



CORRELATION BETWEEN CHRONIC MUCOSAL TRAUMA AND ORAL CANCER: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract – Objective: Squamous cell carcinoma is the most common malignancy in the oral cavity representing the 90% of all oral malignancies that affect oral cavity. Primary risk factors associated with oral cancer are alcohol and tobacco consumption. However, other emerging risk factors have been proposed in Literature, including chronic trauma of the oral mucosa related to dental prostheses and incongruous restorations. Therefore, the aim of this study was to review the literature on the correlation between oral carcinoma and chronic irritative trauma, with the help of a case report and with focus on clinical features and differential diagnosis.

Materials and Methods: A literature search on MEDLINE, PubMed, ScienceDirect, Cochrane Database of Systematic Reviews and Wiley InterScience was performed, using the following words: Oral Cancer, chronic Trauma and Denture Trauma in various combinations.

Results: The review produced 1356 results, but only 8 articles met the inclusion criteria and were involved in the review. No association has been proven between chronic mucosal trauma and oral cancer. Carcinoma has been shown to develop more frequently in trauma regions, particularly in the tongue. As for the data on the gender and age of affected patients, it emerges that most of the greatest incidence occurs around the sixth and seventh decade of life and men are more affected than women.

Conclusions: Due to the heterogeneity of the different studies and the strong presence of other factors such as smoking and alcohol, the role of trauma in carcinogenesis is unclear. Further molecular, epidemiological and case-control studies are needed to define this correlation. It is advisable to carry out more restricted checks in patients at risk with dental prostheses.

KEYWORDS: Case report, Chronic mucosal trauma, Denture trauma, Literature review, Risk factors, Squamous cell carcinoma.

INTRODUCTION

Squamous Cell Carcinoma (SCC) is the most common malignancy in the oral cavity representing the 90% of all oral cancers that affect oral cavity¹. In one of the most recent epidemiological study, SCC affects more than 300.000 people worldwide causing more than 150.000 deaths². Main risk factors

linked with the development of SCC are tobacco smoking (smokeless tobacco and some tobacco-specific N-nitrosamines WHO) and alcohol abuse (a review of the relationship between alcohol and oral cancer, 2011). Other factors related are human papillomavirus infections (mainly genotypes 16 and 18)^{3,4}, ultraviolet radiation exposure⁵, nutritional factors⁶ and chronic trauma⁷. Particularly, although



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not clear, some studies described a possible relationship between chronic irritative trauma and SCC development⁸⁻¹¹. Chronic mechanical irritation caused by dental factors, incongruous prostheses or para-functional habits can cause the onset of various lesions¹². Basically, chronic trauma can:

- stimulate hyperproliferation of the epithelium (frictional hyperkeratosis¹³, *morsicatio buccarum*¹⁴);
- cause hyperplastic tissue growth (fibrous prosthesis hyperplasia, traumatic fibroma^{15,16});
- cause damage to the mucosa (chronic traumatic ulcer⁹).

Oral traumatic lesions are very common in the population¹²; for example traumatic fibroma, according to the epidemiological study by Santana *et al*¹⁷ represent the 15% of diagnosed lesions. *Morsicatio buccarum* prevalence is 750 out of every million individuals¹⁸, with a greater predisposition of women, especially during pregnancy¹⁹. Brantes *et al*²⁰ in a recent cross sectional study show that the lesions most frequently found in patients with prostheses are: denture stomatitis (63%), inflammatory fibrous hyperplasia (19%) and traumatic ulceration (11%). In detail, chronic traumatic ulcer (i.e. lasting more

than two weeks) is relatively common²¹. In fact, in the literature, some SCC cases arising on chronic ulcers are described^{22,23}. In addition, a recent literature study has proposed chronic traumatic ulcer on the lingual edge as a potentially malignant disorder²⁴. Therefore, the aim of this work is to report a case of oral SCC arising from a previous chronic traumatic lesion and to carry out a review on the correlation between chronic irritative trauma and SCC, with a focus on clinical features.

MATERIALS AND METHODS

A review of the literature was made using three databases, PubMed, Web of Science and Scopus. The keywords used were: Oral Cancer AND chronic Trauma; Oral Cancer AND Denture Trauma; Oral Cancer AND Dental Trauma. We included article in English and studies in which the development of SCC is linked to oral trauma. Studies in animals, studies not in English, case reports and reviews were excluded. The review produced 1356 results, but only 8 articles met the inclusion criteria and were involved in the review (Figure 1).

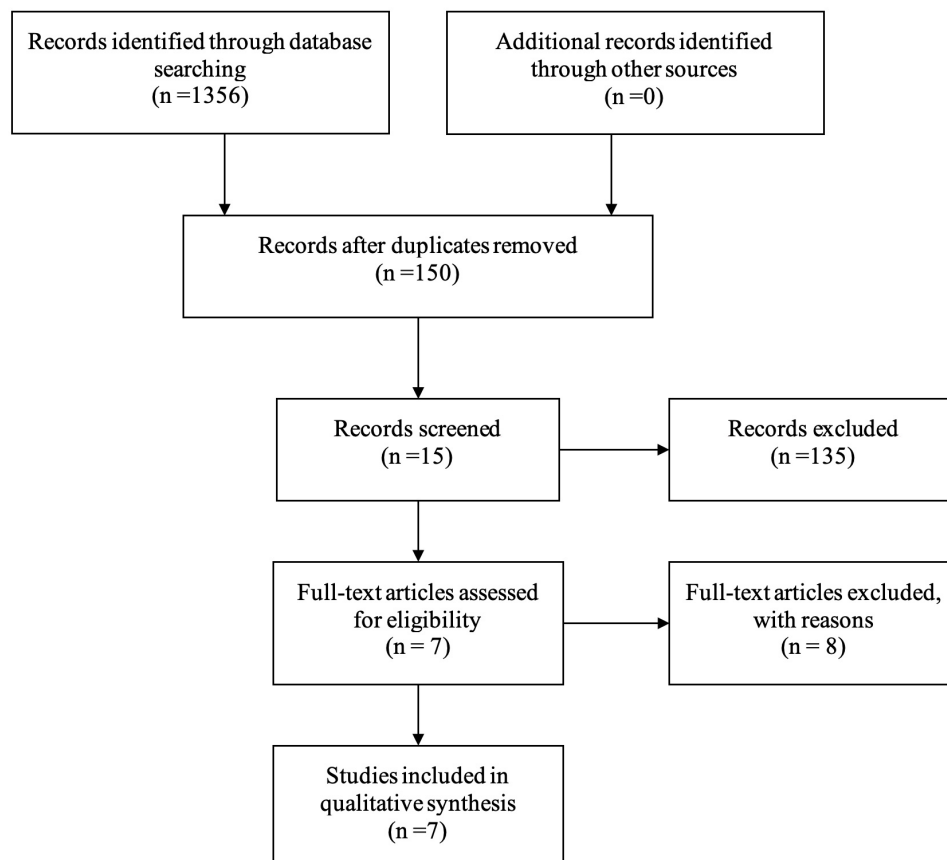


Fig. 1. The review processes.

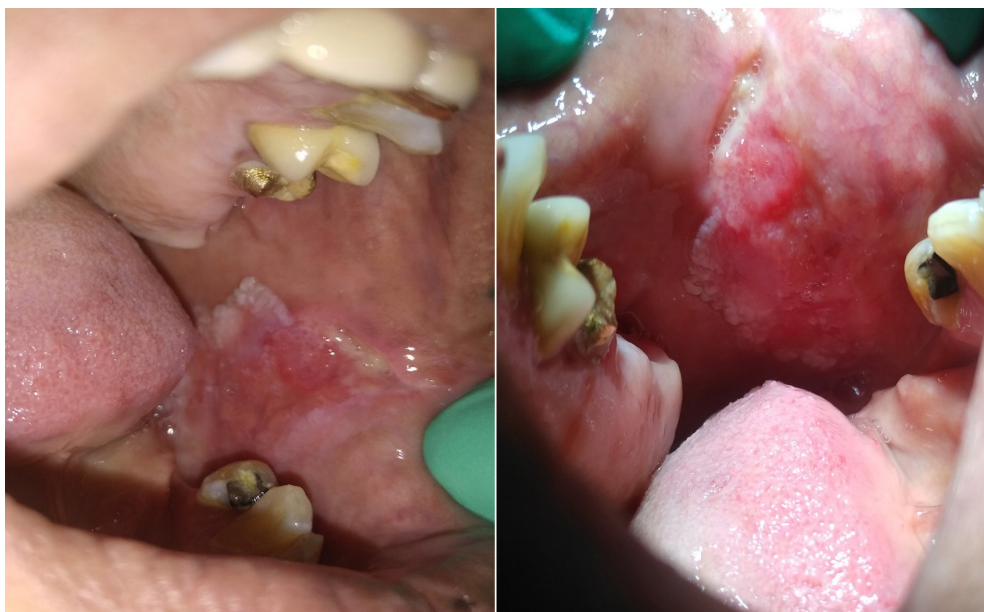


Fig. 2. The lesion as appeared after the incisional biopsy.

CASE REPORT

A 54-years old woman came to visit for a suspected lesion in the left cheek. The patient had a history of periodontitis, slipped disc and she is a tobacco smoker (10 cigarettes/day). Her father was treated for a laryngeal carcinoma. The lesion present in her cheek was 3.5 x 1.5 cm, appeared erythematous with an irregular surface in correspondence of an area with sign of *morsication buccarum*. First, the lesion was treated by removing possible causal factor, as sharp tooth but the lesion did not resolve. Then, the lesion was biopsied (Figure 2), and a diagnosis of SCC was made.

Localization

In literature, tumours appear frequently in traumatized regions like tongue, cheek mucosa and less frequently in palate, gingiva, retromolar region. In the study of Piemonte et al⁸, in the 51% of the cases the tongue was the most involved location, followed by gums and alveolar crest (15%), buccal mucosa (13%), oral floor (9.5%), hard and soft palate (19%) and labial mucosa (2%). Another study, by comparing smoker patient and non-smoker patient, stated that lateral board of the tongue is the most involved site (66%) in the latter group, while for the former, the involvement is lesser (35%)²⁵. Rotundo et al²⁶ showed that (22.5%) had the development of the tumour in the lateral edge of the tongue, (35%) in the oral floor, (22.5%) in the hard palate, (9%) in gingiva, (8.4%) in retromolar trigon and (1.4%) in cheek

mucosa. About tongue localization of the tumour, another study affirmed that lateral edge of tongue was involved in the 77.5% followed by tongue venter 9.5%, dorsum 5.7% and the tip, 1.9%²⁷.

Age and Gender

As for the data on the gender and age of affected patients, the data vary in the articles but for the most, the greatest incidence occurs around the sixth and seventh decade of life and men are most affected than women^{8,25,27,28}. Conversely, in the study of Perry et al²⁵, incidence of oral cancer was higher for men than women in smoker and drinker group (65% vs. 35%); however, incidence was the opposite in non-smoker and non-drinker group (39% vs. 61%). Perry et al²⁵ stated that women who are neither smokers nor drinkers have a 4 times higher risk of developing oral cancer²⁵. The data about gender and sex are collected in Table 1.

Causal factors

The studies involved in the review process presented heterogeneity for number of patients, data, and causal factors studied, so controversies still exist for the role of trauma in tumour formation.

Particularly, a higher consumption of cigarettes per day increases the risk of developing oral cancer. The Odds Ratio (OR) for a consumption of 6-20 cigarettes / day is 3.1 and 7.96 for more than 20 cigarettes/day²⁹.



TABLE 1. Data regarding age and gender of the patients affected by oral carcinoma.

Authors	Gender (M/F, %)	Average age (%)
Albuquerque et al ²⁷	71% M/ 29%F	63.7 yrs
Bektas-Kayhan et al ²⁸	64% M/36% F	52-53 yrs
Perry et al ²⁵	72% M/28% F	61.7 yrs
Piemonte et al ⁸	54% M/46% F	63 yrs

Furthermore, another study found that lower cigarette consumption per day revealed a direct effect, whereby the strength of the pack-year association increased with the increase in cigarettes/day, indicating that for the same packs per day 'year, smoking more cigarettes a day for a shorter duration was more deleterious than fewer cigarettes a day for a longer duration³⁰.

In the study of Albuquerque et al²⁷, 44% of men drink and smoke and do not use a prosthesis vs. 51% of women. In this case, the women who have a tumour on the tongue and do not drink and smoke are 77%. Of this 77%, one third of patients wear prosthesis but not significantly association was found although these data show a higher incidence in women wearing prosthesis. Another study examined the relation between the use of a prosthesis and the formation of an oral tumour. One-hundred-thirty-four patients out of 211 patients affected by SCC wear different prostheses, i.e. crowns, bridges and dentures and of these 34% wear dentures, 22.3% have dentures both above and below; the rest of the patients (64%) have crowns or bridges. However, again, no statistical analysis showed a significant association between the prosthesis and tumour location and onset³¹. In the study of Bektas-Kayhan et al²⁸, 31 out of 47 patients (66%) had a fixed or removable prosthesis and the 44% of patients with tongue cancer had signs of mechanical trauma. However, the high percentage of smokers did not make simple to understand the role of the sole mechanical trauma in carcinogenesis. In another study, patients were divided into non-smokers and smokers/former smokers. Smoking appears to be an important predisposing factor in males compared to females (72% vs. 28%) but, by eliminating the most important factors such as smoking and alcohol, women are more affected than men. In smokers, the localization of the tumour is prevalent in the edge of the tongue, in the floor. In non-smokers, on the other hand, the site mainly affected is that of the lingual border, and trauma was a probable causal factor²⁵. In the study of Piemonte et al⁸ patients were divided into smokers, non-smokers, drinkers, and non-drinkers and by different sources of trauma such as prostheses, dentures and teeth. The article highlights that the multivariate statistical analysis presents an association between trauma, age, and alcohol use while it does

not present it for sex and the use of smoking. Rotundo²⁶ showed that smoking and alcohol are associated with tumour formation. The use of prostheses would not represent a risk (OR 0.67); this risk occurs if the prosthesis should cause the formation of ulcers and decubitus (OR 3.98). Out of 71 patients, 33.8% had a removable prosthesis. In the statistical analysis carried out, it was found that the presence of recurrent oral lesions caused by prostheses can increase the risk of developing oral carcinoma. However, in another study, Vaccarezza et al¹¹ observed that the use of a prosthesis has an impact on tumour development. In multivariate analysis, however, the use of the prosthesis appears less incisive than other factors such as alcohol and tobacco.

CONCLUSIONS

Due to the heterogeneity of the different studies and the strong presence of others factors as smoke and alcohol, the role of traumatism in carcinogenesis is not clear. Chronic trauma and its causal role in oral carcinogenesis remains a dilemma. Further molecular, epidemiological, and case-control studies are needed. Finally, especially in patients at risk, the dentist plays a fundamental role in an early diagnosis of SCC. In addition, patients at risk (drinkers and smokers or with a positive family history) with prostheses should be subjected to repeated checks over a short period of time in order to intervene early in the case of development of traumatic injury and consequent hypothetical development of a possible neoplastic lesion.

ETHICAL COMMITTEE:

The study was conducted according to the Institutional requirements and Helsinki Declaration.

INFORMED CONSENT:

The participant in this study signed the informed consent.

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CONFLICT OF INTEREST:

The Authors declare that there is no conflict of interest.

REFERENCES

- Hao J, Yan F, Zhang Y, Triplett A, Zhang Y, Schultz DA, Sun Y, Zeng J, Siverstein KAT, Zheng Q, Bernlohr DA, Cleary MP, Eglimez NK, Sauter E, Liu S, Suttles J, Li B. Expression of adipocyte/macrophage fatty acid binding protein in tumor associated macrophages promotes breast cancer progression. *Cancer Res* 2018; 78: 2343-2355.
- Lee S-A, Sung H, Han W, Noh D-Y, Ahn S-H, Kang D. Serum adiponectin but not leptin at diagnosis as a predictor of breast cancer survival. *Asian Pac J Cancer Prev* 2014; 15: 6137-6143.
- Leng X, Wu Y, Arlinghaus RB. Relationships of lipocalin 2 with breast tumorigenesis and metastasis. *J Cell Physiol* 2011; 226: 309-314.
- Furuhashi M, Hotamisligil GS. Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. *Nat Rev Drug Discov* 2008; 7: 489-503.
- Storch J, McDermott L. Structural and functional analysis of fatty acid-binding proteins. *J Lipid Res* 2009; 50: S126-S131.
- Lee D, Wada K, Taniguchi Y, Al-Shareef H, Masuda T, Usami Y, Aikawa T, Okura M, Kamisaki Y, Kogo M. Expression of fatty acid binding protein 4 is involved in the cell growth of oral squamous cell carcinoma. *Oncol Rep* 2014; 31: 1116-1120.
- Girona J, Rosales R, Plana N, Saavedra P, Masana L, Vallvé JC. Correction: FABP4 Induces Vascular Smooth Muscle Cell Proliferation and Migration through a MAPK-Dependent Pathway. *PLoS One* 2016; 11: e0146632.
- Xu A, Wang Y, Xu JY, Stejskal D, Tam S, Zhang J, Wat NMS, Wong WK, Lam KSL. Adipocyte fatty acid-binding protein is a plasma biomarker closely associated with obesity and metabolic syndrome. *Clin Chem* 2006; 52: 405-413.
- Tso AW, Xu A, Sham PC, Wat NMS, Wang Y, Fong CHY, Cheung BMY, Janus ED, Lam KSL. Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes-a 10-year prospective study in Chinese. *Diabetes Care* 2007; 30: 2667-2672.
- Chow WS, Tso AWK, Xu A, Yuen MMA, Fong CHY, Lam TH, Lo SV, Tse HF, Woo YC, Yeung CY, Cheung BMY, Lam KSL. Elevated circulating adipocyte-fatty acid binding protein levels predict incident cardiovascular events in a community-based cohort: a 12-year prospective study. *J Am Heart Assoc* 2013; 2: e004176.
- Eynatten MV, Breitling LP, Roos M, Baumann M, Rothenbacher D, Brenner H. Circulating adipocyte fatty acid-binding protein levels and cardiovascular morbidity and mortality in patients with coronary heart disease: a 10-year prospective study. *Arterioscler Thromb Vasc Biol* 2012; 32: 2327-2335.
- Ota H, Furuhashi M, Ishimura S, Koyama M, Okazaki Y, Mita T, Fuseya T, Yamashita T, Tanaka M, Yoshida H, Shimamoto K, Miura T. Elevation of fatty acid-binding protein 4 is predisposed by family history of hypertension and contributes to blood pressure elevation. *Am J Hypertens* 2012; 25: 1124-1130.
- Hao J, Zhang Y, Yan X, Yan F, Sun Y, Zeng J, Waigel S, Yin Y, Fraig MM, Egilmez NK, Suttles J, Kong M, Liu S, Cleary MP, Sauter E, Li B. Circulating Adipose Fatty Acid Binding Protein Is a New Link Underlying Obesity-Associated Breast/Mammary Tumor Development. *Cell Metab* 2018; 28: 689-705. e685.
- Hancke K, Grubeck D, Hauser N, Kreienberg R, Weiss J. Adipocyte fatty acid-binding protein as a novel prognostic factor in obese breast cancer patients. *Breast Cancer Res Treat* 2010; 119: 367-377.
- Guaita-Esteruelas S, Saavedra-García P, Bosquet A, Borrás J, Girona J, Amiliano K, Rodríguez-Balada M, Heras M, Masana L, Guma J. Adipose-derived fatty acid-binding proteins plasma concentrations are increased in breast cancer patients. *Oncologist* 2017; 22: 1309-1315.
- Kim S, Lee Y, Koo JS. Differential expression of lipid metabolism-related proteins in different breast cancer subtypes. *PLoS One* 2015; 10: e0119473.