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KEYWORDS

Early diagnosis, Oral cancer, Squamous Cell Carcinoma.

ABSTRACT

Aim Oral Squamous Cell Carcinoma (SCC) has different clinical presentations, depending on its location, evolution time, precancerous lesions and risk factors. It is apparent that the high mortality due to this malignancy is caused by its detection in advanced stages, despite easy accessibility of the oral cavity for routine clinical examination. This is mainly because these lesions are in most cases asymptomatic in the early stages (pain appears because of nerve/muscles damage or local traumas) and their size does not increase for a long time. The stage of advancement of oral SCC at the time of diagnosis is the most important prognostic factor, even if the course of oral SCC is unpredictable. The purpose of this study is to stress the issue that small-sized oral squamous cell carcinomas are very difficult to distinguish from benign simulants and premalignant lesions, and careful intra and extra-oral examinations should be performed, in order to decrease the risk of malignant transformation.

Case report Two cases are reported, in order show how difficult it can be to establish a differential diagnosis and the importance of biopsy in case of doubt.

Introduction

Oral cancer refers to cancer occurring between the vermilion border of the lips and the junction of the hard and soft palates or the posterior third of the tongue.

Oral squamous cell carcinoma (SCC) is nowadays the sixth most common cancer in the world with two-thirds of cases localized in developing countries (1) and with an incidence of about 275,000 new cases every year, it is an increasing healthy emergency worldwide with lethal effects in over 50% of the cases diagnosed. It affects more frequently males than females (M:F=1,5:1), probably because of the major risk factors exposure.

Oral SCC has different clinical presentations, depending on its location, evolution time, precancerous lesions and risk factors. In most cases it appears as a leukoplastic, erythroplastic or leukoerythroplastic lesion, but it could also resemble a verrucous leukoplakia or may present superficial eroded areas. It sometimes appears as a necrotic ulcer, with irregular margins and raised indurated borders, and some other times it is exophytic and smooth. When increased consistency on palpation is observed, chorion infiltration must be suspected.

It is apparent that the high mortality due to this malignancy is caused by a detection of the disease in advanced stages, despite the easy accessibility of the oral cavity for regular clinical examination, mainly because these lesions are in most cases asymptomatic in the early stages (pain appears because of nerve/muscles damage or local traumas) and their size does not increase for a long time. As result many oral SCCs are diagnosed at an advanced stage and the prognosis is therefore poorer than it could have been if diagnosed earlier (2).

In the recent literature, the role of early oral SCC diagnosis in avoiding more extensive and costly treatments, greater morbidity and poorer survival has been widely highlighted (3, 4, 5). Onizawa et al. (6) reported that extended oral SCC are diagnosed more easily, while there is a later referral of patients affected by T1 tumors, because of difficulties in obtaining an early clear clinical diagnosis of small mucosal neoplastic lesions.

In clinical practice the tumor stage is defined by TNM staging system of oral cavity cancer (designed by the American Joint Committee on Cancer) and tumor dimensions (T) are divided into 4 categories (T1: ≤2
cm; T2: >2-4 cm; T3: >4 cm; T4: extra-site invasive tumor) (7). According to the TNM staging system, small-sized oral SCC belongs overall to stage 1. A subgroup of T1 tumors (tumor extension <2 cm) are also microinvasive SCC (tumor thickness <4 mm) i.e. are early stage relatively thin tumor without invasion of deep tissue and extension of cancer growth into the tissue beneath epithelial surface, nonetheless, as reported in the literature, they may infiltrate lymph nodes and, consequently, reduce survival rates (14).

Small-sized oral SCCs showing a diameter ≤2 cm often do not alert clinicians because of a wide range of clinical appearances in absence of any accompanying symptoms. At its onset a small-sized oral SCC may clinically resemble non-neoplastic lesions as erosions, patches, plaques, ulcers and so on. Indeed, diagnostic delays are especially linked to small-sized carcinomas that appear to be seemingly innocent alterations, in the form of focal color change without surface textural change or small and ulcerated lesions erroneously diagnosed even as aphthae or traumatic ulcers (6, 8).

As far as aspect is concerned, it is not surprising that oral SCCs appearing as ulcerated lesions are reported to have a significant diagnostic delay because they might be clinically misdiagnosed by the initial physician, who might confuse them with benign ulcerative lesions (6).

A further confusing issue is due to the presence in the oral cavity of potentially malignant disorders (PMDs) such as oral leukoplasia, oral erythroplakia, lichen planus and lichenoid reactions, oral submucous fibrosis, discoid lupus erythematosus and actinic keratosis that may significant by increase the risk of oral SCC development with an impossibility to predict which PMDs may transform to cancer (9). Moreover tobacco, alcohol and betel quid usage acting separately or synergistically and HPV infection, particularly of tonsillar and oropharynx area, in young people may contribute to sudden changes of PMDs in neoplastic lesions (10). It is known that exposure to risk factors may result in genomic instability and genomic alterations may precede the phenotypic and cellular manifestation associated with dysplasia. Precancerous lesions are more likely to develop into cancer by the acquisition of multiple genetic alterations and the persistence of these alterations leads to the development of early cellular changes associated with cancer genesis (11, 12).

It is widely known that surveillance of oral epithelial dysplasia results in a number of newly diagnosed cases of oral squamous SCC (13). Furthermore, an early diagnosis permits the clinicians to obtain a complete tumor resection with a higher percentage of tumor-free margins at the histological examination.

Tumor-free margins are an essential surgical strategy for decreasing the risk for local tumor recurrence. Conversely, positive margins increase the risk for local relapse and are an indication for postoperative adjuvant treatment. Since little is known about signs of early small-sized oral SCC, the main aim of our report was to raise an improved understanding of the initial clinical features of these lesions in order to address patients to early surgery.

Case reports

Case 1

In Jan 2012 a 42-year-old man was referred to the dental clinic of the University of Padua (Padua, Italy) by a general dentist who highlighted a small suspicious lesion, 5 mm of diameter localized on the lingual edge, during a dental follow-up visit (Figure 1). The patient was asymptomatic, he did not present drug or restoration-related lichenoid reactions nor dental trauma and he had a history of smoking habits but not alcohol consumption. Clinical examination revealed a white papular lesion, rough to palpation. The color in particular suggested a malignant transformation, therefore a large excisional biopsy was performed.
under conscious sedation (14, 15) (the patient referred anxiety level= 8) and local anesthesia without vasoconstrictor. The biopsy was sent for histological examination. A microinvasive OSCC stage I diagnosis was formulated, with a well-defined margin of invasion stained with hematoxylin–eosin (Figure 2). The human papillomavirus (HPV) typization was negative, and also the margins were tumor-free.

At ultrasonography there was no lymph node metastasis (so no cervical nodes dissection was required), gastroscopy and upper airways endoscopy were negative too. Omolateral submandibular lymph node metastases have not been detected also during the follow-up visits, six and twelve months later.

Case 2
In Jan 2012 a 72-year-old woman was referred to the dental clinic of the University of Padua (Padua, Italy) by a general dentist who highlighted a small suspicious lesion, 5 mm in diameter localized on the ventral lingual surface, detected during a dental follow-up (Figure 3). The patient was asymptomatic, she did not report dental traumas and she did not have a history of exposure to substances known to be carcinogens, such as smoking and/or alcohol. Clinical examination revealed a red lesion on the ventral lingual surfaces. The color of the lesion suggested ulceration and malignant transformation, therefore, a large excisional biopsy was performed, and microinvasive OSCC stage I diagnosis was made with a well-defined margin of invasion at hematoxylin–eosin stained sections (Figure 4).

The human papillomavirus (HPV) typization was negative.

At ultrasonography there was no lymph node metastasis, gastroscopy and upper airways endoscopy were negative too. Omolateral submandibular lymph node metastases were not detected also during the follow-up visits, six and twelve months later.

Discussion
An improved understanding of early small-sized oral SCCs is a critical step to address patients to a prompt treatment, surgical approach, which remains the only effective therapy of oral SCC, and a relatively good prognosis can be attributed only basing on an early detection.

An early stage detection may be the gold standard in small-sized oral SCC management because it is the most effective means in reducing morbidity and duration of treatment (17): the survival rates are much improved when lesions are diagnosed at less than 2 cm in size (i.e. small and localized), with five-year survival rates of up to 90%, compared to survival rates of advanced lesions that are estimated as low as 20% (18). Nonetheless the early diagnosis of small-sized oral SCC remains a challenge for the clinicians and patients with small (T1–T2) oral SCC have more specialist delay than patients with large (T3–T4) tumors (16). In 2013, the official National Comprehensive Cancer Network guidelines have been published. According to those guidelines, the recommended initial options for patients with early-stage oral cavity cancers, are resection (preferred) or definitive radiation therapy, and postsurgical adjuvant treatment options depend on whether adverse features are present. The management is completely different for patients at advanced stages oral cancer, whose treatment includes also a variety of postoperative adjuvant options, such as chemotherapy, radiation therapy and re-resection of positive margins (if possible), taking into account the possibility of nodal involvement and perineural or vascular invasion (19).

It is evident that there is an overlap in clinical features between small-sized oral SCC and benign lesions that delay professional diagnosis, defined as the period from the first consultation with a healthcare professional until the histopathological diagnosis is made (20). A recent report by Pentenero et al. showed that microinvasive oral SCC in stage I consists of thin lesions that tend to look clinically similar to premalignant lesions, presenting as erosions, patches and plaques, whereas the thick lesions were more likely to be ulcerated, with a low prevalence of erosions and/or patches. It may present a risk during clinical examination of underestimating the malignancy of early lesions that resemble premalignant disorders and stresses the importance of careful diagnostic evaluation of any apparently premalignant lesion. No symptoms are present in an early stage of small-sized oral SCC, thus, an early diagnosis of asymptomatic oral SCC requires an experience in detection of oral lesions and it is proved that an accurate clinical examination may achieve a correct diagnosis in almost half of patients (16). On the other hand the biology of lesions may play a role in tumor aggressiveness, determining tumor size and stage at diagnosis (21). Biologically aggressive small-sized oral SCC may grow to an advanced stage after a short period of time, so an early diagnosis could be very difficult. On the contrary, slow-growing tumors may have an early stage at diagnosis even after a substantial period of diagnostic delay.

A further issue in early small-sized oral SCC diagnosis is that it may be asymptomatic at the onset of the disease. Due to the lack of symptoms and clinical manifestations, many patients (approximately 27%) do not recognize the tumor until it reaches an advanced stage. Conversely, alert patients may identify signs or symptoms of oral cancer when it is only a pre-neoplastic lesion, or an early stage cancer (21). This could be the reason why the 5-year survival rate of patients affected by oral SCC has not improved despite advances in diagnostic techniques and treatment modalities.
An improved understanding of oral clinical signs and symptoms such as ulceration, pain, swelling, bleeding, teeth mobility is required, together with an accurate differential diagnosis with non-neoplastic conditions of oral cavity such as periodontal, traumatic, inflammatory or infective lesions. The presence of an oral SCC involving the dentition, particularly in its early stages, may consequently be overlooked by a clinician as a possible diagnosis. The challenge for clinicians who diagnose and treat small-sized oral SCC is to distinguish between malignant lesion and benign simulants, therefore, it is essential to familiarize with the variable clinical manifestations of both PMDs as well as small-sized oral SCC to avoid delayed diagnosis of a small-sized oral SCC that could result in more advanced disease at the time of treatment.

The presence of lesions, such as human papillomavirus and lichen planus, should be a compelling reason to keep those patients under control. Oral lichen planus is a common inflammatory disease of unknown cause, which affects the oral mucosa, probably linked to oral SCC development. There is lack of evidence in the literature on this, but the chronic inflammation is considered to be associated to increased risk of cancer (like ulcerative colitis and Crohn disease are associated with increased risk of colorectal adenocarcinoma) (24, 25).

More accurate visits should be performed also in case of smoking habits and alcohol consumption. It is well known that the most important risk factors for oral SCC are the use of tobacco or betel quid, and the regular drinking of alcoholic beverages. Undoubtedly, prevention is the best way to reduce incidence and morbidity of oral squamous cell carcinoma, so education about risk factors and early signs and symptoms is of paramount importance.

We wish to reinforce the trend of always being vigilant for the presence of an oral SCC, particularly when lesions of the oral cavity do not respond to treatment
as would usually be expected by the clinician (26). GDPs have an essential role in highlighting overall oral cavity lesions and in referral patients to a secondary center, i.e. a hospital. An exhaustive clinical training and a thorough soft tissue examination by GDPs is basilar in the detection of smaller tumors that may be unnoticed because of their small size and/or location when are harder to see and, thus, in avoiding delayed cancer diagnosis. On the one hand, it could be difficult for a GDP to detect small-size oral SCC, but, on the other hand, the predisposing conditions could be most probably identified, and represent the motivation for specialist evaluation.

In our opinion, healthcare practitioners should perform an oral soft tissue examination almost once a year, especially in patients above the age of 40, exposed to risk factors and with poor oral hygiene. Early diagnosis is important not only from the prognostic point of view, but it also improves the patients’ quality of life, both from a subjective and an objective point of view. These tumors compromise basic physiologic functions (the ability to chew, swallow, and breathe), the senses (taste, smell, hearing), and personal characteristics (appearance, voice). The smaller is the tumor at the time of eradication, the smaller are the consequences in terms of loss of functions.

During the last few years, it has been discovered that an oral cancer can arise both from a premalignant lesion, and from a precancerized epithelium. People with a history of head and neck cancer are more frequently subjected to other malignant lesions development. Follow-up visits, with accurate examination of the oral cavity and the oropharynx, are recommended, also because patients previously affected by head or neck cancers have an increased possibility of developing a second primary tumor of the upper aerodigestive tract (27).

Any suspicious areas should be biopsied, especially if erythroplastic (more likely associated with dysplasia or carcinoma, (28). Incisional or excisional biopsy can be performed depending on the surgeon’s preference and the lesion’s size and location.

We strongly believe that further long-term and multicentric clinical investigations will be performed for defining clinical and pathological characteristics of small-sized oral SCC.

Conclusion

GDPs have an essential role in highlighting overall oral cavity lesions and in refer patients to a secondary center. A biopsy, incisional or excisional, should be mandatory in case of doubt or persistence of an ulcerated lesion, even if asymptomatic. Detecting small-sized OSCC is very important, in order to prevent lymphnodes metastasis.

References