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The Relationship Between Periodontal Disease and Neoplasms of the Oral Cavity: A Review Article

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Abstract

Context: Oral cavity is one of the most common sites for neoplasms with a multifactorial etiology. Tobacco and alcohol are the main risk factors. Periodontal disease is an inflammatory disease affecting periodontal tissues such as gingiva, periodontal ligament and alveolar bone. Periodontal disease is linked to many systemic diseases. Recently a link between periodontal disease and cancer is suggested. The current review article aimed to evaluate the association between periodontal disease and risk of cancer in the oral cavity and some related factors.

Evidence Acquisition: Evidence suggests that oral cavity cancer is significantly more prevalent in patients with periodontal disease, poor oral hygiene or more missing teeth. Clinically, gingival squamous cell carcinoma (GSCC) usually appears as an exophytic mass with a granular, papillary or verrucous surface or presents as an ulcerative lesion. Some reported cases of GSCC mimicking periodontal disease include gingival enlargement with no bone invasion, dentoalveolar abscess, erosive erythematosus lesion with keratotic papules, root exposure and tooth mobility, verrucous leukoplakia, verruciform xanthoma and development of hyperplastic granulation tissue after tooth extraction. Greater burden of oral flora that produce carcinogenic metabolites, human papilloma virus (HPV) and other viruses that are residents of periodontal pocket, increased amount of inflammatory mediators and markers and some periodontal pathogens affecting cell cycle leading to mutation and dysplasia are considered as the rational for the relationship between malignant lesions of oral cavity and periodontal disease.

Results: Cancer of the oral cavity and periodontal disease are related from different aspects. Periodontal disease and tooth loss are considered as independent risk factors for cancer. Gingival squamous cell carcinoma can also mimic periodontal disease leading to misdiagnosis and delayed commencement of appropriate treatment.

Conclusions: Based on evidence, dentists and dental health care professionals should consider periodontal disease as a risk factor for the development of neoplasms in the oral cavity. It also seems a good idea to provide periodontal therapy for patients with cancer to achieve ideal therapeutic results.

Keywords: Periodontitis, Neoplasm, Squamous Cell Carcinoma

1. Context

Head and neck squamous cell carcinoma (HNSCC) includes cancer of the oral cavity, pharynx and larynx (1). Almost 94% of all cancerous lesions of the oral cavity are within the category of oral squamous cell carcinoma (OSCC) (2). OSCC is one of the most prevalent cancers and assumed to be one of the main reasons of mortality and morbidity worldwide (3, 4). The risk of occurrence is increased with age and is mostly observed in males in their 40s (2, 5). OSCC is multifactorial (6) and the most important risk factors are tobacco and alcohol (2).

OSCC has various clinical manifestations and the most prevalent sites in the oral cavity include lateral and dorsal surfaces of the tongue (2). Human papilloma virus (HPV), Epstein-Barr virus (EBV) and other viruses as well as bacterial and inflammatory factors are considered to have a role in the etiology of OSCC (7, 8).

OSCC is a life threatening issue but the risk can be considerably decreased by avoiding some harmful habits (9, 10). Early detection is helpful to decline mortality and morbidity rate (11). It is observed that five-year survival rate is 78% in cases of early diagnosis compared to advanced cases with only 19% survival rate (12). Although oral cavity is an accessible environment for dental examination, early detection rate of SCC has remained unchanged (2, 13). It is mainly because SCC is usually painless in early stage (2).

Periodontal disease is a chronic inflammatory condition which is associated with bacterial infection causing deterioration of periodontal tissues. Periodontitis is prevalent in adult population and is absolutely preventable (1, 14).

It has different prevalence rate in different nations and racial groups. The age range of occurrence is wide and includes both adolescents and adults (15). Periodontal disease is associated with many systemic factors such as cardiovascular diseases, low birth weight and some side effects of pregnancy (16). Presence of a relationship between periodontal disease and cancer is suggested in some studies. Scientific rational is the presence of inflammatory mediators associated with both cancer and periodontal disease (16-18). These neoplasms sometimes have symptoms compatible with those of periodontal disease such as inflammation, gingival bleeding, tooth mobility, deep probing depth and bone loss (16). There are so many reports of gingival squamous cell carcinoma mimicking periodontal or periodontal-endodontic lesions (16).

Other cases of malignant lesions mimicking periodontal disease include metastatic cancer of pancreas and osteogenic carcinoma (19). There is increasing evidence that the risk of cancer is significantly greater in patients with periodontitis or those with more missing teeth (17, 18, 20). The current review article aimed to discuss the association between periodontal disease and neoplasms of the oral cavity especially SCC of the gingiva.

2. Evidence Acquisition

An electronic search was made in Pubmed, Medline and Cochrane oral health group specialized trial register and also a manual search was conducted from 1990 to 2015 on the association between neoplasms of the oral cavity and periodontal disease. The keywords included: Periodontal disease, periodontitis, tooth loss, oral cancer studies, oral neoplasms, squamous cell carcinoma and all the possible combinations (Table 1).

Some of the studies are mentioned below:

Tezal et al. (21) evaluated the effect of chronic periodontitis on occurrence of HNSCC in 2009. One millimeter increase in radiographic alveolar bone loss was associated with four times increase in HNSCC. The strongest association was observed in neoplasms of the oral cavity (OR 5.23 for the tongue). Tezal et al. conducted another cohort study to investigate the association between oral tumors and precancerous lesions with periodontal attachment loss and concluded that more than 1.5 millimeters of attachment loss is significantly associated with increased risk of developing oral tumors (OR 4.57) and precancerous lesions (OR 1.55) (22). Guha et al. concluded that poor oral hygiene and tooth loss can be considered as independent risk factors for head and neck cancer (OR 2.89 in Europe and 1.89 in Latin America) (23). There was a cohort study by Michaud, commenced by filling out a questionnaire about history of periodontal disease and the number of teeth lost; unexpectedly, no association was observed between cancer of the oral cavity and periodontal disease (20). Bundgaard et al. (24) also observed that patients with less than 15 remaining teeth are significantly at greater risk for developing SCC (OR 2). Another case control study was designated by Caio Perrella de Rezende et al. using community periodontal index of treatment needs (CPITN) and it was observed that 76% of cancer cases had periodontal pocket depth of six millimeters or more compared to 10% in the control group (25). Garrote et al. (OR 2.7), Hiraki et al. (OR 1.68 for no remaining tooth) and Tongzhang Zheng et al. also reported a significant association between more missing teeth and the risk for oral cancer (26-28). In a case control study by James et al. (29) in the USA, eleven or more missing teeth was significantly associated with increased risk of developing oral cancer (OR 2.7). Based on the study by Rosenquist et al. (30), more than twenty missing teeth was independent risk factor for oropharyngeal cancer. Talamini also reported the similar results (OR 3.9 for those with constant gingival bleeding and 4.5 for patients with poor oral hygiene) (31).

2.1. Clinical Manifestations of SCC in Periodontal Tissues

Gingival squamous cell carcinoma (GSCC) is mainly observed as an exophytic mass with a verrucous or papillary surface with red or mixed red and white color (32). GSCC can sometimes mimic severe periodontal disease with symptoms such as swelling, gingival bleeding, tooth mobility, deep pocket depth and bone loss (33). Some manifestations of GSCC which are sometimes similar to periodontal inflammatory lesions are introduced:

1- A single red epulis-like lesion in dental papilla of the tooth #22. It bled with minor provocation and the probing depth reached seven millimeters. There was no bone invasion radiographically. Dental papilla is a rare site for GSCC (34).

2- There were some case reports of GSCC mimicking dento-alveolar abscess. It was reported as an erythematous papule located within the attached gingiva of the teeth #9 and #10 near mucogingival junction. It had a soft spongy texture. Oozing was observed from a little hole on the lesion. No periodontal pocket, no mobility, bone loss, root resorption or the periodontal ligament (PDL) widening was observed around the teeth (35).

3- There was another case report of a lesion with erosive erythematous appearance and keratotic papules located in

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Case control studies on the relationship between bone/attachment loss and head and neck cancer considered independent from smoking and alcohol	Studies involving cancer originating from somewhere other than head and neck
Case control studies on the relationship between oral hygiene/number of remaining teeth and head and neck cancer considered independent from smoking and alcohol	Studies with unspecified inclusion and exclusion criteria for the samples
Case reports on manifestations of SCC in periodontal tissues	Case control studies with less than 50 samples in each group
Experimental studies and review articles on the relationship between periodontitis and cancer	Case control studies with less than five years of follow-up

buccal and lingual gingiva of maxillary molar teeth unilaterally with no sign of bleeding. Roots were exposed to the oral cavity and grade III mobility could be observed. Abundant bone loss could be observed radiographically in posterior maxilla and teeth were floating within the radiolucent area. Lamina dura and PDL could not be detected (36).

4- There was another paper reporting on SCC case as a verrucous leukoplakia in gingiva. There was an overgrowth in palatal gingiva between the teeth #12 and #13 with extension into rugae area. Poor oral hygiene along with general inflammation, gingival recession and generalized periodontal pockets were observed. There was bleeding tendency with light provocation. Lymph nodes were palpable, mobile, tender and firm in consistency (37).

5- SCC was once reported as verruciform xanthoma. There was a verrucouse plaque in anterior maxillary gingiva. No symptom was reported and it grew slowly within four years. There was simultaneous gingival recession (38).

6- SCC in a fourteen-year-old adolescent with gingival bleeding in premolar area was reported. At first it was thought to be pseudoepitheliomatous hyperplasia. It was an exophytic inflammatory lesion in buccal and lingual surface of mandibular first molar and second premolar with ulcerated and firm surface and lingual alveolar bone erosion (39).

7- Sometimes SCC is manifested as a hyperplastic granulation tissue which appears after tooth extraction. The history reported by the patient was occurrence of a swelling two weeks after tooth extraction which was growing. Necrotic bone was found within the extracted socket. It was painful and bled easily (32).

8- An eighteen-year-old female referred to the dentist with the chief complaint of tooth mobility. She was a heavy smoker. In clinical examination there was a multinodular lesion with ulcerative surface in facial and lingual aspect of the teeth #22 - #27. Severe root resorption could be observed about the involved teeth (40).

9- A white eleven-year-old girl referred to the dentist with the chief complaint of growing a white lesion in buccal gingiva of the right mandible. There was no medical or familial history. Primary diagnosis was fibroepithelial hyperplasia. It was recurred after three years and biopsy confirmed SCC (40).

10- There was a report of a growing papillary and nodular mass in facial maxillary gingiva. No history of alcohol or tobacco was reported. Some degree of desquamation could be observed. Well differentiated SCC was confirmed after biopsy (40).

11- In another case report which was finally diagnosed GSCC, patient complained of a growing painful nodule on his gums. It was there for three months as proliferative lesion with purulent exudate. It did not respond to periodontal treatment. Recession and suppuration around the tooth #11 could be observed. Other periodontal tissues except for gingiva were intact (41).

12- There was another report of de novo intraosseous carcinoma. Intraoral examination revealed a non-ulcerative hyperplastic lesion adjacent to mandibular alveolar ridge. It was swollen and tender. There was no evidence of invasion to lymph nodes or nerves (42).

2.2. Rational for the Relationship Between Malignant Lesions of Oral Cavity and Periodontal Disease

Periodontitis is an inflammatory disease related to Gram-negative bacteria. It can cause constant release of bacterial and inflammatory markers in saliva and blood stream leading to tissue destruction (21). Some of the rationales for the association between malignant lesions of oral cavity and periodontal disease are mentioned:

1- Bacterial species in the oral cavity of patients with periodontitis turn nitrate into nitrite or produce acetaldehyde (23). Evidence suggests that carcinogenic metabolites are produced in the presence of periodontal infection. For example, increased nitrosamine in a mouth with poor oral hygiene could act as a carcinogen. Acetaldehyde is a metabolite of ethanol which is assumed to be the risk factor for cancer of the upper esophagus (18, 43). Based on scientific evidence, poor oral hygiene and periodontal disease can cause increased acetaldehyde production twice as much as that of a mouth with good oral hygiene (44).

Some viruses such as EBV and cytomegalovirus (CMV) are residents of periodontal pocket considered to be the risk factors for cancer (23).

2- HPV is another virus which is found in periodontal pockets (45). Inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) stimulate proliferation of HPV and expression of its oncogenes E6 and E7 in gingival epithelial cells. E6 and E7 can bind to tumor suppressors p53 and pRb and deactivate them. This mechanism is responsible for carcinogenic potential of this virus in the oral cavity (1).

3- Increased level of mediators and inflammatory markers: inflammatory cells in the presence of increased level of chemokines, cytokines and prostaglandins are considered to be associated with development of tumors (46). Microorganisms and their products stimulate neutrophils, macrophages, lymphocytes and fibroblasts to produce reactive oxygen species (hydrogen peroxide and free oxygen radicals), reactive nitrogen species (nitric oxide), lipids and matrix metalloproteinase which finally leads to DNA damage in epithelial cells (1, 47, 48). Cytokines, growth factors and some other cellular mediators create an appropriate environment for cell proliferation and migration. They also downregulate cell apoptosis leading to probable mutation (1).

4- Compromised epithelial barrier in periodontal disease causes carcinogenic materials produced by alcohol and tobacco consumption to penetrate the underlying tissues (22).

5- Deficient immune system plays an important role in both periodontal disease and cancer, such as deficiency in neutrophil function. Neutrophils are basic elements of defense system in periodontal attachment apparatus (28, 49).

6- There is increasing evidence that *Porphyromonas gingivalis* are periodontal pathogens that exist within the specimens of squamous cell carcinoma (40, 48). *Porphyromonas gingivalis* are important etiologic factors in periodontal disease found in a great number in the oral cavity of patients with poor oral hygiene or severe periodontitis (40). These bacteria affect cell cycle related molecules and can downregulate cell apoptosis which is a protective mechanism in cancer affected cells. It is done through modification of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway which controls intramitochondrial cell death avoiding programmed cell death. *Porphyromonas gingivalis* also increases longevity and proliferation of host cells (40).

2.3. Differentiating GSCC from Periodontal Disease

Unlike periodontal disease, GSCC lesions are stable and unresponsive to routine therapies. Periodontal disease is usually more generalized in oral cavity than malignant lesions (40).

In periodontitis, horizontal or vertical bone loss, widening of periodontal ligament space and destruction of inter radicular bone are apparent. In GSCC, bone supporting a tooth is invaded; also leading to widening of periodontal ligament space, but with a more invasive appearance. The tooth is sometimes floating within the radiolucent area. Lamina dura is usually absent, so is the periodontal ligament space. Borders of the lesion are often ill defined and non-corticated (36, 45).

Many of the times, severe periodontal disease and malignancy cannot be easily differentiated radiographically because both of them cause severe bone resorption and tooth mobility (45).

3. Results

Cancer of the oral cavity and periodontal disease are related from different aspects. Rate of occurrence of cancer is significantly related to tooth loss and other periodontal parameters such as attachment loss and alveolar bone loss; therefore, periodontal disease and tooth loss are considered as independent risk factors for cancer. Gingival SCC can also mimic periodontal disease leading to misdiagnosis and delayed commencement of appropriate treatment.

4. Conclusions

Based on evidence, dentists and dental health care professionals should consider periodontal disease as a risk factor for development of neoplasms in the oral cavity. It also seems to be a good idea to provide periodontal therapy for patients with cancer to achieve ideal therapeutic results.

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Footnotes

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