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CASE REPORT

Multiple Second Primary Oral Squamous Cell Carcinomas in a Nonsmoker and Nondrinker Woman: Case Report and Review of the Literature

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ABSTRACT

Aim: This manuscript aims to describe an unusual case of multiple second primary squamous cell carcinomas (SCCs) in several sites of the oral mucosa in a nonsmoker and nondrinker woman and to discuss the diagnostic criteria, clinicopathological aspects and outcome of second primary tumor (SPT).

Background: Patients treated for SCC of the head and neck are at high risk for developing SPT arising from the same dysplastic mucosal field. Currently, there is no reliable method to predict which of the patients will develop SPT.

Case description: A 64-year-old nonsmoker and nondrinker woman developed several second primary oral SCCs in 7 years of follow-up, most of them being synchronic, treated by surgery without and with chemotherapy and radiotherapy.

Conclusion: Patients treated for SCC require a long-term and careful follow-up as the development of SPT contributes with significantly negative impact on the prognosis.

Clinical significance: This report describes the diagnosis and management of a very unusual case of several SPTs affecting different sites of the oral mucosa in the same patient. Moreover, the patient had no apparent risk factors associated with the development of the oral cancer. Therefore, a brief update concerning SPT and its diagnosis and management is also provided.

Keywords: Oral cancer, Squamous cell carcinoma, Second primary neoplasms, Treatment outcome, Case reports.

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INTRODUCTION

Squamous cell carcinoma (SCC) of the head and neck is a very common malignancy and has one of the lowest 5-year survival rates among all cancers. Although new surgical techniques, improved radiotherapy (RT) and use of concomitant chemotherapy improve locoregional control, improvement of survival has not been achieved over the last decades.[1] One of the main reasons for this lack of efficacy seems to be that, apart from failure of loco-regional disease control, head and neck cancer patients are at high risk of developing second primary tumors (SPT) arising from the same dysplastic mucosal field.

Some authors have described the multifocal occurrence of SCC of the upper aerodigestive tract, but in 1933, Lund[2] first reported the presence of SPT in 6% of patients with oral SCC.[3] The risk for second cancer in patients with oral-maxillofacial malignancies varies between 1.8 and 4.3% up to 30%.[4] Warren and Gates[5] were the first who published criteria that should be fulfilled when a malignant tumor is to be recognized as a second primary. Field cancerization can explain SPT as progression from

one or multiple precancerous lesions in morphologically abnormal tissue surrounding the tumor site.[6] Currently, there is no reliable method to predict which of the patients will develop SPT.

These tumors may appear due to extensive initiation and promotion by various carcinogens mainly tobacco and alcohol, leaving to a widespread disorder of the epithelial maturation and differentiation with a field effect. Thus, environmental factors which cause the development of the first tumor (index tumor) probably cause the subsequent premalignant and malignant changes. In this context, biological models of gradual accumulation of genetic alterations form the current understanding of neoplastic transformation from normal to malignant cells and, more recently, attempts have been made to explain the biological origins of the intriguing problem of SPT.[6]

This article describes a case of multiple second primary tumors that appeared in a nonsmoker and nondrinker 64-year-old woman, who developed multiple second primary SCCs over a 5-year period, additionally, we discuss some important aspects concerning the condition in the current literature, such as clinicopathological aspects and outcome of SPT.

CASE REPORT

A 64-year-old nonsmoker and nondrinker woman, leucoderm, was referred to our department in March 2005, presenting an incipient white plaque of 5 weeks of duration in bilateral buccal mucosa, measuring approximately 6.0 × 3.0 × 2.0 mm. The medical history revealed that 4 years prior, the patient was submitted to RT and chemotherapy treatment for breast cancer. The patient reported leukopenia and eosinophilia during treatment for breast cancer and also the use of tamoxifen (Taxofen®) for the past 2 years. Physical examination at that moment revealed no cervical lymphadenopathy and the clinical diagnostics for the lesions were leucoplakia and lichen planus. The patient was submitted to an incisional biopsy and the microscopic analysis revealed a poorly differentiated oral SCC (UICC, $T_1N_0M_0$, stage I). Therefore, it was performed a surgical resection of the lesions with wide security margin without RT in a reference service. However, 3 months after the surgical resection, the patient exhibited multiple incipient plaque-shaped lesions, with white color and irregular surface in maxillary alveolar mucosa (Fig. 1) and palate. The patient remained without cervical palpable lymph nodes and on radiographic analysis there was no evidence of invasion of the alveolar bone. Surgery for removal of all lesions with security borders was performed and the histopathologic examination showed well-differentiated SCCs in both specimens with marked keratinization (UICC, $T_1N_0M_0$, stage I) (Fig. 2). In October 2005, new lesions appeared with same clinical characteristics in bilateral buccal mucosa, where was performed excisional biopsies that confirmed oral SCC over again. In October 2006, new white plaques (Fig. 3), 18 × 9 × 6 mm in size, with evident bone erosion appeared in mandibular alveolar mucosa along with a gingival swelling in the area of left mandibular premolars, which were absent. The patient was submitted to a newly surgical resection for the lesions and a diagnosis of poorly differentiated SCC (Fig. 4) was confirmed. Additionally, at that moment the patient exhibited one palpable node, firm on palpation, 10 × 6 × 6 mm in size, in the cervical region on the right side. Neck dissection was performed and metastasis in three lymph nodes was evident (UICC, $T_2N_1M_0$, stage III). At this occasion, also was detected the presence of human papillomavirus (HPV) in the esophageal mucosa, but this virus was not identified in the oral lesions. Six months

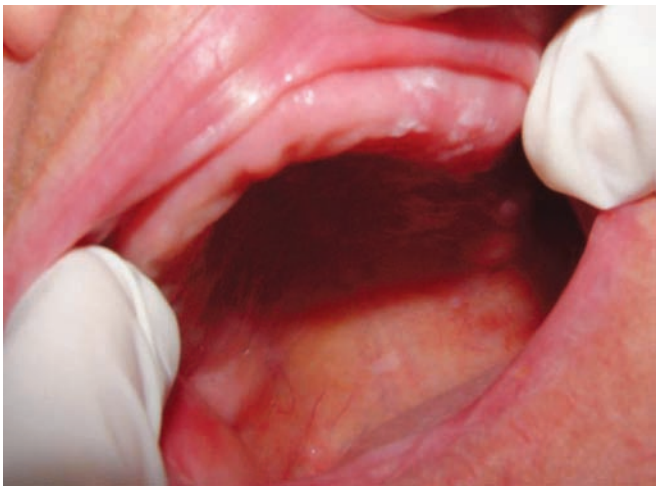

Fig. 1: Multiple incipient plaque-shaped white lesions with irregular surface in maxillary alveolar ridge

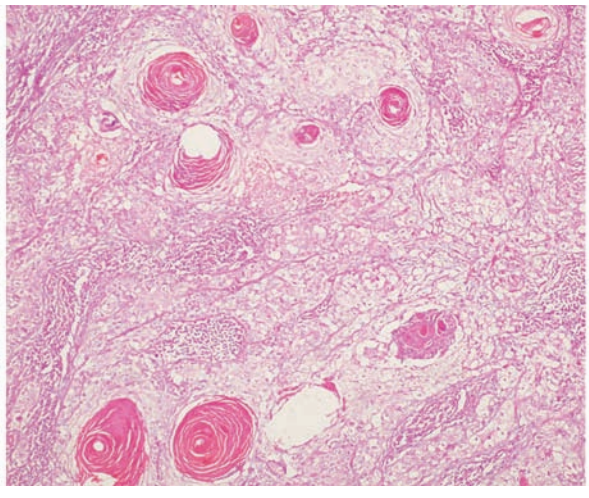

Fig. 2: Microscopic appearance of specimen from the incisional biopsy of maxilla alveolar lesion showing a marked keratinization in well-differentiated squamous cell carcinoma (H&E stain at 100× magnification)

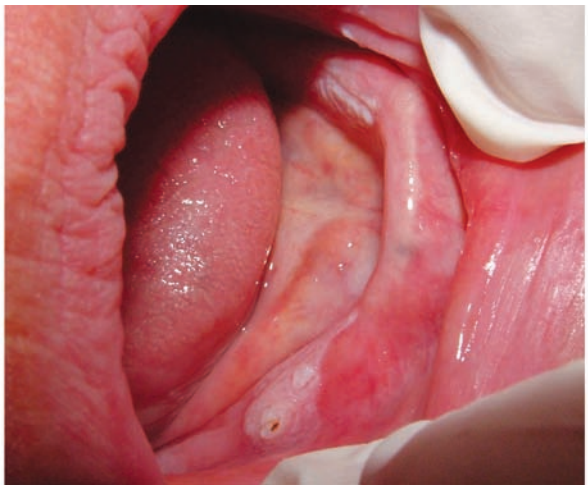

Fig. 3: Intraoral photograph showing new plaque-shaped lesions white in color in mandibular alveolar mucosa, with gingival swelling in the area of absent left mandibular premolar with evident bone erosion

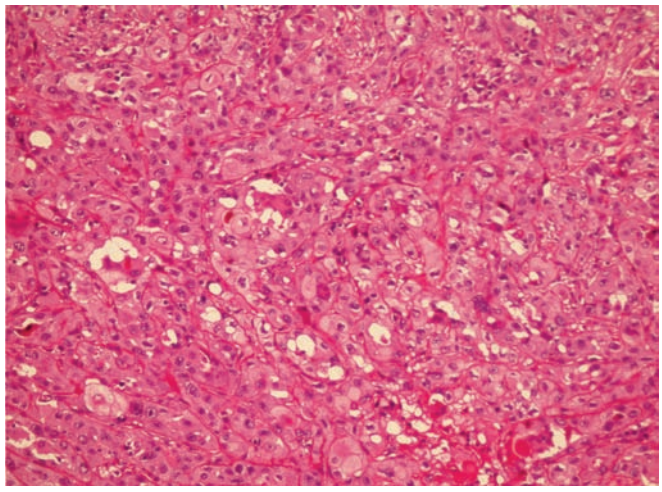

Fig. 4: Microscopic examination showing poorly differentiated squamous cell carcinoma in specimen of mandibular alveolar mucosa lesion (H&E stain at 100× magnification)

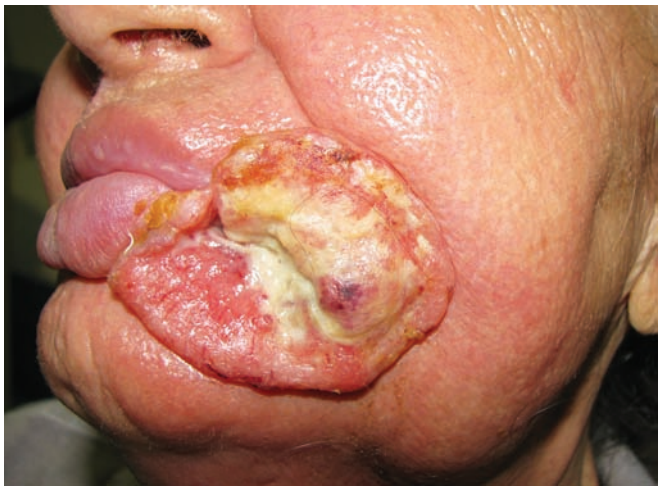

Fig. 5: Large ulcer in the buccal mucosa

later, a new plaque-shaped lesion appeared in the mandibular alveolar ridge, with ulcerated area, 6 × 8 × 8 mm in size. It was performed mandilectomy with reconstruction. Radiation therapy with a dose of 60 Gy was administered in head and neck region and during this treatment, the patient exhibited oral mucositis characterized by diffuse erythema in upper and lower lip, buccal mucosa and palate, for which the patient received additional treatment with systemic analgesics with nonsteroidal agents. In May 2008, new plaque-shaped lesions clinically diagnosed as SCCs appeared in hard palate (25 × 10 × 8 mm in size), buccal mucosa (15 × 7 × 7 mm) and dorsum of tongue (16 × 9 × 9 mm). Surgical resections of these lesions were performed and the diagnostic of moderately differentiated SCC was confirmed in all lesions. Thereafter, the patient was admitted on January 2009 and received a new intravenous chemotherapy with vincristine sulfate (VCR) 4 mg, PEP 30 mg, methotrexate (MTX) and mitomycin-C. Irradiation at 60 Gy was also carried out. After chemo- and radiotherapies, the patient stayed free of disease for 11 months. However, the patient was again admitted on March 2010 displaying large ulcerated lesions located in palate, dorsum of tongue and buccal mucosa (Fig. 5), which were clinically diagnosed as SCC. We performed an additional p53 immunohistochemical study, where some tissue sections were cutted (3 µm thick). Deparaffinized tissue sections were immersed in absolute methanol containing 0.3% H_2O_2 for 10 minutes at room temperature to block endogenous peroxidase activity. After washing with phosphate-buffered saline (PBS; pH 7.4), the sections were immersed in a microwave oven for 15 minutes. After further washing with PBS, they were incubated in PBS containing 2% bovine serum albumin for 15 minutes at room temperature to block any nonspecific reactions. Diluted mouse monoclonal anti-p53 antibody (Clone DO-7, Dako Corporation, Glostrup, DK) (1:25) was applied to the sections for 60 minutes at room temperature. The tissue sections were then washed twice in PBS and treated with labeled streptavidin biotin complex (LSAB; Dako, Carpinteria, CA, USA) at ambient temperature to bind the primary antibodies. Peroxidase activity was visualized by immersing tissue sections in diaminobenzidine (D5637; Sigma Chemical, St Louis, MO, USA), resulting in a brown reaction product. Finally, the tissue sections were counterstained with Mayer hematoxylin and coverslipped. As negative control, samples were treated as above, but the primary antibody was repaced by a solution of bovine serum albumin in PBS. The immunohistochemical analysis of this protein showed diffuse nuclear immunoreactivity in the cancerous cells of all tissues studied (Figs 6 and 7). At last, the patient received intravenous chemotherapy (6 cycles), but succumbed and died 2 months after the last cycle.

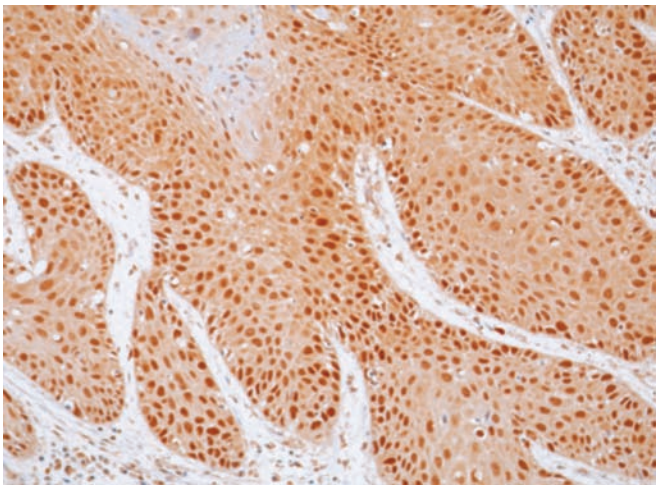

Fig. 6: Diffuse and intense nuclear p53 immunopositivity in the malignant cells

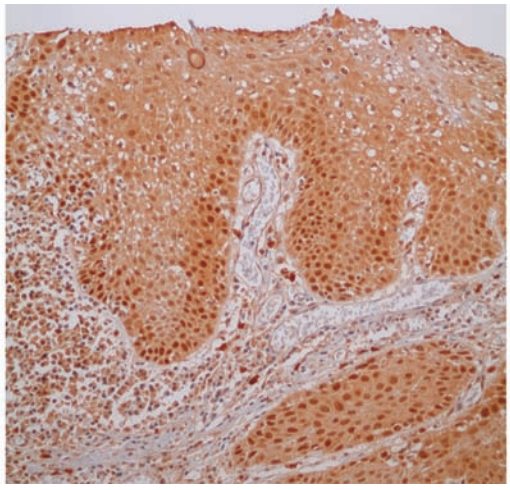

Fig. 7: Diffuse nuclear p53 immunoreactivity in the epithelium adjacent to cancerous cells

DISCUSSION

Warren and Gates[5] studied 1,259 cases of multiple primary tumors arising from nonrelated sites and defined the criteria for a second primary carcinoma: confirmation of malignancy in both tumors, each tumor must be distinct, and the second primary must be ruled out as metastatic spread from the first cancer. The requirement for separation by normal non-neoplastic mucosa is at present often replaced by a distance of 2 cm. Since the definition of these criteria in 1932, it has become widely recognized that patients with primary malignancy (especially in the head and neck area) are at high risk for developing additional primary malignant tumors.[7] This article reports multiple oral SCCs that fulfilled the described criteria for multiple primary malignant neoplasms.

The term 'field cancerization' was first introduced to explain why premalignant change may occur in any area of the upper aerodigestive tract epithelium exposed to carcinogens, which may lead to the development of multiple primary tumors and locally recurrent cancer.[8] Consequently, patients with oral potentially malignant lesions or cancer are at risk of developing multiple primary lesions, both synchronously and metachronously, within the upper aerodigestive tract. These lesions are usually considered to be biologically unrelated (clonally independent), but there is some evidence that second primary tumors can share some or even all genetic markers with the index tumor, indicating that both tumors have arisen from a common clonal progenitor cell.[9,10] However, our patient did not exhibit any history of previous potentially malignant lesion or extrinsic factors associated with the lesions in oral mucosa.

Most of the oral cavity cancers is located in a horseshoe-shaped area that extends from the anterior floor of the mouth and tonsillar pillar/retromolar trigone complex, because of concentrated carcinogens suspended in saliva that are pooled in these areas encouraging carcinogenesis.[11] In our case, the lesions of oral SCC appeared disseminated in oral mucosal of the patient, affecting buccal mucosa, alveolar ridge (maxilla and mandible), lower lip, commissure, tongue and hard palate, explaining an existence of a large field of cancerization in our patient.

Considering the time of diagnosis, multiple tumors can be classified into synchronous (diagnosed simultaneously or within 6 months after the diagnosis of the index tumor) or metachronous (diagnosed after a time interval of 6 months).[3,12] The majority of the second primary tumors occur at least 6 months after the detection of the primary one.[10] Furthermore, patients with metachronous SPT located in upper aerodigestive tract are thought to have a better prognosis than those with synchronous or located in other sites.[12] Cianfriglia, Di Gregorio and Manieri[3] reported that 90% of patients with synchronous oral SCCs are over than 40 years of age, which can correlate to our patient, as she was a 64-year-old woman who presented 12 oral SCCs in 7 years of follow-up, most of them being synchronic. To our knowledge, there are no reports in the literature of so many oral SCC lesions affecting several sites of the oral mucosa of the same patient in such a short period of time as the reported in this article.

The vast majority of individuals who develop SCC of the upper aerodigestive tract have a history of smoking tobacco and many of these individuals also consume alcohol regularly.[13] However, less often, patients with no history of smoking or drinking develop head and neck cancer. Farshadpour et al[6] reported that the rate of SPT development is similar in the patients exposed to tobacco and alcohol and those nonsmoking and nondrinking. Other authors explained that head and neck cancer in individuals with no history of smoking tobacco or drinking alcohol must be considered a distinct clinical entity, suggesting that these individuals tend to be elderly,

female and are predisposed to second primary tumor development.[11] Our patient fits these last characteristics as considering her age and the history of not smoking tobacco or drinking alcohol.

Others factors, such as dietary habits, genetic factors, viral infections and impaired or pathological immune functions, must be considered in order to explain field cancerization in nonsmokers and nondrinkers who also develop new tumors at a considerable rate.[3] Moreover, many patients treated with radiation therapy suffer from adverse effects, including the development of a second malignant neoplasm.[14] Different factors other than smoking or drinking can be related with the development of the oral SCCs in our patient, such as RT utilized to treat breast cancer 4 years before the emerging of the first oral SCC and later for the SCC in the buccal mucosa, or perhaps viral infections as well as HPV infection. Jégu et al[15] reported that in a recent population-based estimated that 4.9% of SPC may be related to radiotherapy in head and neck cancer survivors in the USA. Rusthoven et al[16] explained that patients with primary oral cavity cancers treated with RT can be at an increased risk of second head and neck cancers compared with patients treated without RT, differently from cancers located in other areas of the head and neck as pharyngeal sites.

Lately, a rise in incidence of HPV-associated head and neck SCC has been recorded.[15] A recent study suggested that the infection of HPV in early-stage oral SCC enhances the susceptibility of developing secondary malignancy, especially HPV-18.[17] However, other authors reported a lower risk of SPT in HPV-positive oropharyngeal SCC, emphasizing that this fact may be a major contributor to the demonstrated superior survival outcomes among patients with HPV-positive disease.[18] The presence of HPV was detected in the esophageal mucosa of our patient, but the oral lesion was HPV-negative.

As the development of SCC remains not totally understood, mainly in patients that lack the habit of tobacco and alcohol, modern molecular techniques may elucidate overall understanding of the biology of these tumors and ways to devise therapeutic strategies to best manage these lesions and improve prospects for survival.[7] It has become accepted that alterations in several oncogenes and tumor suppressor genes are the genetic basis for human carcinogenesis. Among the genetic changes involved in this process, inactivation of the p53 tumor suppressor gene by point mutation and allele loss is considered to be the most common event underlying malignancies of every organ. In addition, it has been described that cancer with the mutated p53 gene is resistant to radio/chemotherapy and the patient has a poorer prognosis than a cancer patient with the wild-type p53 gene. Furthermore, expression of p53 is related to the SPT risk in head and neck cancer.[12,19] Mutation of TP53 has been suggested to be one of the earliest events giving rise to a field of cancerization with malignant potential and loss and gain of TP53 gene (17p13.1) were described as shared genetic alterations between primary tumors and second primary tumors.[20] The SCCs of the palate, buccal mucosa, alveolar maxilla and mandible of our patient showed diffuse nuclear immunoreactivity for p53 protein.

Additionally, we performed a research in English literature in the database Medline/PubMed, from 1996 to 2013, about patients with multiple head and neck SCC with emphasis on oral cavity (Table 1). It became clear that the vast majority of cases affected men with mean age ranging from 50.19 to 84 years and the predominant treatment was marginal resection with or without RT with survival between 30 and 60 months. Kunkel et al[21] suggested that positron emission tomography (PET) with [18F]-2-fluorodeoxyglucose could be important to clinical management in patients with OSCC considered with 'high-risk' to develop recurrence and SPT, as the PET had 92% of sensitivity for recurrence or second primaries in cases treated with second-line therapy.

According to Tsou et al,[22] in managing SPT in patients with head and neck SCC, curative rather than palliative treatment is preferred when the index tumors have been diagnosed early, when SPT are metachronous and occurs in the head and neck region and also in cases of patients younger than 70 years. The chosen treatment for our patient was curative ranging from surgical resection with and without RT/chemotherapy.

Despite marked improvements in locoregional control of head and neck SCC over the past 40 years, the overall 5-year survival rate has not changed since the 1960s, ranging from 40 to 50% and even that locoregional recurrence and distant metastasis collaborate to the low survival rate, the development of SPT also contributed with significantly negative impact on the prognosis.[22] After the third year follow-up, the diagnosis of a SPT becomes the most important cause of morbimortality in head and neck cancer patients, especially in those treated for cancers early diagnosed.[12] Further, they often develop in a region previously treated, making the new treatment limited and challenging by the time they are diagnosed.[23]

CONCLUSION

The development of SPT is an intriguing problem in head and neck SCC and currently, there is no reliable method to predict which of the patients will develop a SPT. Therefore, the ability to accurately predict the risk of a future SPT would be a significant diagnostic and therapeutic step forward. More studies should be accomplished seek-

Table 1: Profile of patients with multiple head and neck in the literature. Natal, RN-2013

Article	*n cases*	*Oral cavity*	*Gender prevalence*	*Mean age*	*Treatment*	*Survival-months*
Cianfriglia et al[3]	28	11	Male	≤ 64	Surgery	40%, 60 months
Friedrich[4]	77	47	Male	58.5	Ablative surgery and/or radiotherapy/chemotherapy	48 months
Farshadpour et al[6]	33	26	NS[a]-Female S[b]-Male	NS[a]-72 S[b]-60	Surgery	—
Wiseman et al[11]	39	16	Female	60	Surgery and/or radiotherapy	—
Gutiérrez et al[20]	19	7	Male	57	Surgery	67%, 28 months
Kunkel et al[21]	41	41	—	58	Marginal resection with or without radiotherapy	Pet (+) 35% Pet (-) 71% 33.6 months
Tsou et al[22]	108	33	Male	50.19	Surgery and/or radiotherapy/ chemotherapy	32.9%-36 months
Li et al[23]	28	28	Male	56	Surgery and/or radiotherapy	50%, 36 months
Present case	01	01	Female	64	Surgery without or with radiotherapy/chemotherapy	60 months

a: nonsmoker; b: smoker

ing a better understanding of the biological behavior of these tumors in situations similar to the case reported here, aiming mainly a better life quality for those patients.

CLINICAL SIGNIFICANCE

This manuscript adds an uncommon case of multiple second primary oral SCC in a nonsmoker and nondrinker woman, emphasizing the diagnosis and management. It is important that patients with oral SCC undergo to a long-term and careful follow-up, since the screening of those sites at increased risk for SPTs has demonstrated to effectively improve early diagnosis and consequently the prognosis.

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