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Cancers of the Oesophagus and Stomach: Additional Insight from the Oral Cavity- Mini Review

SUMMARY

Periodontitis as a chronic infection that affects between 10 and 15 percent of the world's population. It is characterized by the loss of connective tissue attachment and alveolar bone. Periodontitis and the resulting systemic inflammation are associated with numerous systemic diseases such as cardiovascular disease, diabetes, chronic kidney disease, rheumatoid, arthritis, respiratory diseases, impairment of cognitive function. The exact mechanism of the association between periodontitis and UGI cancers is not known, but may include direct bacterial ingestion, chronic inflammation, and immune modulation. Considering that about 15% of tumors are the result of chronic inflammation, it is necessary to examine in detail the relationship between chronic periodontal disease and UGI cancer. Specifically, keystone periodontal pathogens, including Porphyromonas gingivalis and Treponema denticola may react with the molecular hallmarks of gastrointestinal cancers, triggering mutations, and generate a permissive immune microenvironment by impairing anti-tumor checkpoints.

Key words: UGI Cancers, Periodontitis, *Helicobacter pylori*

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Introduction

Upper Gastrointestinal (UGI) cancers consider malignancies of the digestive tract and its accessory organs, i.e cancers of oesophagus, stomach, small intestine, pancreatic cancer, liver cancer and cancers of the biliary system[1]. Among them, cancers of the stomach and oesophagus are the third and sixth leading causes of cancer mortality in the world, respectively[2].

Oesophageal cancer is represented by the two main histological subtypes squamous cell carcinoma and adenocarcinoma. Squamous oesophageal cancer is the most common type in the Western countries. This disease is about 3 times more common among African Americans, and also 3 times more common in men in the USA. The most common type of oesophagus cancer in White Americans is adenocarcinoma, contrary to squamous cell carcinoma observed in African Americans. Oesophagus cancer is 10 to 100 times more common in Asia and the southern Africa than in the United States. Stomach carcinoma is mostly histologicaly represented by the adenocarcinoma type[2,3].

Cancer etiology is in general multifactorial, but tobacco smoking and alcohol intake are consider to be of the utmost importance for elevated incidence of both oesophagus and stomach cancers[4,5] Association of the dietary habits and development of the UGI cancers was in the focus of many studies. It was suggested that drinking of hot and strong tea statistically significant increased risk of both cancers.

Concerning eating of fried and spicy food, or barbecuing meat, it was previously assocoiated with the increased risk of the esophageal cancer[6-8], but this was refuted by the novel work of Ibebiele et al.[5]. In case of gastric cancer, it was also reported that daily consumption of red meat and dairy products along with habitual salt intake and spicy food intake are in line with the increased risk for gastric cancer[4,9,10]. This was explained by irritation of the stomach wall leading to the development of cancer[4,11]. Further, it was also suggested that overeating

and/or a high meal frequency (>3 times/day) is in line with increased risk of gastric cancer. This was explained by physical damage to the gastric mucosa caused by repetitions of compulsory expansion of the stomach lining[4].

Genetic factors are also considered to be involved in the etiology of both cancers. In case of oesophagus cancer their influence seems to be generally low[3]. Similary, hereditary gastric cancers are considered to contribute approximately 1-3% of total cases of stomach cancers and it typically develops at a younger age[11,12]. On the other hand, considerably significant number of gastric cancers is *Helicobacter pylori (H. pylori*) and Epsteine Barr virus (EBV) infections[13]. It was suggested that *H. pylori* infection affects immune mediated reaction in the gastric mucosal cells[14], while EBV upregulation of genes with pro-tumor and anti-apoptotic activity[15].

The prognoses of oesohagsus and gastric cancers are in general poor, despite the available surgical or other technics such as radiation, chemotherapy, and targeted drug therapies[1]. An overall 5-year survival of the patients suffering from stomach cancer is approx. 42.9% [16], while in case of the oesohagus it is below 20% [3]. For that reason identifying the risk or causative factors is important to prevent afore-mentioned cancers[17]. Concerning a fact that novel literature data are dedicated to explore the link between oral health and cancers of esophagus and stomach this review will put the special focus on that.

Periodontitis and UGI Cancers: Can the Link be made?

Periodontitis as a chronic infection that affects up to 50 % of the world's population. It is characterized by the loss of connective tissue attachment and alveolar bone[18]. The main risk factors of periodontitis are the poor oral hygiene (accumulation of subgingival plaques), smoking, diabetes, usage of the certain medications, age and stress[18]. The presence of certain microorganisms, especially anaerobic gram-negative bacteria in subgingival plaques significantly contributes to the progression of periodontitis.

Although the exact mechanism of the association between periodontitis and UGI cancers is not known, the several mechanisms have been proposed so far. Firstly, oral bacteria and their products may be directly ingested and may modify the present microbiome and activate the inflammasome complex generating the pathological processes[19]. The second mechanism implys immune regulation by inducing T helper 17 (Th17). These cells are able to migrate to the intestinal lymph nodes, and stimulated by ingested oral bacteria may cause inflamation[19]. Importantly, recent study shows that these processes may have bidirectional effect. And thirdly, systemic inflammation induced by periodontitis, disrupting the gastric barier, increasing the local oxidative stress and bypassing immunogenic response.

A significant increase in the systemic inflammation markers C-reactive protein and interleukin-6 in patients with periodontal diseases was confirmed[2]. While significant reduction of the systemic inflammation markers was obtained when the periodontal therapy was applied[2], all demonstrating that periodontitis may add to the systemic inflammatory burden of effective individuals. Considering that about 15% of tumors are the result of chronic inflammation, it is necessary to examine in detail the immunological relationship between chronic periodontal disease and UGI cancer.

Periodontal pathogens and UGI cancers

The main bacteria linked to the periodontitis are *Porphyromanos gingivalis, Actinobacillis actinomycetemcomitans, Tannerella forsythensis*, *Treponema denticola* and *Fusobacterium nucleatum*[18].

Literature review suggested that patients with gastric cancer experience a high level of bleeding on probing, high levels of *T. denticola* and *A. actinomycetemcomitans* (periodontal disease associated microorganisms) and less bacterial diversity in saliva and dental plaque compared to healthy individuals. Mechanisms linked between above mentioned periodontal pathogens and UGI cancers were dentilisin degradation of IL-8 and TNF-α, cleavage of pro-MMP-8 and 9 [19]. It is also proven that *P. gingivalis* and *T. denticola* (periodontal disease associated microorganisms) stimulate chronic inflammation by adhesion to keratinocytes, invasion and induction of NF-kB pathway which can contribute to carcinogenesis. These oral pathogens have been detected in oesophageal and gastric cancer tissues as well[19]. Moreover, oral bacteria may also generate carcinogenic metabolites, such as *Streptococcus mutans* that reduces nitrate to nitrite, precursors to nitrosamines associated with oesophageal cancer[19]. The study of Ahn et al. investigated the relationship of serum antibody levels of *P. gingivalis* with orodigestive cancer mortality[20]. The authors concluded the higer rate of orodigestive cancers in patients with periodontitis, as well as the fact that mortality increased with the severity of periodontal disease[20]

Recent studies showed the intention of the researchers to understand the link between the oral status of the patient and its supscessibility to the above mentioned cancers. Undoubtely it was suggested that poor oral health, indicated by the presence of periodontitis and leading to the tooth loss, has been linked with increased risk of various cancer types, including UGI cancers. Interestingly, the overall mean number of lost teeth that was linked to UGI cancers was 18.3. The protective effects of tooth brushing was emphasized and atributed to the removal of dental plaque, including removal of afore mentioned bacteria[2]. Overall, daily tooth brushing was related to reduced risk of developing UGI cancers with a linear trend. Daily tooth brushing (vs. never) was linked

with a significantly risk reduction for oesophageal cancer while for gastric cancer, daily tooth brushing (vs. never) was marginally associated with a lower risk[2]. Regarding the tooth, significant linear trend for both UGI cancers was observed. In addition, the highest the tooth loss was, it was linked with an approximately 60% higher risk for both oesophageal and gastric cancers.

H. pylori as periodontal pathogen

Helicobacter pylori as a gram negative bacterium was classified as as a Group 1 carcinogen by The International agency for research on cancer classified[21]. In 1989, Krayden et al.[22] isolated *H. pylory* from the dental plague, and then its presence in saliva was confirmed by Ferguson et al.[23]. Since then, *H. pylory* was associated with different oral diseases, including halitosis, caries, recurrent oral ulcers, chronic gingivitis and periodontitis. Studies have indicated that *H. pylori* rate in patients with periodontitis is higher compared to periodontally healthy individuals[24,25]. Taking into account that more than 50% of the global population suffers from periodontitis, it is of the most importance to determine the connection with *H. pylory* induced periodontitis and UGI cancers.

Today, it has been established that certain types of *H. pylory* have different virulence and hence may be causative of periodontitis. There are two genes associated with the *H. pylory* virulence: vacuolating cytotoxin gene A (vacA) and cytotoxin-associated gene A (cagA)[26], responsible for damaging the lysosome and endoplasmic reticulum. The cagA gene has been confirmed to cause cellular inflammation by interfering with the EMT-associated signaling pathway, miRNA-584, miRNA-1290. Also a combination of the two most important alleles, the signal peptide region (s region) and the middle region (m region) define the virulence of *H. pylori:* s1m1 > s1m2 > s2m1 > s2m2 from strong to weak, accordingly[26].

The study by Zheng and Zhou confirmed the significant presence of cagA gene of *H. pylori* in patients with moderate or severe periodontitis, i.e. correlation with *H pylori* infection[27]. *H. pylori* is statistically significantly more present in the stomach of patients who have the same in subgingival plaques, which led to the conclusion that the oral environment is the source of the same bacteria. Therefore, the *H. pylori* control in the subgingival plaques must be taken into account during therapy[28].

Conclusions

Keystone periodontal pathogens, including *Porphyromonas gingivalis* and *Treponema denticola* may interact with the molecular hallmarks of gastrointestinal cancers, inducing genomic mutations, and promote a permissive immune microenvironment by impairing anti-tumor checkpoints. The exact mechanism of the association between periodontitis and UGI cancers is not known, but may include direct bacterial ingestion, chronic inflammation, and immune modulation. Further research must be focused on the biomarkers detections reflecting this interactions and explore local treatment modalities that may affect general status of the patient.

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