosis factor-alpha, IL: Interleukin, PGE: Prostaglandin, LPS: Lipopolysaccharide

race/ethnicity, among others. The oral cavity can act as a reservoir and a potential source for dissemination of pathogens to distant body sites. Access to nonoral sites is facilitated by bacteremia, which occurs following even minor oral routines, such as daily toothbrushing, as well as by dental procedures.[19]

Indeed, gingivitis and periodontitis can also induce a series of immune changes in circulating immune complexes, due to the failure of autoimmune regulation and tolerance, contributing to the emergence and progression of autoimmune diseases.[26]

Accordingly, dental and medical care should be more carefully integrated. Then, health education program should encourage the improved oral health beside the current healthy lifestyle guidelines, alongside smoking cessation, satisfactory diet, and exercise. These current evidence are such that prevention and treatment of PD may reduce chronic systemic disease risk and the onset of others immune-inflammatory diseases.[25,26]

About Oral Mucositis

OM is an acute reaction associated with radiotherapy, chemotherapy, or a combination of both treatments.[27] It is one of the most common complications of oral anticancer treatment, being found in about 40%–46% of patients receiving chemotherapy.[28,29]

Among patients with head-and-neck tumors treated with radiotherapy, 90%–97% presents some degree of mucositis, and in general, 50% develop Grade III or Grade IV mucositis.[30]

The clinical manifestations of OM include signs and symptoms of inflammation, varying from mild erythema, edema, and soreness to extreme pain and ulceration that require analgesic medication. Severe OM interferes with daily activities, such as speaking, eating, and swallowing, resulting in dehydration, malnutrition, and opportunistic infections, with a negative impact on the quality of life.[31-33] When severe OM develops, cancer treatment may be modified or even halted which can limit the efficacy of treatment, and this is estimated to occur in about 10%–25% of all patients, although interruption rates as high as 47% have been reported.[3,33]

The development of OM has been described in five stages.[1,34] The initiation phase is characterized by two events: injured DNA and strand breaks resulting in clonogenic death of basal epithelial cells directly by radiation and chemotherapy. Even more significant from the aspect of ultimate tissue damage is the production of reactive oxygen species (ROS), which decreases the cell turnover, attacking epithelial cells, and connective tissue and affecting, in particular, epithelium, and blood vessels. The following stage is characterized by primary damage response to chemotherapy, radiation, and ROS initiating a series of interacting biological events. Transduction pathways caused by DNA strand breaks and lipid peroxidation induce the activation of transcription factors, such as nuclear factor-kappa B (NF-κB), Wnt signaling pathways, and p53. NF-κB can be directly activated by chemotherapy and radiation and indirectly by ROS. Genes, whose expression is governed by NF-κB, are those associated with the production of molecules, which showed activity in the pathogenesis of mucositis comprising cytokines and cytokine modulators, stress responders (i.e., COX-2, inducible nitric oxide synthase, and superoxide dismutase), and cell adhesion molecules. An important consequent event of effects of NF-κB in normal cells is apoptosis.[1]

Therefore, there is a production of various inflammatory mediators such as TNF-α, IL-1 β, and IL-6 that stimulate pro-apoptotic enzymes, block the growth and differentiation mechanisms, and initiate the tissue damage.[34] This stage is recognized by signal amplification.

Ulceration is the most symptomatic and probably the most complex stage. The bacteria on the ulcer surface are active contributors to the mucositis process. Cell wall products (i.e., lipopolysaccharides, lipoteichoic acid, cell wall antigens, and α-glucans) penetrate into the submucosa, now rich in macrophages, and stimulate those cells to further secrete pro-inflammatory cytokines. In granulocytopenic patients, there is a risk that intact bacteria may invade submucosal vessels to produce bacteremia or sepsis.[2,9,34]

The majority of cases of OM cure spontaneously. The active biological process in which signaling from the submucosa's ECM guides the proliferation, migration, and differentiation of the epithelium bordering the ulcer is responsible of its ulcer heal. This is the healing stage.[1]

The severity of mucositis depends of a number of factors including the administered dose, the dose fraction, the volume of tissue treated, and the type of radiation given. The patient factors include the type of malignancy, patient age, and oral health.[35]

Biological Links between Oral Mucositis and Periodontitis

The debilitating effects of mucositis can result in unplanned treatment interruptions or even premature cessation of treatment. The risk of systemic infections and even death is increased in patients with mucositis, since the lesions act as a gateway of oral bacteria into bloodstream, which can lead to bacteremia and sepsis, with a high morbidity and mortality in susceptible individuals.[36-38]

The role of the PD in some systemic conditions has been demonstrated. Some studies have shown that it plays an important role in cardiovascular, metabolic, autoimmune diseases and neurovascular conditions.[19,22,23,39] PD can be related to refractory craniofacial pain and also to worsening of Alzheimer's disease.[23,24] In these studies, the main pathophysiological mechanisms involved are related to the constant release of cytokines that generate systemic inflammation as well as aspects related to bacteremia.[40]

Thus, both OM and PD are immunoinflammatory condition characterized with the continuing presence of systemic inflammation and bacteremia.[6,19,32] These conditions are prevalent in patients receiving cancer therapy and could put them at risk of systemic complications.[9,27] Considering these data, it is plausible to explore the possibility of link between OM and PD. However, clinical and/or laboratory studies involving OM and PD interrelationships are scarce in the scientific literature available.

Recently, it was suggested a "two-hit" model to justify the association between radiation-induced OM and periodontitis.[41] This model suggests that inflammation at the periodontium level which is periodontitis (first "hit") followed by radiation (second "hit") can lead to an exacerbated response in the form of OM. The converse may also hold true in that radiation-induced OM (first "hit") exacerbates the inflammatory response of developing periodontitis (second "hit").[41]

Really, many factors can directly affect the change of mucosal exposure to radiation, the protection of mucosal cells, and the local inflammatory response.[42] It was reported that reducing dental plaque and gingival inflammation by oral care was positively correlated with OM, corroborating the idea that oral inflammation is predictive of OM incidence and healing time.[32,43] Furthermore, preliminary findings showed that there was a trend toward a greater proportion of periodontitis patients in the mucositis groups than in the nonmucositis group.[41]

Another relevant feature in this association is that the cytokines involved in the pathogenesis of OM are common to those involved in the pathogenesis of PD. The progression of both, PD and OM, occurs due to a combination of factors, including increased levels of pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-α), metalloproteinases, PGE2, low levels of anti-inflammatory cytokines (such as IL-10), and transforming growth factor-beta.[5,7,34]

As indicated previously, NF-κB is thought to play an important role in the pathobiology of mucositis, particularly with respect to the upregulation and subsequent expression of the pro-inflammatory cytokines TNF, IL-1b, and IL-6. The activation of NF-κB can be facilitated by various factors including radiation and chemotherapy as well as infectious agents and inflammatory cytokines,[34] such as PD.

On the order hand, the inflammatory response altered by radio/chemotherapy puts patient at risk for progression of PD,[27,38] triggering a new cycle of upregulation of cytokines [Figure 2].

Despite these findings, the role of microorganisms in the development of mucositis is unclear. Independent of bacterial numbers, the increase in Gram-negative organisms was noted during ulceration, and the recovery of normal bacterial proportions was a condition for spontaneous ulcer resolution.[1] Clinical trial results suggest that antibacterial strategies have been ineffective as OM interventions.[44] However, the interventions analyzed were systemic antimicrobial therapy, and the mechanic removal of dental biofilm (root planing) is crucial to disturb periodontal biofilm.

Further, clinical and laboratorial systematic investigations are required about PD and OM patients. The clinical success of prevention and therapy of OM depends on several biological factors. Moreover, it is important to achieve more insight into the pathobiology of mucositis as well as into periodontitis, both with individual discrepancies and genetic variances that support susceptibility.

Conclusion

Investigating the association of PD and OM is particularly important. PD is a treatable condition, and if it really can interfere with the incidence and severity of OM, the

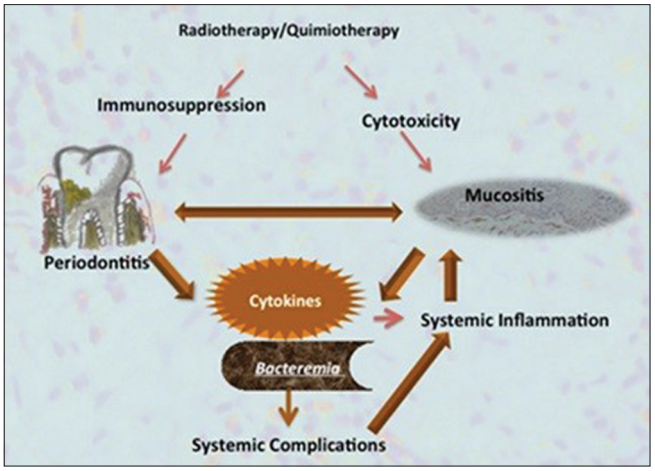

Figure 2: Radio/chemotherapy changes the immunoinflammatory response and puts the patient at risk for progression of periodontal disease (immunosuppression) and has cytotoxic effect on the oral mucosa cells. The progression of periodontal disease and oral mucositis includes increased levels of pro-inflammatory cytokines and induces bacteremia triggering a new cycle of upregulation

establishment of specific interventions to reduce efficiently PD could better control the OM, a serious adverse effect of cancer treatment. Despite advances in medical care to improve survival in cancer patients, infectious diseases are responsible for significant morbidity and mortality in these patients. Prompt diagnosis, appropriate management of oral infections, and preventive procedures are crucial to optimal assistance.

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Conflicts of interest

There are no conflicts of interest.

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