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Potentially Oral Malignant Disease and Oral Cancer - Case Series and Review

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Abstract

Awareness of epidemiology of oral cancers, especially squamous cell carcinoma, may provide effective and appropriate treatment plans without delay, morbidity and mortality reduction. Hence, have a better quality of life. Potentially Malignant Lesions (PML) such as leukoplakia, erythroplakia, smokeless tobacco keratosis, oral sub mucosal fibrosis, oral lichen planus, Condylom Acominatum and actinic queilitis, should be address in each consultation to prevent late stage diagnosis of oral cancer.

We present two cases from our hospital in Argentina, during this last year. Two clear examples of oral cancer and potentially malignant lesion, and we review the literature with the most updated information on early diagnosis and screening.

Keywords: Oral cancer, Oral mucosa cancer; Potentially malignant disease; Leukoplakia; Oral dysplasia

Introduction

Oral cancer annual estimated worldwide incidence is approximately 275,000, and it is increasing [1]. There is a broad geographic discrepancy in the incidence of the disease with two-thirds incurring in low and middle-income countries from Latin America as our patients in this article, South and South East Asia, and Eastern Europe. In South America and Caribean countries it is the 5th cancer in frequency in men and 6th in females. Brazil is the country with the highest reported prevalence, followed by Argentina and Uruguay with an average 5-year survival rate of approximately 60%. Over 90% are Oral Squamous Cell Carcinomas (OSCC) in both males and females and is associated with invasion and destruction of local tissues and maxillofacial [2].

Oral mucosal disorders with increased risk of cancer transformation are termed Potentially Malignant Disorders (PMDs) of the oral mucosa by the World Health Organization [3]. Oral PMDs are categorized into leukoplakia, erythroplakia, actinic cheilosis, and oral submucous fibrosis, palatal keratosis associated with reverse smoking, oral lichen planus, discoid lupus erythematosus, and dyskeratosis congenita and epidermolysis bullosa [3]. The etiology of the previously mentioned disorders varies from genetic aberrations predisposing for altered tissue regeneration, inherited diseases, disorders caused by exogenous factors such as tobacco, alcohol, HPV, cannabis use, chronic inflammation and immune-mediated disorders [4].

Case Presentation

Case 1

Female patient, 90 years old, consul the dermatology department for a painful white lesion in the lateral border of the tongue, which persisted for over 6 months and measured 1.5 cm × 0.5 cm in diameter (Figure 1). She had received fluconazole 150 mgs per week for 6 weeks and nystatine mouth wash without any response. Neither has she been a smoker nor a social alcohol drinker. No marihuana use or HPV diagnosed previously. In the ultrasound no adenopathy was observed. The histopathology report said moderate epithelial dysplasia (Figure 2). She refused to have surgery or any other treatment for now.

Case 2

Female patient of 74 years old, presented for an oral mucosal check up, reporting she was a smoker since 15 years of age of 1.800 cigarettes per year and alcohol drinker of 250 ml of gin three times a week. We observed an asymptomatic, 4 mm × 4 mm hard elastic lesion in the inferior left

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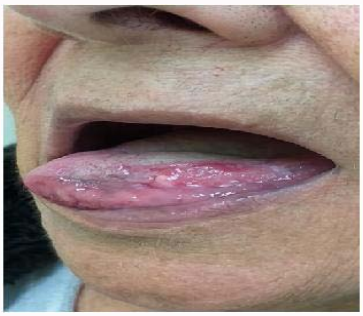

Figure 1: Female patient with moderate dysplasia in the border of her tongue.

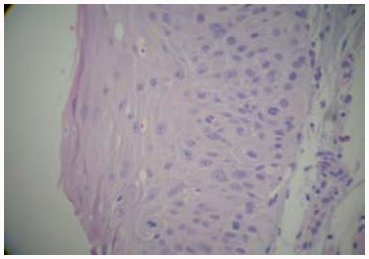

Figure 2: Histopathology image of a moderate dysplasia of the lateral border of the tongue in a female patient. Arquitectural disorder in the inferior two thirds of the epithelium where atypical mitosis are seen.

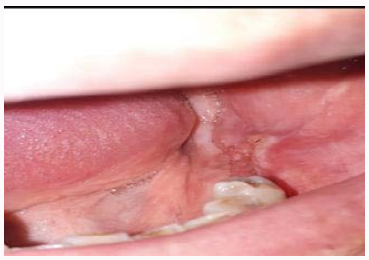

Figure 3: Female patient with oral squamous cancer.

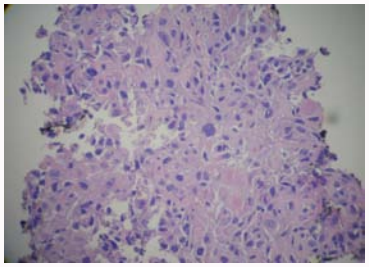

Figure 4: Histopathology image of the corion with squamous atypical cells from an Oral Squamous Carcinoma.

oral mucosa beside the retro molar area with palpable submandibular nodes in the same side (Figure 3). The histopathology report came back with a diagnosis of squamous epithelial carcinoma (Figure 4).

The most common form of potentially malignant disease is leukoplakia with a worldwide estimated prevalence of 2.6%. Its overall malignant transformation rate is up to 5% [5]. However, the extent and rate of progression of dysplasia in leukoplakia is not uniform and can vary from site to site and within the same lesion, so predicting malignant transformation is problematic [5-7].

There have been reports on oral mucosa vital stains used to help select the specific area of a PMD for a biopsy, such as 1% Methylene Blue, Lugol solution or 1% Toluidine Blue. The latter, is said to have 90% sensibility, 69% specificity and less toxicity [8]. Apart from the mentioned stains, there are also adjuvants for cancer detecting based on light and spectrophotometry, which show different absorption and reflection between healthy tissues and those with structural and metabolic disorders. Some other method is the oral cytology, obtaining epithelial cells from the mucosal surface through rubbing with a cytobrush and using light microscopy [9]. Sperandio et al. [10] published a retrospective study evaluating dysplasia and aneuploidy (the change in the chromosome number) in biopsies of lesions with clinical suspicion of malignancy. They showed that dysplasia and aneuploidy gave a higher predictive value than any other technique for malignancy.

The incidence of head and neck cancer subsets such as cancers of lip, oral cavity, larynx, hypo pharynx, and nasopharynx has declined significantly during the past 20 years in the United States and other developed countries, largely due to declines in the habit of tobacco smoking [11-12]. In contrast to this pattern, the incidence of oropharyngeal and oral tongue cancers has significantly increased during the same period, attributed to increased acquisition of oral Human Papilloma Virus (HR-HPV) types 16 and 18 probably related to an increase of oral sex practice [13].

The reason of most failures to treatment after oral cancer diagnoses is the late arrival to it. It is usually diagnosed in advance stages (III and IV), larger than 4 cm or with metastasis, with a survival of 20% to 50%. On the other hand, if diagnosed in stage II, or I the survival is between 50% till 80% [2]. The most important determinant factor in cancer survival is diagnostic delay [14]. Additionally, the morbidity associated with surgery is high; the probability of a second primary tumor is greater than any other type of cancer (3% to 7% annually) which is frequently the cause of death [15].

Important risk factors in the development of the Potentially Malignant Disease (PMD) or in oral cancer are tobacco, alcohol, HPV, betel quid, age, male gender and sunlight [6]. The known carcinogenetic compounds known today in tobacco smoking which can have primary role in oral cancer development are: Butadiene, Naphthylamine, Amino biphenyl, Benzene, Acetaldehyde, Ethylene oxide, Formaldehyde, Toluidine, Vinyl chloride, and metals such as Arsenic, Beryllium, Cadmium, Chromium (VI), Lead and Nickel compounds [16,17]. People especially in India and Sweden consume smokeless tobacco and areca nut (betel quid) which both contain psychoactive products nicotine in the case of tobacco and arecoline in the case of areca nut [1,18].

Heavy drinkers and smokers have 38 times the risk of developing oral cancer compared to abstainers [19]. This is thought to be due to acetaldehyde, the first metabolite of alcohol, which is classified as a Group 1 carcinogen and is also present in tobacco [20].

Epidemiological evidence from USA populations indicates a strong association between HPV and oropharyngeal cancers [21]. Update information from the United States of America show a substantial increase of HPV-positive 16 and 18 in oropharyngeal cancers, rising by 225% in the period between 1984 and 2004 [22].

Recreational Cannabis smoking has importantly increased among individuals all around the world raising the hypothesis of a role as a risk factor for oropharyngeal and oral tongue cancer [23]. Nevertheless, epidemiologic studies that have overlooked the

association of marijuana use with head and neck oral cancers have been inconsistent [24]. Marks in et al. [13] 2013 observed that cannabis use was inversely associated with oral tongue cancer, which is similar to what has been reported previously [23-26]. The rationalization to this finding is related to the major bioactive cannabinoid compound found in marijuana smoke, D-Tetra Hydro Cannabinol [D-THC], which has been shown to have anti carcinogenic potentialities through engagement of specific cell surface receptors CB1, expressed on a variety of cell types and CB2 present predominantly on a variety of immune cells, suppressing the release of inflammatory products with an antitumor effects as a consequence through strengthening of apoptosis, arrest of uncontrolled cell growth, and down regulation of angiogenesis and cellular migration [27,28]. Conclusions to marijuana and cancer should be taken with caution as the pooled analysis of 9 case control studies from USA and Latin America in 2014 showed heterogeneity through the measurement of marijuana use, study sample recruitment, demographic and other risk factors for HNSCC [25].

The immunohistochemistry markers are not usually used as a routine. They are still used for investigation protocol. The only one that is used in certain histopathology laboratories is the protein Ki-67 (also called *MKI67*). This protein is exclusively observed in those cells, which are in proliferation process in human tumors, in cell cycle G1, S, G2 and M. Its high expression is related to worse outcome according to a recent Meta analysis [29].

Saliva is a valuable body fluid for disease diagnosis, due to its noninvasive nature, and has been increasingly used as a source for discovery of oral cancer biomarkers [30]. The ability to detect molecules in saliva from patients with head and neck cancer and defining abnormal values is a critical step before the clinical implementation [31]. Salivary molecules have already been proposed as potential oral cancer biomarkers. For example, salivary soluble CD44, salivary Cyfra 21-1, tissue polypeptide anti-gene, and CA125 have been proposed as oral cancer markers [32]. Nevertheless, no single bio molecule has been shown to meet the real-world requirement for high accuracy in identifying early disease onset, suggesting that multiple biomarker candidates are needed for high accuracy and sensitivity in detecting OSCCs [33]. End products of free radical damage and nitrite levels are importantly increased in individuals with oral leukoplakia. Reciprocally, levels of glutathione S-transferase and uric acid are decreased. An elevated level of reactive species with a concomitant reduction in antioxidants in leukoplakia denotes its potential as an early diagnostic marker [34].

Evidence shows that a visual oral examination of high-risk individuals is a cost-effective screening strategy and the development and use of adjunctive aids together with biomarkers is becoming increasingly common [35]. The gold standard method for diagnosis of oral cancer today, is still the traditional biopsy [33].

Conclusion

Oral cancer is a significant worldwide healthcare matter, its incidence is increasing and late-stage presentation is common with high mortality and morbidity. Oral examination of high-risk individuals is a cost-effective screening strategy. Screening programmes must be implemented for oral cancer and potentially malignant disease detection, especially leukoplakia. Till today there is no molecular or even histopathological pathognomonic hallmark that can predict malignant transformation of a PMD, the accurate clinical observation of oral lesions remains the only way to control the development of oral cancer and the biopsy is today still the gold standard but biomarkers use is becoming more common and helpful each year.

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