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Letter to the editor

Comment on "'Chronic traumatic ulcer of lateral tongue' – An underestimated 'oral potentially malignant disorder'?"

Dear Editor,

We agree with the Letter to the Editor by Panta et al. (2018), about the underestimation of Chronic Traumatic Ulcer (CTU) as an oral potentially malignant disorder (OPMD) [1]. CTU is the prototypical lesion caused by chronic mechanical Irritation (CMI), and the focus of our discussion. We consider that CMI is undervalued as risk factor for oral squamous cell carcinoma (OSCC), essentially because it is not registered in epidemiological studies. However, there are some characteristics that we believe is necessary to mention.

In the multifactorial context of oral cancer, assigning a causal role to CMI only in non-smokers/non-drinkers would dismiss the risk of the interaction between CMI with tobacco and alcohol. In this matter, based on unpublished data, individuals with OSCC in relation to CMI had less consumption of both tobacco and alcohol than the ones without CMI [2]. Thus, if CMI is present, minor cumulative consumption of tobacco and alcohol are needed to develop an OSCC. Chronic trauma may act in combination with other well-known oral cancer risks factors, which may allow the redefinition of population oral cancer prevention strategies worldwide.

Furthermore, taking into account available papers, we consider that there is an increase of the risk of OSCC not only in CTU of the lateral tongue, but in many other CMI associated lesions, and also in different sites of the oral mucosa exposed to CMI [3,4].

Oral lesions produced by CMI generate a mucosal response with inflammation and proliferation, that could easily be added together with [cellular and] tissue intrinsic conditions of the affected anatomical area. Although tongue border shows an hyperproliferative status comparing to other zones, we have found that CMI associated cancers are indeed located specifically where there was a contact with a CMI injuring agent. This suggests an interaction between the oral mucosa and CMI. As an example, we have found that tongue border and buccal mucosa are the most affected sites for CMI associated lesions [5]. However, the lateral border of the tongue showed more OSCC and CTU, whereas on buccal mucosa presented mostly benign hyperplastic lesions. Another reason for this difference could be due to *functional factors* (e.g. tongue interposition, swallowing disorders), which are seldom registered. They allow abnormal contact between mucosa and teeth/dentures, increasing frequency and magnitude of the mechanical injury. In countries where betel chewing is common, buccal mucosa is the most affected site. Particularly, this habit could be aggressive mechanically and interact with the chemical carcinogens of betel quid.

A low-grade inflammatory process occurs not only in CTU but also in numerous CMI lesions. Such is the case of atrophic zones associated with CMI, which also could exist on oral potentially malignant disorders, probably increasing the risk of malignant transformation. A similar situation has been described in the so-called Marjolin's Ulcers on the skin, which reflects malignant degeneration arising within a pressure ulcer [6]. It has been mentioned also in on oral lesions such as oral submucous fibrosis and oral lichen planus [7].

How could the lack of evidence between CMI and OSCC be explained? We have discussed it with renowned experts in many scientific meetings, asking their opinion on the subject. While some of them discredit the idea, most of them admitted that such association could indeed be likely, but there is still no evidence to support it. We believe that mostly this is due to methodological difficulties intrinsic to CMI study.

One of them is an ethical facet that prevents cohort studies of CMI in humans. Both oral lichen planus and leukoplakia have been studied using this methodology because such diseases tend to persist regardless of treatment. On the other hand, once a CTU is identified, it should be treated removing the irritating agent, which produces its healing in a matter of weeks. Obviously, it would not be ethically conceivable to keep a CTU untreated in order to assess its malignant transformation. There have been some experimental studies to overcome this difficulty [8].

Another limitation is the size of CTU lesions, which usually are of less than 2 cm of diameter. Whereas more than 60% of oral cancer are diagnosed when they largely surpass that dimension (T3 and T4). Accordingly, a cancer that could have been arisen from a CTU may have lost entirely the clinical appearance of the precursor lesion. Instead, when an OPMD such as leukoplakia develops cancer, typically could be identified by lesions in surrounding areas.

Moreover, CMI is not only an overlooked condition, but the few studies that delve into it offer heterogeneous criteria to define its occurrence. The finding of defective tooth/dentures – and what is defective is not specified- is not enough to develop a CMI associated lesion. As a matter of fact, a patient could have many sharp/broken teeth and a defective denture with no lesion whatsoever. Therefore, to determine CMI an objective clinical lesion in direct contact with the injuring agent is needed [3]. This contact is facilitated by functional factors in more than 70% of the CMI lesions [5]. It should be determined that the injuring agent was existent before the onset of the lesion; temporal correlation is also a requisite to define CMI [9].

It is important to emphasize that studies dealing with risk factors for OSCC should not be restricted only to tobacco/alcohol consumption but also consider other variables reflecting the dental condition. Furthermore, we also hope to see an increase in studies exploring the biological pathways of CMI and OSCC.

Finally, we strongly believe that rigorous methodological standards are required to systematize CMI research, since there is not even consensus on the terminology used to describe it. A tooth/denture could be a CMI agent if and only if it actually produces a lesion on the oral mucosa. It is also essential to assess functional factors, as they increase contact intensity and frequency. In consequence, clear methodological guidelines are needed for CMI: criteria, examples, definitions, and even

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a glossary of CMI vocabulary.

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