Chronic mechanical irritation (CMI) as the latest evolving oral carcinogen: A review

Manali Kulkarni[1*], Bhakti Patil[2]

[1]Post Graduate Student, [2]Associate Professor, Dept. of Oral Medicine and Radiology, G.D. Pol. Foundation Y.M.T.D.C, Navi Mumbai, Maharashtra, India

***Corresponding Author: Manali Kulkarni**
Email: manalikulkarni1126@gmail.com

Abstract
Traumatic oral lesions are a relatively common finding in dental practice which may be caused by acute and chronic trauma. Such repeated injury to the oral mucosa by deleterious agents is termed as chronic mechanical irritation (CMI). CMI could be precipitated by a combination of dental, prosthetic and functional factors which require early diagnosis and immediate elimination to ensure cure. Recent literature links chronic mucosal irritation to carcinogenesis. This review potentiates the role of chronic mucosal irritation (CMI) in development of cancer.

Keywords: Chronic trauma, Etiological factor, Oral cancer, Oral carcinogenesis.

Introduction
Oral cancer is the sixth most common malignancy in the world accounting for about 3,00,000 new cases every year. It has a mortality rate of about 1,45,000 deaths annually. As the severity of oral cancer increases the overall survival rate of the patient decreases. Five-year survival of patients diagnosed with early stages of oral cancer range between 55% and 60% which further decrease to 30% and 40% in advanced cases.[1] Despite the progress in research and therapy, survival has not improved significantly in the last years, representing a continuing challenge for biomedical science. Its delayed clinical detection in early stages, poor prognosis, inability to have specific biomarkers for the disease and expensive therapeutic alternatives have contributed to its high mortality rate. Its etiopathogenesis is based on the individual's lifestyle, with major risk factors being the use of tobacco, betel quid, areca nut, smoking and heavy alcohol consumption. Other risk factors include family history of cancer, dietary habits, HPV infection, poor oral hygiene and genetic predisposition. In addition to these, long standing irritation has also been proposed as a major risk factor in the process of carcinogenesis. Chronic irritation may result from poor oral hygiene, poor dentition, missing teeth and ill-fitting dentures. However, the role of these conditions in developing oral cancer has been debatable. This paper highlights the role of chronic trauma in oral carcinogenesis.

Oral carcinogenesis
Oral carcinogenesis is a highly complex multifactorial process that takes place when squamous epithelium is affected by several genetic alterations. Tobacco and alcohol are often considered as the major risk factors for oral cancer. However, there have been individuals who do not present with such habits, but still develop malignancy. This fact implies that there are other etiological factors responsible for triggering carcinogenesis, and among them, chronic mechanical irritation (CMI) has been recently postulated.[2]

Chronic mechanical irritation (CMI)
Chronic mechanical irritation (CMI) results from low-intensity, repeated injury to the oral mucosa by mechanical action of an intraoral deleterious agent. This includes malpositioned teeth or those having sharp margins because of decay/fractures, ill-fitting dentures having (sharp or rough surfaces, lack of retention, stability or overextended flanges) and/or parafunctional habits (e.g. oral mucosa biting or sucking, tongue interposition or thrusting), acting individually or together (Table 1).[2]

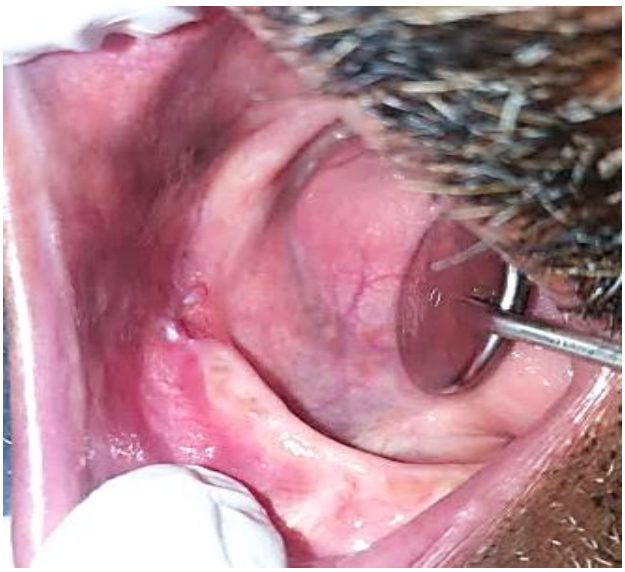

Fig. 1: Chronic non-healing ulcer with frictional keratosis buccally involving the edentulous ridge and right buccal vestibule of 45,46 due to chronic mechanical irritation by an ill-fitting denture in a 70 year old denture wearer without any associated habits

Table 1: Three types of CMI factors

Dental	Prosthetic	Functional
1. Malpositioned teeth 2. Fractured teeth or carious teeth having sharp margins 3. Rough or defective restorations	1. Ill- fitting dentures 2. Sharp or rough surfaces of dentures 3. Overextended flanges 4. Lack of retention and stability	1. Swallowing, occlusal and other dysfunctional disorders.

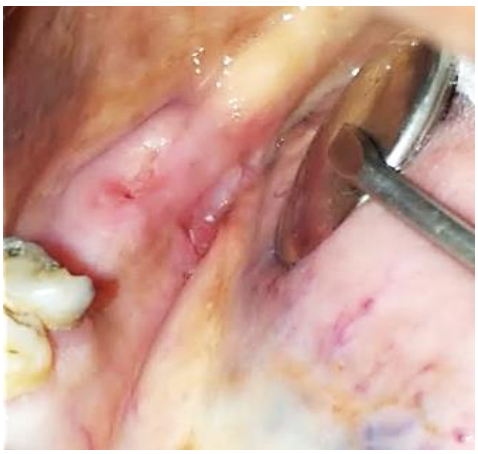

Fig. 2: An ulcero-proliferative growth on the edentulous ridge of 45, 46, 47 obliterating the right buccal vestibule and extending lingually caused due to extended flanges having sharp edges

Oral mucosa is capable of presenting many lesions originating from chronic mechanical irritation (CMI) either from teeth or dentures. The most common CMI lesions are tongue/cheek biting (Morsicatio Buccarum), frictional keratosis, indentations more commonly on the lateral borders of the tongue, chronic traumatic ulcers, papillary hyperplasia, denture-induced fibrous hyperplasia, and focal fibrous hyperplasia. In addition, CMI has the capacity to further worsen pre-existing oral lesions, such as bullous pathologies, oral lichen planus, leukoplakia, or aphthous stomatitis.[3]

CMI is responsible for producing several alterations in the oral mucosa depending upon its duration and intensity. Effects could range from a hyperproliferative epithelial response if the stimulus is mild termed as frictional keratosis, to different levels of tissue injury which may involve atrophy, erosions and ulcers (Fig. 1,2). If the irritation is for a prolonged time it may produce chronic traumatic ulcers clinically accompanied by fibrous connective tissue growth termed as Reactive Hyperplasia, e.g. Denture-induced fibrous hyperplasia).[2]

2 mechanisms have been hypothesized in increased malignant transformation rate due to chronic irritation (Chart 1). The 1st mechanism being increased activity of Poly – ADP - Ribose Polymerase (PARP) enzyme, consequently causing DNA damage and cancer formation and the second resulting from inflammation. Inflammation releases chemical mediators such as cytokines, prostaglandins, and Tumour Necrosis Factor, producing free radicals which create an environment of severe oxidative stress in an individual. This could induce genetic and epigenetic changes damaging the DNA, inhibiting its repair, altering transcription factors, preventing apoptosis, and stimulating angiogenesis, thus resulting in carcinogenesis.[1] In a nutshell, inflammation may act at different steps explaining its role in initiation, promotion, conversion and progression of oral cancer.

The role of Poly – ADP - Ribose Polymerase (PARP) in initiating DNA damage response

The genetic information stored in the DNA may be damaged by environmental and internal hazards such as ultraviolet light, mutagenic chemicals, ionizing radiation and reactive oxygen species. Exposure to these genotoxic stresses may cause DNA single-strand breakages (SSBs) and double-strand breakages (DSBs). If not repaired these breakages can bring about a drastic change in the genome. Fortunately, cells have evolved a sophisticated DNA damage response system to repair these DNA breakages and maintain genomic stability.

DNA damage induces an immediate reaction in a cell which detects various DNA faults using DNA damage sensors. In the presence of DNA damage, these sensors initiate signals to recruit DNA damage repair (DDR) factors and activate other relevant biological processes, such as cell cycle arrest, to facilitate the repair process. Accumulated evidence indicates that PARP1, the founding member of PARP family, recognizes both SSBs and DSBs.

PARylation - dependent early DNA damage response has emerged as an important aspect of the complex repair process in response to new DNA lesions. The biological function of PARylation in response to DNA damage, focuses on the fact that PARylation may serve as an early signal to initiate the DNA damage response.

Factors contributing to Denture related carcinogenesis

Denture - related sores may cause colonization by candida. Colonization of denture-based materials by candida may induce inflammation of the mucosa.[4] A Japanese retrospective study reported that human papillomavirus (HPV) may be present in the oral cavity, especially in those of denture wearers.[5] They suggested that dentures may serve as a reservoir of HPV from where HPV-associated diseases, such as oral cancer and other oral lesions, may develop. Thus, the use of dentures is found to be associated with co-existing candida and HPV infection which may contribute to cancer formation.

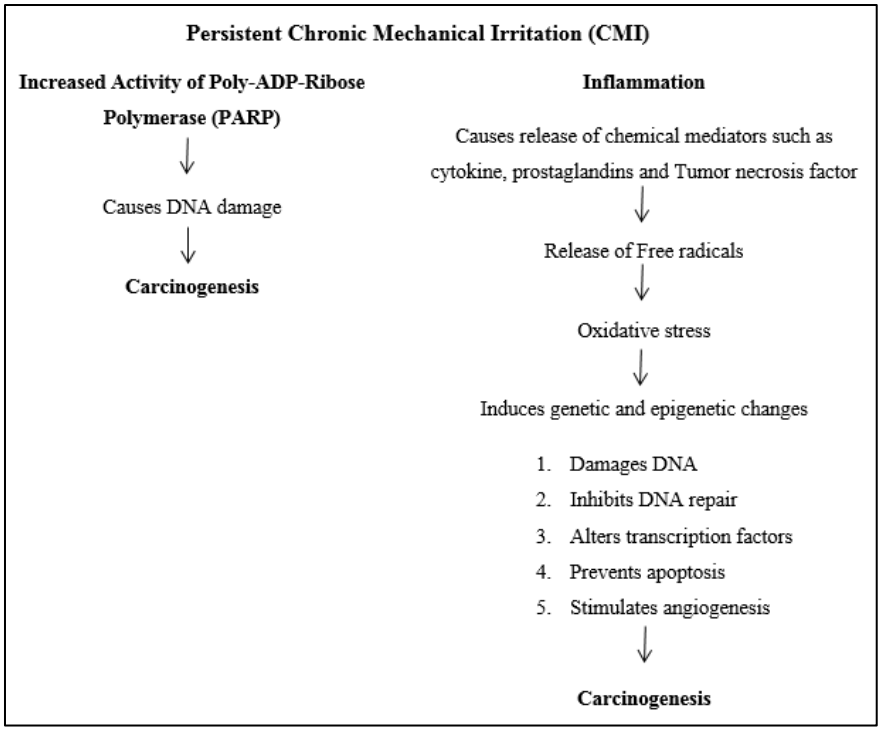

Fig. 4: Mechanisms involved in promoting oral carcinogenesis following Chronic Mechanical Irritation (CMI)

Dental implants and its relation to oral cancer

Recent literature[6-8] have reported squamous cell carcinoma occurring in close proximity to dental implants. Several theories have been proposed which report release of corrosion products, metallic ions and migration of malignant cells through the sulcus around the implant.

Denture material and its relation to oral cancer

Few articles[9-12] have reported that the residual monomer present in the denture base causes mucosal irritation and sensitization of tissues. Many studies have even found that chemicals leached out from acrylic resin can also cause irritation of the oral tissues, inflammation, or even an allergic reaction.

Conclusion

Thus, from this review, we can conclude that the cause of oral cancer is not only associated with deleterious habits of tobacco, areca nut and alcohol consumption but relies on an amalgamation of dental, prosthetic and functional factors. Such trauma related cancers may be seen more often over the lateral borders of the tongue and over the alveolus having a female predilection. Chronic mechanical irritation (CMI) is the latest evolving carcinogen exhibiting malignant potential, which has brought about a paradigm shift in the existing knowledge on the etiology of cancer, from the known to the unknown.

Abbreviations

Chronic mechanical irritation – CMI, Poly- ADP- ribose polymerase – PARP, Single-strand breakages – SSBs, Double-strand breakages – DSBs, Human Papilloma Virus – HPV.

Source of funding

None.

Conflict of interest

None.

References

1. Singhvi HR, Malik A, Chaturvedi P. The Role of Chronic Mucosal Trauma in Oral Cancer: A Review of Literature. *Indian J Med Paediatr Oncol* 2017;38(1):44–50.
2. Piemonte E, Lazos J, Belardinelli P, Secchi D, Brunotto M, Lanfranchi-Tizeira H. Oral cancer associated with chronic mechanical irritation of the oral mucosa. *Med Oral Patol Oral Cir Bucal* 2018;23(2):e151–e60.
3. Jerónimo P. Lazos, Eduardo D. Piemonte, Hector Eduardo Lanfranchi, and Mabel N. Brunotto. Characterization of Chronic Mechanical Irritation in Oral Cancer. *Int J Dent* 2017Article ID 6784526, 7 pages.
4. Jainkittivong A, Aneksuk V, Langlais RP. Oral mucosal conditions in elderly dental patients. *Oral Dis* 2002;8:218–23.
5. Nishimura Y, Maeda H, Hattori M, Azumaya F, Muramatsu I, Kameyama Y, et al. Human papillomavirus infection in the oral cavity of denture wearers. *Nihon Hotetsu Shika Gakkai Zasshi* 2004;48:713–22.
6. Schache A, Thavaraj S, Kalavrezos N. Osseointegrated implants: A potential route of entry for squamous cell carcinoma of the mandible. *Br J Oral Maxillofac Surg* 2008;46:397–9.
7. Abu El-Naaj I, Trost O, Tagger-Green N, Trouilloud P, Robe N, Malka G, et al. Peri-implantitis or squamous cell carcinoma? *Rev Stomatol Chir Maxillofac* 2007;108:458–60.
8. Bhatavadekar NB. Squamous cell carcinoma in association with dental implants: An assessment of previously

hypothesized carcinogenic mechanisms and a case report. *J Oral Implantol* 2012;38:792–8.
9. Basker RM, Sturdee DW, Davenport JC. Patients with burning mouths. A clinical investigation of causative factors, including the climacteric and diabetes. *Br Dent J* 1978;145:9–16.
10. Kallus T. Evaluation of the toxicity of denture base polymers after subcutaneous implantation in guinea pigs. *J Prosthet Dent* 1984;52:126–34.
11. Ali A, Bates JF, Reynolds AJ, Walker DM. The burning mouth sensation related to the wearing of acrylic dentures: An investigation. *Br Dent J* 1986;161:444–7.
12. Giunta JL, Grauer I, Zablotsky N. Allergic contact stomatitis caused by acrylic resin. *J Prosthet Dent* 1979;42:188–90.

How to cite this article: Kulkarni M, Patil B. Chronic Mechanical Irritation (CMI) as the latest evolving oral carcinogen: A review. *Int J Maxillofac Imaging* 2019;5(3):47-50.